THE EFFECT OF THE HAND DOMINANCE ON POST OPERATION REHABILITATION AFTER KNEE ARTHROPLASTY

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There are many factors impact on rehabilitation of the patient post knee arthroplasty. To evaluate the effect of hand dominance on patient's rehabilitation following knee Arthroplasty both short and long-term evaluation.

We evaluated a cohort of TKR patients operated on within 2 years period, we assessed the effect of hand dominance on post-operative recovery, length of hospital stay, Range of movement and patients reported outcomes using reintegration to normal living index.

A total of 130 patient had total knee replacement during the period, 98 of them participate 65 females and 33 males. Two groups: Dominant side operated they are 52 patient's and non-dominant side operated are 46 patients. The average length of stay in the TKR group were 5.3 days in non-dominance side group and 7.6 days in the dominance side surgery. The average RNLI (reintegration to normal living activity) after TKR performed in the dominant side was 86.6 while in the non-dominant side was 91. Statistical testing performed using regression analysis with STATA software.

Hand dominance showed an effect on length of stay and post-operative rehabilitation following TKR with significant difference in LOS and RNLI index post operatively.

COMPARISON OF DERMAL AND TENDON FIBROBLASTS FOR SCAFFOLD-FREE TENDON TISSUE ENGINEERING APPLICATIONS

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Healthcare expenditure for human tendon injuries exceeds €145 billion per year. Actual repair procedures of critically injured tendons usually rely on the use of tendon tissue grafts, which have a limited regenerative efficacy. Scaffold-free tissue engineering (SFTE) is a promising approach to produce tissue equivalents *in vitro* but is limited by the generally slow rate of extracellular matrix deposition which occurs under standard cell culture conditions. Macromolecular crowding (MMC) is a biophysical phenomenon that accelerates *in vitro* matrix deposition by several orders of magnitude and has been proved to decrease the culture times needed for the production of tissue equivalents *in vitro*, thereby showing promise for helping the translation of SFTE techniques to the clinic. Both tendon (TFs) and dermal fibroblasts (DFs) have shown good performance in tendon regenerative settings, which makes them suitable cell sources for tendon tissue engineering.

Herein, we sought to compare the performance of DFs and TFs in SFTE to evaluate its further application in tendon regenerative procedures. Cells were seeded at 25,000 cells / cm^2 and treated with MMC during 3, 6, and 9 days. Non-MMC treated cells served as controls. Media was changed every 3 days.

Significant increase in collagen deposition in the MMC-treated groups was appreciated by SDS-PAGE. Immunocytochemistry showed significant increases of different extracellular matrix proteins in the presence of MMC. Cell viability was not affected by MMC.

These data show the potential of the application of MMC in the development of SFTE constructs with TFs and DFs for tendon tissue engineering.

PULSED ELECTROMAGNETIC FIELD ACTUATED BIOMATERIALS FOR INFLAMMATION REGULATION IN TENDONS

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Inflammation is an important process of tendon healing. However, excessive, persistent or unresolved inflammation may result in impaired healing, ultimately leading to degeneration and loss of functionality. Pulsed electromagnetic field (PEMF) has shown potential to reduce inflammation and increase tissue healing rates, being a FDA approved therapy for orthopaedics. Previously, we reported that PEMF actuated membranes holding magnetic responsiveness have potential to modulate inflammation *in vivo*. However, the cellular mechanisms involved were not properly understood.

Thus, in the present study, we propose to investigate the influence of PEMF actuation provided by a magneto therapy device (Globus) on the behaviour of human tendon derived cells (hTDCs) cultured onto magnetic membranes, exploring their modulatory role under an inflammatory environment induced by IL-1β. Magnetic membranes were produced by solvent casting, incorporating iron oxide magnetic nanoparticles into a blend of starch/polycaprolactone (SPCL).

Under a PEMF actuation, magnetic membranes moderated cell mediated inflammatory reactions *in vivo* while *in vitro* hTDCs treated with IL-1β and cultured on magnetic actuated membranes showed an attenuated protein and gene expression of inflammatory associated markers, such as IL-6, TNF-α, and MMPs, assessed by ELISA assays and real time RT-PCR analysis.

Collectively, these results illustrate the beneficial synergistic effect of magnetic biomaterials and PEMF in modulating cell responses to inflammatory cues, contributing for the resolution of inflammation in tendon healing.

EFFECT OF PRO-INFLAMMATORY CYTOKINE COMBINATIONS ON EXPLORATORY BIOMARKERS OF CARTILAGE DEGRADATION

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Proteomic analysis of osteoarthritic synovial fluid, cartilage secretome and the membranome of chondrocytes has identified lumican (LUM), chondroadherin (CHAD) and low-density lipoprotein 1 (LRP-1) as potential biomarkers of joint disease.

Our aim was to confirm the presence of these exploratory biomarkers, in an explant model of cartilage degradation, and isolated chondrocytes, and quantify levels in response to different combinations of pro-inflammatory cytokines. Bovine articular cartilage explants and isolated bovine chondrocytes, seeded at high density, were cultured in serum-free DMEM with or without 10, 2.5 or 0.5 ng/ml bovine interleukin-1β (IL-1β) and 50, 10 or 2.5 ng/ml oncostatin M (OSM), or 10ng/ml tumour necrosis factor-a (TNF-α), for 14, and 7 days, respectively. Biomarker levels in explant and chondrocyte secretome, or chondrocyte lysate, were determined by western blotting. Gene expression was determined by qPCR.

Intracellular LRP-1 expression decreased 4-fold with OSM/IL-1β and TNF-α/IL-1β treatment ($p<0.001$, n=3), and the effect was observed with lower concentrations of cytokines. LRP-1 was released into explant secretome with OSM/IL-1β, but not TNF-α/IL-1β. LUM in chondrocyte secretome was elevated 4-fold with OSM/IL-1β ($p<0.05$, n=3), and the effect was observed with lower concentrations of cytokine. LUM and CHAD release from explants was induced by OSM/IL-1β ($p<0.001$, n=6), but not TNF-α/IL-1β. Both cytokine combinations decreased CHAD gene expression by 5-fold ($p<0.0001$, n=4). Individuals (41 re-infections) with available data on comorbidities and infecting organism type, HR 1·71 (0·39, 7·50; p=0.479).

We have confirmed the presence of these exploratory biomarkers in both cartilage explant and chondrocyte models. Differences in expression, and release from the matrix, with different cytokine combinations, suggests these biomarkers may have differing roles in disease progression.

SHORT TERM TREATMENT OF CHONDROCYTES WITH IL-1B INHIBITS MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION

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The avascular nature of articular cartilage, with limitations in the rate of nutrient and oxygen diffusion from the synovial fluid, has led to the concept that chondrocytes are reliant on glycolysis to meet their energy needs. It has been suggested that a minimal flux of oxygen through the mitochondrial respiratory chain may be required to stabilise glycolytic enzymes, with mitochondrial reactive oxygen species helping to maintain cellular redox balance in favour of glycolysis.

The aim of this study was to assess the impact of short-term pro-inflammatory cytokine exposure on chondrocyte bioenergetics. Primary bovine articular chondrocytes were seeded at 160,000 cells per well of a Seahorse XF24 cell culture microplate and cultured in serum free DMEM with ITS media supplement for 18 hours in the presence or absence of either IL-1β or TNF-α or control media. Following 18 hours chondrocytes were subject to the Mito Stress

Test using a Seahorse XFe24 Analyzer, to measure key parameters of mitochondrial function. Only chondrocytes cultured in the presence of IL-1β but not TNF-α exhibited significant differences in mitochondrial function. Chondrocytes exposed to IL-1β displayed a significant reduction in basal respiration, proton leak, spare respiratory capacity, ATP production and maximal respiration.

These results indicate that chondrocytes exposed to TNF-α still utilise mitochondrial oxidative phosphorylation, while chondrocytes exposed to IL-1β oxidative phosphorylation is significantly reduced with a predominant switch to glycolysis. These preliminary findings demonstrate the short-term effect of pro-inflammatory cytokines on mitochondrial function and further studies will reveal more about mitochondrial dysfunction associated with osteoarthritis.

3D PRINTING AND ITS ROLE IN COMPLEX REVISION HIP ARTHROPLASTY

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Revision hip arthroplasty requires a comprehensive appreciation of areas of bony insufficiency, deficiency and discontinuity in order to conceptualise complex corrective reconstructions. Advances in radiology combined with advances in computer and manufacturing technology have made the three-dimensional (3D) representation of anatomic structures obtainable.

Life size three dimensional models were manufactured from CT scans of two patients with complex acetabular defects waiting for second stage hip revisions. The models were constructed from 3D images, using MIMCs software, and manufactured using the rapid prototyping process, Selective Laser Sintering. The models allowed accurate templating using the actual prosthesis weeks prior to surgery. Acetabular cup size, augment and buttress sizes, as well as cage dimensions were selected in advance.

The malleable cage template was adjusted according to the contours of the model and were then re-sterilised. Screw trajectory simulation was carried out on the models, thus reducing the chance of neurovascular injury and allowing best use of available bone stock to ensure best construct stability.

With 3D printing technology, complex pelvic deformities can be better evaluated and can be treated with improved precision. The life size models allow accurate surgical simulation, enabling preoperative simulation. The accuracy and cost-effectiveness of the technique were impressive, and its use could be incorporated as a tool to aid clinical practice.

THE EFFECTIVENESS OF PERI-OPERATIVE INTERVENTIONS IN PREVENTING CHRONIC PAIN IN PATIENTS RECEIVING PRIMARY TOTAL KNEE REPLACEMENT: A SYSTEMATIC REVIEW

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For patients receiving total knee replacement (TKR), features of peri-operative care may be associated with chronic pain after surgery. Effects may be direct, e.g. through nerve damage or complications, or indirect by limiting mobilisation and rehabilitation. This systematic review evaluated whether peri-operative treatments can prevent chronic pain after TKR. PICOS criteria were: adults receiving primary TKR for osteoarthritis; peri-operative non-surgical intervention; control receiving no intervention or alternative; pain assessed at ≥6 months post-operative, and adverse events; with evaluation in a randomised controlled trial (RCT).

We searched major bibliographic databases up to February 2018. After screening, two reviewers evaluated relevant articles. Studies at low risk of bias according to the Cochrane tool were included in our analysis. Searches identified 1514 RCTs of which 43 assessed pain and were at low risk of bias. Intervention heterogeneity precluded meta-analysis and definitive statements on effectiveness.

There was encouragement for further research into local infiltration analgesia, ketamine infusion, pregabalin, and electric muscle stimulation. Surgery without a tourniquet was associated with fewer early complications but not chronic pain and merits further research. There was no evidence that prevention of blood loss with tranexamic acid was associated with chronic pain. Extensively researched interventions including venous thromboembolism prevention have not been evaluated in relation to chronic pain.

Our review summarises evidence on peri-operative treatments for the prevention of chronic pain after TKR and highlights aspects of care for further evaluation in well-conducted RCTs. Long-term consequences of many widely researched treatments have not been reported.

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INFLUENCE OF CROSS-LINKING CONCENTRATION ON THE SHEAR DEFORMATION OF COLLAGEN FIBRILS AS DETERMINED USING PIEZORESPONSE FORCE MICROSCOPY

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During aging, collagen undergoes a series of post-translational modifications that lead to an accumulation of collagen cross-links, which impacts mechanical strength and thus cellular function. Collagen is naturally piezoelectric and such electromechanical coupling may play a role in bone remodeling. As such, it is important to assess whether cross-linking also influences collagen piezoelectricity.

In this study, we report on the influence of glutaraldehyde (GTA) cross-linking on the measured piezoelectric properties of collagen fibrils as determined by piezoresponse force microscopy (PFM). Fourier-transform infrared spectroscopy has been used to evaluate the chemical structure of collagen before and after cross-linking.

Amide A and OH bands (from water bonded to collagen) are in the same range in FTIR spectrum (3700-3100 cm-1), hence, the width between the area of the band was measured. It was found that increasing the crosslinking concentration will result in a smaller band area, which suggests that during crosslinking collagen might lose the intramolecular water bridges and intermolecular bridges between fibrils are formed instead.

Besides, cross-linked fibrils with 15% GTA showed greater resistance to collagenase, where only 13% was degraded in 7 hours compared to the control sample, which dissolved within 3 hours. PFM results show a reduction in the piezoresponse for cross-linked samples (GTA 15%), in comparison to the control sample (0.6 ± 0.4 pm/V and 1.2 ± 0.1 pm/V, respectively).

We conclude that increases in cross-linking restricts the fibril's capacity to shear. Reduced electromechanical coupling could interfere with the ability of cells to sense and adapt to mechanical stress.

PREVALENCE OF MRSA AMONG HEALTH CARE WORKERS

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The major challenges faced the by health care system are the hospital acquired infections and the resistance to the antibiotics. Most of the time the organism involved in hospital acquired infection is staphylococcus Aureus. It also frequently colonizes the humans and it is found that approximately one third of population carry staphylococcus Aureus in nose. The organism is broadly categorized into methicillin sensitive (MSSA) and methicillin resistant (MRSA). MRSA, also known as “Super Bug” is resistant to commonly prescribed antibiotics and thus difficult to treat. Screening can be done with swabs taken from nose, axilla and groin.

According to American Society of Microbiology, nasal swabs have higher MRSA detection rate when compared to axilla and groin swabs. The nasal carriage rate of MRSA increases with increasing incidence of infection and the transmission can be halted by treating the carriers. The rate of MRSA colonization varies widely as different studies show different rates. At present, no study is published to described MRSA colonization rate among health care workers in Pakistan.

The objective of our study is to determine the prevalence of MRSA among health care workers and the study was carried out in Shaheed Mohtarma Benazir Bhutto Trauma Centre, Karachi, Pakistan. The nasal swabs taken from 237 health care workers taking part in this screening were processed using standard laboratory techniques.

Out of 237, MSSA was found in nasal cavity of 9.7% (23) and MRSA was detected in 8.8% (21).

This data revealed significantly higher rate of MRSA prevalence among health care workers.

FISH SCALE AS A NOVEL REINFORCEMENT IN POLYMERIC SCAFFOLDS FOR BONE ENGINEERING APPLICATIONS

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Fish scales are used as collagen sources in biomaterial applications due to their Type I collagen and hydroxyapatite (HAp) content and similarity to bone tissue with distinctive collagen arrangement mimicking the bone matrix. Besides, these structures are bioactive biocompatible, low antigenic and biodegradable.

In our previous studies, fish scales were decellularized with combination of physical, chemical, enzymatic methods and used as templates for MG-63 attachment and proliferation.

Results indicated that, cells were attached and proliferated on fish scale surface due to its collagen-Hap based composition and patterned surface morphology (microchannels) inducing suitable surface with high roughness. However, there has been no study concerning the use of fish scale as reinforcement in polymeric biomaterials.

Therefore, in this study, it is aimed to design a new composite scaffold with fish scale microparticle incorporation to chitosan matrix for hard tissue regeneration. Fish scales were disrupted physically and Fish scale microparticles (100 μm) were dispersed in chitosan matrix with ultrasonic homogenization. Chitosan/fish scale (FS/CS) scaffolds were fabricated by lyophilisation technique and characterized in terms of mechanical, morphological and physical properties with FT-IR, degradation and swelling test. SEM and porosity results showed that FS/CS scaffolds have uniform pore structure showing high porosity with increasing fish scale content. *In vitro* cytotoxicity, proliferation and osteogenic activity of fish scale reinforced scaffold were obtained with Saos-2 cell line.

Results indicated that fish scale reinforcement did not cause any cytotoxic effect and found suitable for cell proliferation. In conclusion FS microparticles show promising effects as reinforcement agents for bone regeneration.

CAN WE REDUCE THE NUMBER OF MRSA SCREENING SITE SWABS IN ELECTIVE ORTHOPAEDIC PATIENTS?

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This study evaluates the possibility of reducing the number of MRSA swab sites as part of a quality improvement project.

Patients on the waiting list for elective orthopaedic procedure in our trust who had a MRSA positive swab from either four sites were analysed over the time period from January 2012 to December 2014. Positive swabs of different regions were recorded and compared.

There were 138 MRSA positive patients, giving an incidence of 31 per 10000 screen/year over that time period. Some patients (n=31, 22.5%) had a positive swab in more than one site. The positive sites were as follows: nose (69.60%, n=96), groin (26.10%, n=36), throat (25.30%, n=35) and axilla (8.70%, n=12). In our cohort, we would miss a significant proportion of positive patients if we change it to a two-swab screening policy. However, we would only miss 2.2% of cases for a nose, groin and throat three-swab policy.

A three-swab combination of nasal, throat, and groin swabs improves pick up rate of MRSA significantly compared to a two-swab policy and misses only 2.2% compared to a four-swab policy. Axilla swabbing does not make a significant difference to the results.

Based on this study, the policy has now been changed from a four-swab to a three-swab screening in our trust. This has been audited 4 times and they were all negative. This has helped reduce cost in terms of staff time and resources.

DOES INTRAMEDULLARY GRAFTING INCREASE STABILITY OF PLATED PROXIMAL HUMERUS FRACTURES?

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Treatment of complex distal radius fractures, commonly managed by volar locking plates, is challenging. Combined volar and dorsal plate fixation is valuable option, however, current biomechanical investigation on competency of supplemental dorsal plating is scant. This study's aim is to investigate biomechanically double-plated distal radius fractures in comparison to volar locking plating.

Complex intra-articular distal radius fractures AO/OTA 23-C2.1&C3.1 were created in 30 artificial radii assigned to 3 groups. Lunate facet was divided in 3 equally-sized fragments in group 1, split in smaller dorsal and larger volar fragment in group 2, and divided in 2 equal fragments in group 3. Following fracture reduction, each specimen was first instrumented with volar locking plate and tested non-destructively in 40° flexion, 40° extension and 0° neutral position. Mediolateral radiographs were taken under 100N loads in flexion and extension, and under 150N loads in neutral position. Subsequently, all biomechanical tests were repeated after supplemental dorsal locking plating.

Stiffness in neutral position increased after supplemental dorsal plating in groups 2 and 3, but not in group 1. In addition, stiffness in extension remained after dorsal plating without increase, whereas in flexion it increased in each group. Angular displacement between shaft and lunate facet decreased after dorsal plating in neutral position and flexion in each group, whereas in extension it decreased in groups 1 and 2, but not in group 3.

In conclusion, supplemental dorsal locked plating increases fixation stability of unstable distal radius fractures after volar locked plating. However, its effect depends on fracture pattern.

DOES INTRAMEDULLARY GRAFTING INCREASE STABILITY OF PLATED PROXIMAL HUMERUS FRACTURES?

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Locked plating of proximal humerus fractures is still associated with high complication rates. The aim of this study was to investigate the biomechanical competence of PHILOS plating augmented with supplemental intramedullary graft in comparison to conventional PHILOS fixation. Complex four-part proximal humerus fractures were set in thirty artificial humeri assigned to three study groups (n=10). Group 1 was characterized by loss of medial support, group 2 – by aggravated bone quality, and group 3 – by combination of the two features. Following PHILOS plating, each specimen underwent non-destructive quasi-static biomechanical testing in 25° lateral angulation under axial loading between 150N and 400N in 50N increments, accompanied by consecutive anteroposterior x-ray imaging. Subsequently, an additional 3D-printed intramedullary graft was inserted into each specimen and all tests were repeated. Grafting resulted in significantly higher axial stiffness in groups 1 and 3 ($p<0.01$), but not in group 2 ($p=0.12$). Non-grafted specimens represented significantly higher stiffness in group 2 compared to groups 1 and 3 ($p<0.01$), whereas no significant differences were detected among the three groups in grafted state ($p>0.99$). Varus deformation decreased significantly in each group after graft insertion ($p\leq0.04$). Non-grafted specimens in group 2 showed significantly lower varus deformation compared to groups 1 and 3 ($p\leq0.04$). No significant differences were registered among the three groups post grafting ($p\geq0.65$). From biomechanical perspective, PHILOS plating augmented with intramedullary graft has the potential to increase significantly the stability against varus collapse in unstable proximal humerus fractures, when compared to conventional PHILOS fixation.

3D GEOMETRY OF FEMORAL REAMING

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The Reamer-Irrigator-Aspirator (RIA) is a minimally invasive technique used for bone graft harvesting by reaming the medullary canal of the femur. In contrast to bone graft harvesting from the iliac crest it allows the extraction of large amounts of bone graft. However, postoperative femur fractures have been observed after RIA. The reaming diameter is one of the most discussed reasons for these fractures. Therefore, the 3D morphology of the reaming (the decrease of femoral wall thickness) was analysed considering different reaming diameters with regard to the fracture morphology.

Forty-five human cadaveric femora were randomized to three groups (G1-G3) and reamed with a +1.5mm (G1), +2.5mm (G2) and +4mm (G3) larger diameter than the isthmus. For morphological examination CT scans were made in intact bones, after reaming and after fracture creation in internal rotation. The relative reduction of the wall thickness was calculated and visualized for the complete femoral shaft. The region with the strongest relative decrease in wall thickness (Max-Dec) was determined and checked for an overlap with the fracture.

It was found that regardless of the reaming diameter, the strongest relative decrease (G1=24.9%±9.6%, G2=28.4%±14.9%, G3=39.7%±14.3%) in femoral shaft wall thickness occurred medially (73%) in the second (10.8%), third (62.2%), and fourth (18.9%) eighth of the femoral shaft. As the diameter of the reaming increases, however, an overlap of the fracture line with the Max-Dec becomes more frequent (G1=33.3%, G2=50% and G3=61.5%).

This suggests that a reaming-associated fracture is most likely to occur in this region.

THE FIXATION STRENGTH AND CUT-OUT RESISTANCE OF TFNA HELICAL BLADES AND SCREWS CAN BE INCREASED BY BONE CEMENT AUGMENTATION

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The effect of cement augmentation on the fixation strength and cut-out resistance of TFN-ADVANCED Proximal Femoral Nailing System (TFNA) blades and screws within the femoral head has so far not been evaluated biomechanically.

Therefore, ten pairs fresh-frozen osteoporotic and osteopenic human cadaveric femoral heads were randomized to 2 equally sized paired groups for instrumentation with either TFNA blade or screw. One side of each pair was augmented with PMMA-based bone cement, whereas the contralateral side was left without augmentation. All specimens were biomechanically tested under progressively increasing cyclic loading until failure in a setup simulating unstable intertrochanteric fracture with lack of posteromedial support and load sharing at the fracture gap. An inclinometer mounted on the femoral head was used to monitor varus tilting. A Varus collapse of 5° was defined as clinically relevant failure and number of cycles to failure and load at failure were determined for each specimen. Statistical evaluation was performed at level of significance $p=0.05$.

Cycles to failure for augmented/non-augmented TFNA blades and screws were 30492±8715 / 19131±11160 and 19307±802 / 12612±9138, respectively. The corresponding loads at failure were 4049.2±871.5N / 2913.1±1116.0N and 2930.7±802.1N / 2261.2±913.8N. Both cycles to failure and loads at failure were significantly higher for augmented versus non-augmented TFNA blades ($p=0.003$) and TFNA screws ($p=0.032$).

Implant augmentation with PMMA-based bone cement significantly increases the fixation strength and cut-out resistance of TFNA blades and screws within the femoral head. From a biomechanical perspective it is a valid supplementary treatment option in osteoporotic bone.

ELECTROSPUN PVA NANOFIBERS FOR BONE DISEASE THERAPY USING MESENCHYMAL STEM CELL

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Mesenchymal stem cells (MSCs) constitute multipotent stromal cells that can differentiate into a variety of cell types. This characteristic provides a great potential as a cell source for tissue engineering (i.e. bone formation) and cell-based therapy for many diseases (i.e. bone diseases). It has been reported that electrospun nanofibers developed using hydroxyaptite exhibit osteoconductivity and significantly stimulate the bone forming ability, however it is difficult to produce on a large scale with controlled strength, degradation, and nanostructure with great flexibility. Previous reports of our research group have demonstrated that polyvinyl alcohol (PVA) has great potential for biomedical applications owing to its biocompatibility. Given that the interaction between MSCs and the scaffold surface is crucial to achieve directed differentiation of MSCs in tissue regeneration, the purpose of this study is to develop a biocompatible hydroxyaptite/PVA scaffold.

To accomplish that, PVA nanofibers will be fabricated using electrospinning technique and will be characterized using scanning electron microscopy (SEM), swelling studies, differential scanning calorimetry (DSC), fourier transform infrared spectroscopy (FT-IR) and rheometry. After that, the MSCs will be seeded into the scaffold, after a period of culture *in vitro*, the cell viability, capacity of infiltration in the nanofibers and morphology will be analysed.

The results of this study will help us understand how polymeric fibers can enhance the formation of new bone tissue with increased of cell adhesion and may help us develop better scaffolds to use in the therapy of bone diseases.

PREPARATION OF POLYVINYL(ALCOHOL) ALIGNED POROUS CRYOGELS USING UNIDIRECTIONAL FREEZING TECHNIQUE FOR BONE TISSUE HEALING APPLICATIONS

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The technique of unidirectional freeze polyvinyl alcohol (PVA) hydrogels can mimic the structure of bone tissues and it leads the chains in the freezing-thawing technique to produce uniform structures that can also improve the mechanical properties. However, no studies have been performed in terms of investigating how the freezing affects the chain reaction.

Therefore, in this work PVA solution with a known concentration was transferred to a polytetrafluorethylene (PTFE) mould and insulated with heat insulation tapes which has a range of working from -40°C to +100°C. The mould was immersed into liquid nitrogen at a speed of 100 mm min^{-1} until it was fully immersed. The frozen sample was then thawed at ambient temperature for 1 h. This cycle was repeated three times. The PVA freeze thawed by unidirectional freezing was evaluated using a thermal camera during the whole freezing experiment.

Trough thermal Camera it was possible to observe that as the mould decreases towards the liquid nitrogen, the temperature decreased, and a linear upward freezing was obtained; unidirectional freezing occurs in the middle region and it induces an oriented distribution along the freezing direction. Through SEM it was possible to observe that the sample presented different structures in different parts and for all samples analysed, the middle region presented a fibrous structure. Conversely, the external parts of the sample presented the normal structure of hydrogels.

The easy method developed and processed was confirmed to produce an unidirectional freezing which can be used as a potential apparatus.

ANTIBIOTIC LOADED COLLAGEN FLEECES, DISADVANTAGES AND THE LACK OF EVIDENCE FOR CLINICAL TREATMENT OF CHRONIC OSTEOMYELITIS

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Chronic osteomyelitis treatment requires surgical debridement accompanied by local and systemic antibiotics administration. Local antibiotics administration through biodegradable carriers has interest to obtain one-stage treatment. This systematic review according to PRISMA studied clinical evidence and results of antibiotic loaded collagen fleeces in osteomyelitis treatment based on level of evidence, methodological quality and risks of bias.

Clinical efficacy was defined as eradication of infection and distorted bone and wound healing. In addition, *in vivo* pharmacokinetics of the different collagen fleeces were evaluated. Ten studies were included detailing 2 types of antibiotic-loaded fleeces. 413 patients were treated with either of the two gentamicin loaded fleeces with a success rate of 91%. Rough estimation of wound exudate concentrations of the gentamicin-sulphate fleeces shows that local antibiotic concentrations dropped below the minimal inhibitory concentration (MIC) at a maximum of 5-7 days.

Adverse events reported were fistulas, prolonged wound leakage and wound healing problems. In addition, the general quality of all included studies was weak to moderate and there was a moderate to high risk for bias. Quality and level of evidence of the included studies are low and the risk of bias in these studies is high.

This makes evidence regarding these fleeces inconclusive and no clinical decision-making can be based on these studies. This systematic review emphasizes that evidence is lacking; that these collagen fleeces have several disadvantages, and that there are better alternatives such as S53P4 bioactive glass with established level of evidence for one stage treatment chronic osteomyelitis.

OSTEOCLASTIC RESORPTION OF THE PRECIPITATED CALCIUM PHOSPHATE LAYER ON BIOACTIVE GLASS SURFACES

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In vivo degradation of S53P4 bioactive glass (BAG), clinically used to treat osteomyelitis, is very slow. The role of cells in the degradation process remains unclear. Therefore, this study aimed to determine the capacity of human osteoclasts to resorb the calcium phosphate layer formed on BAG, when in contact with (body) fluids.

Human monocytes were seeded on BAG discs that were pre-soaked in PBS for three days, to ensure calcium phosphate precipitation. Osteoclastic differentiation was induced with MCS-F and RANKL supplemented to the culture medium. Cultures on hydroxyapatite discs served as controls. Scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDX) were performed to detect resorption pits, as an indication for osteoclast resorption.

Comparable numbers of resorption pits were observed on both disc types. The resorption pit surfaces on BAG were very smooth and uniform, while the pits on hydroxyapatite had an irregular appearance. EDX confirmed the initial calcium phosphate precipitation on the BAG discs, due to pre-soaking. It also indicated an incomplete removal of this layer by osteoclasts, since calcium and phosphate were the main detected elements on the surface in the resorption pits on BAG. The smooth and uniform appearance of these resorption pits suggests that the osteoclastic resorption was initiated but later hindered. The silica layer underneath the precipitated calcium phosphate might be the reason for the hindrance.

In conclusion, osteoclasts were at least partially able to resorb the precipitated calcium phosphate on BAG surfaces.

BALANCING BONE RESORPTION AND OVERZEALOUS BONE GROWTH IN LUMBAR INTERBODY FUSION WITH RHBMP-2 IN THE SHEEP MODEL - A QUESTION OF DOSE AND/OR CONCENTRATION

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Thirty-six Merino sheep underwent right-anterior lumbar interbody fusion at L1-L2 and L3-L4 with the addition of a polyetheretherketone (PEEK) cage either filled with one of four different concentrations/doses of rhBMP-2 (interventional groups:0,4mg/ml, total dose of 4,0mg; 2,0mg/ml, total dose of 2,0mg; 1,0mg/ml; total dose of 1,0mg; 0,5mg/ml, total dose of 0,5mg) or the control group filled with an absorbable collagen sponge (ACS) or left empty. A pedicle screw system was implanted in all surgical levels. Thin cut CT image were taken directly postoperatively, after 3months, 6 months and 12 months to assess bone resorption, cage subsidence and migration (indirect marker of bone resorption) and overzealous bone growth.

In comparison with the control group, rh-BMP-2 groups showed a higher fusion rate at 3 (72% vs.13%), 6 (90%vs30%) and 12 (95%vs70%) months CT scans. Overzealous bone growth was detected at the right ventral circumference of the vertebral body as sign of the direct operative access. No ectope ossification was detected in all groups. The incidence of bone resorption as well as cage migration and cage subsidence as indirect marker of bone resorption were higher in the BMP2 groups.

In this animal model the application of rhBMP-2 in the different concentrations/ doses showed much better fusion rates compared with the control group. These results could be shown in the 0,5mg BMP-2 group with clear reduction of adverse effects. Higher doses of BMP-2 doesn´t cause a benefit in fusion rate but an increase in side effects like cage migration and subsidence as marker of higher bone resorption. No inflammation reaction or systemic side effects were detected in the BMP-2 group.

MODELLING THE DEGENERATE NICHE TO INVESTIGATE EFFICACY OF MESENCHYMAL STEM CELL DELIVERY WITHIN A THERMALLY TRIGGERED HYDROGEL TO REGENERATE THE NUCLEUS PULPOSUS

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We have previously published the development of an injectable hydrogel (NPgel) which promotes differentiation of mesenchymal stem cells to nucleus pulposus (NP) like cells, integrates with IVD tissue following injection and restores mechanical properties. However the degenerate disc is a harsh environment with low glucose, pH and O_2 and catabolic cytokines. Thus this study investigates the behaviour of MSCs within NPgel in environments mimicking the degenerate niche.

NPgel containing MSCs were cultured under low glucose, low pH and 5% O_2 ± IL-1. Whilst expression of collagen type II was decreased initially in degenerate culture media + IL-1, levels increased following 4 week culture. Similarly MMP3 expression was initially induced in MSCs cultured in NPgel in the degenerate niche conditions but expression decreased with culture duration.

When NPgel containing MSCs was injected into tissue explants, MSCs increased expression of Np matrix proteins. In addition in human degenerate NP explants where NPgel+MSCs was injected a significant increase in anabolic and decrease in catabolic factors was observed in comparison to controls. Suggesting that viability and differentiation of MSCs in NPgel is maintained even under degenerate conditions.

Thus NPgel + MSCs has the potential to regenerate the NP and provide mechanical support, whilst reducing the catabolic phenotype of degenerate NP cells, as a treatment strategy for IVD degeneration.

BIOCOMPATABILITY AND OSTEOCONDUCTIVE CAPACITY OF DEVITALIZED CORAL

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The gold standard in bone trauma repair is autograft, a procedure largely in decline due to the requirement for a secondary invasive procedure required to harvest bone from the patient. Coral skeletons are excellent bone grafting materials due to their biocompatibility and osteoconductive properties. The coral's native architecture is designed to host life, influence cellular behaviour and encourage cellular adhesion, qualities retained after scaffold devitalization and preparation as a biomaterial. With newly developed controlled, environmentally responsible cultivation techniques, the GMP production of coral scaffolds for orthopaedic, dental and veterinary use is possible. Here the composition, structure and biocompatibility of cultivated coral were investigated.

Using scaffolds derived from four species of devitalized coral samples, the structure and composition were characterized. The scaffolds were composed primarily of calcium carbonate ranging in density from 1,753-1,903mg/cm^3. The interconnected porosity changed with species, ranging from 3.7%-41.5%. LIVE/DEAD staining viability, MTS and proliferation assays demonstrated maintained, high levels of MSC viability, metabolism and cellular proliferation indicating biocompatibility. MSCs were directly seeded onto coral scaffolds and cultured for 14 days before SEM visualization.

A thick, confluent, organized layer of fibroblast-shaped MSCs was observed on the external surface of the coral skeleton and both covering and lining the calice (external pore-like) structures. The four coral species evaluated in this study were deemed biocompatible, supporting bone marrow derived MSC viability, metabolism, adhesion and growth.

They are therefore prime candidates for further investigation as a replacement for auto- or allograft.

IMPACT OF DIABETES MELLITUS ON BONE MARROW PROGENITOR CELL NUMBER AND PROLIFERATIVE CAPACITY AND OSTEOCONDUCTIVE CAPACITY

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Abnormal bone mineral density and/or distribution patterns and delayed bone fracture repair are complication of type 2 diabetes mellitus (DM). Bone marrow isolated from pre-clinical models of DM contains significantly fewer multi-potential progenitor cells (MSCs) with reduced differentiation capacity as compared to non-diabetic isolates. A return to glucose homeostasis does not restore the capacity of previously diabetic MSCs, indicating the environment selectively depletes the population of MSCs.

This study proposes that alterations in human bone marrow MSC number and capacity in individuals living with DM contributes to the pathology underlying DM-associated osteopathy through MSC inability to support organ homeostasis.

Although all donor groups displayed comparable mononuclear cell (MNC) counts and CFU-F numbers indicating an analogous baseline for MSC-maintenance of bone homeostasis, differences were observed in the capacity of MSCs residing within a DM environment. Marrow donations from women living with DM contained ~10 times fewer CFU-Fs as compared to their male counterparts, indicating a gender disparity in the impact of DM. Further, MSCs isolated from individuals living with DM contained nearly half of the number of osteogenic clones as non-DM samples, indicating an impact of the DM environment on MSC potential to maintain bone homeostasis.

Finally, MSCs isolated from the DM environment exhibited a 66% increase in doubling time, indicating a lesser capacity to respond to an injury stimulus. Together, these data indicate a biologically significant impact of the DM environment on MSCs residing within the bone marrow that may underpin DM-associated osteopathy.

SILK FIBROIN / HYDROXYAPATITE SCAFFOLDS COMBINING LYOPHILISED SPONGE AND NANOFIBERS FOR BONE REGENERATION

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Silk fibroin is a natural fibrous protein derived from *Bombyx mori,* which is well-studied for tissue engineering and regenerative applications. Silk can be fabricated to different forms including hydrogels, films or sponges. Combination of both lyophilized sponge 3D structure and nanofibers mimics conditions inside the bone and provides mechanical support for the bone cells. Biocompatibility of silk fibroin and hydroxyapatite provides possibility for osteogenic cells to proliferate and gradually repair bone defect without scarf formation, vascularization or significant effect to patient immune system.

Influence of different amounts of hydroxyapatite addition to biocompatibility to human cell lines was tested under *in vitro* conditions. We also studied mechanical properties, degradation rate and morphological changes in dependence on the different conditions of material stabilization and sterilization.

In conclusion, the bicomponent scaffolds prepared in this study show very promising properties for bone tissue engineering.

CAN WE DEVELOP A BIOMECHANICAL FUNCTIONAL SCORE TO QUANTIFY THE JOINT MECHANICS OF THA PATIENTS?

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THA is a reliable methods to improve the quality of life in osteoarthritis patients. However, it is still unclear whether it would lead to improved functional mobility. The purpose was to develop a biomechanical functional score to quantify the joint mechanics of THA patients compared to healthy participants (CTRL).

Twenty-four THA patients and 12 CTRL (age-, sex-, and BMI-matched) participants were recruited and underwent motion analysis for different ADLs tasks prior and nine months after THA. Three-dimensional joint kinematics and ground reaction forces were collected and five kinematic and six kinetic variables were included in the analysis. The normalized root-mean-square-deviation (nRMSD) was calculated between the THA and the CTRL groups for both pre- and post-op conditions: $nRMSD = \sqrt{\frac{\sum_{t=1}^{n}(x_{1,t}-y_{1,t})^2}{n}} \Big/ x_{max} - x_{min}$. Kinematics and kinetics improvement scores (KMIS and KNIS) were calculated to estimate pre/post-op differences: $KMIS = \sum_{i=1}^{n}(KM_{pre/ctrl\,i} - KM_{post/ctrl\,i})$; $KNIS = \sum_{i=1}^{n}(KN_{pre/ctrl\,i} - KN_{post/ctrl\,i})$. THA patients experienced post-op improvements, with kinetics variables closely resembling the CTRLs, especially on hip and knee power production.

Total improvement scores showed that THA experienced greater improvements during squat task and this can be a practical approach to evaluate the change in biomechanical function and highlight small improvements that may go unnoticed with traditional statistical analysis.

EARLIER USE OF JOINT REPLACMENT SURGERY: WORSENING ADHERENCE TO GUIDELINES FOR THE NON-OPERATIVE MANAGEMENT OF HIP AND KNEE OSTEOARTHRITIS

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Evidence based consensus guidelines for the management of hip and knee OA were published in 2008. This cross-sectional study benchmarked adherence with these recommendations in 2009 and re-evaluated this 5 years later.

Patients listed to undergo hip or knee replacement at a single NHS teaching hospital were interviewed to review clinical management prior to surgery. Data is reported as percentage adherence to guidelines, analysis was by t-test or Mann-Whitney U-test. 195 patients were reviewed in 2008 (90 TKA, 105 THA) and 215 in 2014 (110 TKA, 105 THA). In the TKA cohort (compared to 2008) symptom duration prior to surgery reduced ($p= 0.01$). Age, gender and BMI were consistent.

Weight reduction was discussed less frequently ($p<0.01$). Walking aids and insoles were issued less frequently ($p<0.02$). Physiotherapy exercises reduced and activity advice increased ($p<0.05$). Pharmacological management was unchanged in usage of paracetamol and NSAIDS ($p=0.35$) Prescription of opioid and narcotic medication reduced ($p=0.02$). In the THA cohort, symptom duration prior to surgery reduced ($p<0.01$). Age, gender and BMI were consistent. Weight reduction was discussed less frequently ($p<0.01$). There was no change in the provision of walking aids ($p=0.16$) or insoles ($p=1.0$). Physiotherapy exercises reduced ($p<0.01$), advice to increase activity was unchanged ($p=1.0$). Paracetamol usage increased ($p=0.02$). Oral NSAIDS usage was unchanged ($p=0.12$), however topical NSAIDS reduced ($p<0.01$). Opioid and narcotic medication was unchanged ($p=1.0$).

Patients are undergoing joint arthroplasty earlier with a corresponding reduction in community management. Pharmaceutical management meets minimum treatment guideline in approximately 70% of cases, however it would seem that ‘hands on’ physiotherapy is being replaced with activity advice.

TARGETING PHYSIOTHERAPY TO PATIENTS AT RISK OF POOR OUTCOMES FOLLOWING TOTAL KNEE ARTHROPLASTY: THE TRIO RCT

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Physiotherapy is typically employed following TKA however evidence for improving patient outcomes is lacking. TRIO is the largest ever trial of physiotherapy following TKA, performed at 15 UK centres to evaluate whether therapy could be targeted to those deemed at risk of poor outcome and determine if outpatient-led therapy offered superior results to home-based rehabilitation.

Patients were screened 6-weeks post-op based on a classification of the Oxford Knee Score (OKS) and randomised to rehabilitation arms comprising 18 sessions over 6-weeks. The outpatient-led group undertook a progressive functional rehabilitation protocol in contrast to a static home-exercise protocol. Primary outcome was comparative OKS at 52-weeks. Secondary outcomes evaluated pain VAS and a battery of satisfaction questions post-intervention, at 26 and 52-weeks. 334 patients were randomised, 8 were lost to follow-up, compliance was >85%.

Clinically meaningful improvement in OKS was seen in both intervention arms ($p<0.001$). Between group difference in 52-week OKS was 2.25 (95%CI, 0.61-3.90) points favouring the outpatient-led therapy ($p=0.008$). Secondary outcomes demonstrated non-significant 5% reductions in pain VAS, enhanced satisfaction with pain-relief (OR 1.65, $p<0.02$), ability to perform functional tasks (OR 1.66, $p<0.02$), and heavy functional tasks (OR 1.6, $p=0.04$) in the outpatient-led group. Therapy was successfully targeted to patients deemed at risk of poor recovery post-TKA and both intervention arms made clinically meaningful improvements in OKS at 52-weeks. The confidence intervals around the 52-week OKS suggest that any difference which might exist is too small to be clinically relevant.

Future work could investigate which patients are most likely to respond which may enhance the overall effectiveness of a stratified approach.

VIRTUAL METHODOLOGY FOR PLANING FEMORAL OSTEOCHONDROPLASTY FOR CAM-TYPE IMPINGEMENT OF THE HIP

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Surgical bone resection is the most effective treatment to alleviate the abnormal contact between femur and acetabulum on patients with cam-type femoroacetabular impingement (FAI). This is a phatomechanical pathology resulting from the excess of bone presented on the femoral head-neck region. The surgical procedure known as osteochondroplasty, focuses on reshaping the femur to its ideal morphology.

The virtual methodology consisted of developing finite element models from CT scans of patients diagnosed with FAI to determine the range of motion (RoM) and impingement areas of the joint. Models predicted the RoM and localised the impingement areas during internal rotation of the femur at different flexion angles. Five models were developed, four from patients exhibiting cam-type impingement and one of normal morphology. Internal rotation RoM was measured when the anteroposterior region of the femur came into collision with the acetabular rim. Then a virtual osteochondroplasty was performed based on the impingement areas in order to obtain the normal RoM. but keeping the volume of bone removal to a minimum.

The virtual technique was validated by comparing results with CT scan based models of an FAI hip obtained from prior and post actual osteochondroplasty. The virtual osteochondroplasty performed on the hip resulted in increased RoM to values closer to the normal RoM than the actual surgery for a smaller femoral head volume resection demonstrating that the tool can be used to optimize the amount of bone removed during femoral osteochondroplasty to enable normal hip RoM to be restored with a minimum resection volume.

QUANTIFYING RADIAL HEAD INSTABILITY AND LIMITATIONS IN HAND ROTATION AFTER IOM AND ANNULAR LIGAMENT INJURY

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The interosseous membrane (IOM) is a key stabilizer of the forearm that is often injured in conjunction with disruption of the annular ligament. In the present study, motion of the radial head is quantified after simulated injury to the IOM and annual ligament to demonstrate how forearm stability changes as the arm is actively pronated and supinated.

Fourteen fresh-frozen cadaveric arms, mid-humerus to fingertips, were used. Soft tissue was removed proximal to the carpals leaving the main stabilizing structures intact. A custom fixture supported the arm and hand with the elbow flexed 90 degrees and simulated active muscle loading of the biceps and pronator teres to rotate from a neutral forearm position to full supination and full pronation, respectively. A 10-camera Optitrack motion capture system tracked the motion of the radius for several stages of sequential sectioning: intact, annular ligament sectioned, proximal band sectioned, central band sectioned, and distal band sectioned. The position and orientation data of each sectioning stage was compared to the neutral forearm position (0 degrees) of the intact stage.

In pronation, the radial head relative translations were not significantly different along each axis for any sectioning stage. In supination, the radial head moved posteromedially then anterolaterally, increasing with all sequential sectionings. After sectioning the central band, little radial rotation occurred, decreasing maximum hand supination from a mean of 36 degrees (intact) to 6 degrees. Central band sectioning had the greatest effect on radial head translations, changing the biceps' role from flexor/supinator to exclusively a flexor.

PHOTOPOLYMERIZATION FOR FILLING POROUS CERAMIC MATRIX: IMPROVEMENT OF MECHANICAL PROPERTIES AND DRUG DELIVERING BEHAVIOUR

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The present work presents the photopolymerisation of composite scaffolds where a prefabricated ceramic scaffold was impregnated with Poly(ethylene) glycol dimethacrylate (PEGDMA) macromer solution.

The PEGDMA solution penetrates the porosity of ceramic scaffold where it cures in situ thereby enhancing their mechanical properties. The mechanical properties of the obtained composite approximates the mechanical properties of cancellous bone.

The Young´s Modulus of the composite developed was 106±5 MPa. PEGDMA exhibited excellent gel fraction (96%), which was preserved when introduced into the ceramic scaffold as was swelling volume (134%). Thus indicating that the photoinitiation and the polymerization processes were carried out successfully despite of the ceramic scaffold tortuosity. Furthermore, thanks to their swelling properties, the composite was able to control the release vancomycin and dexamethasone. The efficacy of in situ delivery of vancomycin was verified by the inhibition of bacteria colony proliferation. Dexamethasone released is recorded for up to ten days using UV Vis spectroscopy.

These excellent results make photopolymerization and PEGDMA strong candidates for the manufacture of different loaded bone void fillers.

AGE-RELATED DECLINE OF OSTEOGENESIS DEPENDS ON INHIBITION OF PROTEIN KINASE A (PKA) BY PROTEIN KINASE INHIBITOR GAMMA (PKIΓ)

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Aging bone is characterized by decreased osteogenesis and increased adipogenesis resulting in bone loss and diminished repair capacity. We previously showed that PKIγ terminates PTH-induced activity of the cAMP/PKA pathway in mesenchymal precursor cells and that the termination of anabolic primary PKA-response genes (*c-fos*, IL-6, and LIF) reduces osteogenesis and enhances adipogenesis *in vitro*.

We generated and characterized PKIγ$^{-/-}$ mice, which were indistinguishable from wild-type littermates by body weight and fertility. μCT analysis of aging mice revealed that vertebrae of female PKIγ$^{-/-}$ mice exhibit protection from age-related trabecular bone loss (BV/TV, 12-month: 13.9±0.5% vs 10.5±0.4%, p=0.0006 and 24-month: 13.4±1.0% vs 8.0±0.5%, p<0.0001) - resulting from increased Trabecular Number, not Trabecular Thickness. Accordingly, Trabecular Spacing was decreased and Connectivity Density increased with more plate-like geometry (SMI). Substantially smaller increases were seen in female femora, vertebrae and femora of males, and younger mice. Based on the age dependence of the μCT results, we speculated that the decline in osteogenesis with aging would be lessened in PKIγ$^{-/-}$ mice.

We investigated intramembranous bone formation 7 days after placing a unicortical titanium implant in the distal femoral metaphysis. Biomechanical pull-out testing showed the expected age-related decline in osteogenesis in wild-type but not in PKIγ$^{-/-}$ mice. As a result, osseointegration in 12-month old PKIγ$^{-/-}$ males was significantly greater than in 12-month old wild-type males: Ultimate Force (7.6±1.7 vs 3.8±2.7N, p=0.02) and Average Stiffness (6.7±1.6 vs 3.4±2.4N/m, p=0.005).

These results suggest that disrupting PKIγ regulation of PKA in aging bone can enhance endogenous activators of bone formation.

BONE APATITE NANOSTRUCTURED COATINGS TO PROMOTE OSSEOINTEGRATION: ANALYSIS OF DIFFERENT APATITE PRECURSORS

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To boost integration of bone implants, highly adhesive coatings having a composition as similar as possible to the host bone have been proposed. To achieve this goal, both synthetic apatites with an increasing number of ionic substitutions and deposition from biogenic apatite have been pursued. The Authors have proved the possibility to deposit bone-apatite like thin films directly by ablation of deproteinized bovine bone, by Ionized Jet Deposition.

Highly adhesive nanostructured coatings were obtained, capable of promoting host cells attachment, proliferation and differentiation. Because the technique allows a precise control over the coating composition, here, several bone apatite precursors (bovine, equine, ovine and porcine bone) were compared in terms of composition and morphology (grazing incidence XRD, FT-IR, SEM/EDS, MIP), to be possibly used as deposition targets. Interestingly, the differences can be of interest for xenografts, bone cements, granulates and other biomaterials composed of biological apatite. Then, several post treatment annealing treatments were compared to optimize crystallinity.

Despite all biological samples being essentially composed by hydroxyapatite and carbonated hydroxyapatite, some differences were evidenced in their composition, especially regarding the content of carbonates and magnesium, while essentially no differences were assessed in terms of crystallinity. Significant differences, instead, were assessed in terms of microstructure. A crystallinity very similar to that of bone can be obtained by annealing the coating at temperatures between 350°C and 425°C (formation of cracks is detected at 450°), that do not cause alterations in the coatings composition.

BIRMINGHAM HIP RESURFACING AND THE ASR: REGISTRY DATA FOR METAL-ON-METAL HIP RESURFACING AT A MINIMUM OF 10 YEARS

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This was a retrospective study of registry data from a National Orthopaedic Hospital. Only ASR and BHR resurfacing systems with a minimum of 10 year data were included in the analysis. Univariate and multivariate analyses controlling for confounding variables were performed to compare outcomes between the BHR and ASR. 392 (119 ASR and 273 BHR) systems were implanted into 364 patients with 10 year follow-up data.

Twenty-Seven patients had died on review. There were 38 revisions and 5 re-revisions recorded for all causes of revision. Mean time to revision was 46 months. Mean patient age was 55 and 72% were male. WOMAC scores at 10 years compared to preoperative scores (mean 19.1 at 10 years vs 53.9 preoperative) were much improved. For all-cause revision, the ASR had a 21.8% 10 year revision rate versus a 4.3% 10 year revision rate in the BHR. Other negative predictors of revision included the use of the posterior approach ($p<0.01$). Causes of revision in order of decreasing frequency included periprosthetic fracture (n=7), aseptic loosening (n=7), adverse reaction to metal debris (ARMD) (n=7), infection (n=5), dislocation (n=3) and pain accounting for the remainder. ASR has a significantly higher rate of revision at 10 years.

The BHR has significantly better implant survival at 10 years when compared to the ASR using multivariate analysis. Acceptable 10 year outcomes can be achieved with the BHR only based on our experience. This is the first paper to directly compare these two implants using the Irish NOH joint registry.

DAY CASE PELVIC OSTEOTOMY FOR DEVELOPMENT DYSPLASIA OF THE HIP (DDH)

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We report the results of a pilot study analysing the implications of performing pelvic osteotomies for DDH as a day-case. The financial ramifications and reduction in overnight bed consumption is reported. This was a prospective study analysing Salter and Pemberton pelvic osteotomies performed for DDH for the year 2017. Economic costings were sourced from the official *'HSE specialty costing report 2016'* which was released in February 2018. 28 Salter and Pemberton osteotomies were performed in 2017.

11 of these cases were performed as day-case procedures. A total reduction in 22 in-patient bed-days were reported. For 11 day case patients, the total cost to treat amounts to €29,370. Calculating the difference, a total saving of €75,174 was made by the hospital. Day case pelvic osteotomies can significantly reduce the number of inpatient bed days in an elective paediatric orthopaedic setting. Economic gains made by treating only 11 patients in this manner amounted to €70,422. This figure accounts for a single readmission. There was no adverse impact on the standard of clinical care.

We propose that the introduction of day case pelvic osteotomy procedures can significantly improve the cost-effectiveness of managing DDH in a paediatric population. Provided there is a stringent analgesic protocol provided on discharge with close clinical follow-up via telephone the following day, this is a safe and very effective innovation in this field which has not yet been described in the literature.

A VIRTUAL CLINIC FOR DEVELOPMENT DYSPLASIA OF THE HIP (DDH)

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This was a retrospective analysis of the activity seen in the virtual DDH clinic for OLCHC during 2017. Dedicated clinical nurse specialists collected the information prospectively and recorded this in the DDH database. Written referrals were discussed at the weekly consultant-lead virtual DDH clinic and radiographs were reviewed in conjunction with the DDH CNS and administrative staff.

350 patients were reviewed in the virtual DDH clinic during 2017. The majority (67%) were referred from area medical officers, while 29% were referred from GP's. On consultant orthopaedic review, 99 patients were referred on to the physical DDH clinic in OLCHC. The discharge rate from the virtual clinic was 72% which in turn prevented 251 unnecessary patient visits to the physical clinic in 2017. The time saved amounted to between 33 hours and 49.5 hours of clinical time. With the average cost of an out-patient appointment estimated at €129, the overall hospital savings amount to an estimated €32,379. Waiting lists were significantly reduced through the introduction of this virtual clinic also.

No patients that were discharged subsequently re-attended the physical clinic, implying that this is a safe means of review. We demonstrate here that the principle of virtual patient care in the setting of elective paediatric DDH can have many significant positive implications for hospital finances, personal patient costs, waiting lists and clinic overcrowding.

We recommend the usage of virtual DDH clinics on a national scale for the safe, effective and economic provision of paediatric DDH care.

THE ROLE OF CIRCULAR FRAMES IN THE MANAGEMENT OF LOWER LIMB TRAUMA

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To assess the clinical course and outcomes of patients with tibial fractures managed in circular frames. A retrospective review of all patients requiring circular frame application for tibial fracture management was performed using clinical records, radiographic imaging and patient-reported clinical outcome scores (SF-12 form).

46 patients fulfilled the inclusion criteria. Mean patient age was 45 (10-82). 77% were male. Each had a mean number of 3.8 interventions (2-6, σ=1.179), 3.5 admissions (1-7, σ=1.73) and a total mean length of stay of 33.4 days (3-156, σ=32.5). Mean time to union was 8 months with a 17% rate of non-union. Factors significantly increasing time to union included 'number of interventions' ($p<0.01$), 'use of bone graft' ($p<0.01$) and 'graft type' ($p<0.05$) where the addition of synthetic graft to either allograft or autograft was found to increase the time to union. 25 patients (53%) experienced a delayed union. Deep tissue infection significantly increased the risk of delayed union ($p<0.05$) as did the use of bone graft ($p<0.01$). The rate of deep tissue infection was 43%. 11% of patients underwent ankle fusion at a later date. The duration of frame application ranged from 1 to 30 months (mean 6.3, σ=5.37). SF-12 scores ranged from 18-32 (mean 26.9, σ=3.52).

Circular frame management incurs a significant burden on both the patient and the health service providing resources to this cohort. Deep infection rates are high and have a significant impact on delayed union. Graft types may also impact on the time to union.

EXTENDED TROCHANTERIC OSTEOTOMY (ETO) FIXATION FOR FEMORAL STEM REVISION IN PERIPROSTHETIC FRACTURES: DALL-MILES PLATE VERSUS CABLES

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Extended trochanteric osteotomy (ETO) is a well established surgical technique used for femoral stem retrieval in revision hip arthroplasty procedures. Fixation of ETO is commonly achieved through wire, cable or cable-plate fixation. No evidence exists to date to suggest which method is superior when used in an acute traumatic setting.

30 cases of acute periprosthetic fracture requiring femoral stem revision with an ETO were identified over a 10 year period. Each case had a loose femoral prosthesis which was revised using an ETO approach. 19 of these were fixed using cables only and 11 were fixed using a cable-plate construct. Radiographic outcomes measured included subsidence, osteolysis, union, time to union and overall success using the Beals and Tower classification. Clinical outcomes were assessed using the modified Harris Hip Score. 23 Vancouver B/C type fractures were identified. The remaining 7 consisted of other fracture types with a loose femoral stem requiring revision through ETO.

Mean followup was 32 months in the cable group and 12 months in the cable-plate group. The cable-plate construct performed better than cables alone. Mean subsidence rates were 1.7cm lower in the cable-plate group ($p<0.05$). Beals and Tower classification of radiographic outcomes was significantly better in the cable-plate group ($p<0.01$). Modified Harris Hip scores were better in this group also ($p<0.05$).

When utilising an ETO approach for femoral stem revision in acute periprosthetic fractures, superior clinical and radiographic outcomes can be achieved if fixation involves a cable-plate system instead of cables only.

THE PRIMARY CILIUM AS A POTENTIAL CAMP RESPONSIVE MECHANOSENSOR IN MESENCHYMAL STEM CELLS

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Bone adapts to its mechanical environment by sensing fluid flow-induced shear stress within the tissue. However, it's unclear how mesenchymal stem cells (MSCs) sense and convert this biophysical signal into a biochemical bone forming response. A potential candidate in MSC mechanotransduction is the primary cilium which may act through the 2nd messenger, cyclic adenosine monophosphate (cAMP), which is regulated by Adenylyl Cyclases (AC).

Primary cilia (IFT88) and Adenylyl Cyclase6 (AC6) expression was inhibited using siRNA technology. Transfected cells were placed in custom bioreactors where oscillatory fluid shear (OFS) at 1Pa, 1Hz was applied for 15min for cAMP activity analysis or for 2 hours for osteogenic gene expression analysis.

cAMP levels peaked after 15mins of shear before returning to basal levels. Following siRNA treatment targeting IFT88 and AC6, expression was significantly knocked down. OFS-induced increases in cAMP were lost when the primary cilium was abrogated. Furthermore, AC6 was found to be expressed in MSCs, where it localises to the primary cilium. As with primary cilia knock down, increases in cAMP following OFS were lost in AC6 siRNA treated cells. MSCs displayed an increase in osteogenic gene expression in response to a mechanical stimulus, however, this response was lost in AC6 knockdown samples like that seen with IFT88 knockdown in previous studies.

This study demonstrated a novel molecular mechanism of cilia-mediated mechanotransduction in MSCs, where the primary cilium and AC6 are required for flow-mediated increases in cAMP in MSCs, demonstrating that the primary cilium may act as a cAMP responsive mechanosensor, acting via AC6.

PROFILING EXTRACELLULAR VESICLES DERIVED FROM EQUINE MESENCHYMAL STEM CELLS AND TENDON DERIVED CELLS FOR TENDON REGENERATION

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Tendon injuries represent a clinical challenge for treatment in humans and horses. Extracellular vesicles (EVs) secreted by mesenchymal stem cells (MSCs) are known to be involved in repair and inflammation resolution processes in different tissues and animal species. The main aim of this study is to investigate the role of EVs derived from MSCs and tendon derived cells (TDCs) in promoting tendon regeneration and inflammation pro-resolution pathways via paracrine mediated cellular communication.

An equine *in vitro* model of tendon inflammation was used to characterise EVs released by IL-1β stimulated equine MSCs and TDCs at 24 and 48 hours. EVs were quantified in the media by flow cytometry (FCM). The chosen parameters were optimal to detect microspheres from 0.1 to 1 μm diameter simultaneously on the FSC-PMT and Annexin V conjugated with PE was used to AnnexinV-PE was used to count PS positive events. EVs were acquired at medium flow rate for 1 minute. Aliquots of fresh media were tested in the same conditions to establish EV's background presence. F

ACS analysis conducted on media (n=3 horses) showed a basal expression of EVs in control conditions. There is no significant difference in EVs numbers produced by either cell types under IL-1β stimulation vs control conditions (no IL-1β) at 24 hours ($p = .089$) and 48 hours ($p = .768$). Although, the IL-1β stimulus does not induce a change in the quantity of EVs, it may trigger a qualitative change in the EV cargo.

We are currently investigating the potential effect of IL-1β activated EVs to modulate the expression of inflammation pro-resolution markers.

HEME OXYGENASE-1 PREVENTS GLUCOCORTICOID AND HYPOXIA-INDUCED APOPTOSIS AND NECROSIS OF OSTEOCYTE-LIKE CELLS

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Glucocorticoid and hypoxia induce apoptosis and necrosis of osteocyte-like cells. These cell deaths are possibly involved in the development of glucocorticoid-related osteonecrosis (ON). Heme oxygenase-1 (HO-1) has antioxidant and anti-inflammatory effect. We evaluated the cytoprotective effect of HO-1 on glucocorticoid and hypoxia-induced cell deaths in osteocyte-like cells.

Murine osteocyte-like cell (MLO-Y4) was cultured. Hemin was used as a HO-1 inducer. After MLO-Y4 was cultured with 10 μM hemin for 18 hours under normoxia (20 % O2), the gene and protein expression of HO-1 in hemin (+) group were compared with hemin (-) group by real-time RT-PCR and Western blotting respectively.

In hemin (+) group, HO-1 gene expression significantly increased compared with that in hemin (-) group ($p < 0.01$), and protein expression also increased. Cells were divided into the three groups as follows: control group: cultured under normoxia; DH group: cultured under hypoxia (1 % O2) with 1 μM Dexamethasone (Dex) for 24 hours; DH-h group: cultured with 10 μM hemin for 18 hours under normoxia, and then cultured under hypoxia and 1 μM Dex for 24 hours. The ratios of apoptosis and necrosis were measured by flow cytometry and compared between the three groups. The proportion of apoptosis and necrosis (11.93%, 3.02%) in DH-hemin was significantly lower than those (14.95%, 7.56%) in DH ($p < 0.01$).

Hemin reduced glucocorticoid / hypoxia-induced cell deaths in osteocyte-like cells. The up-regulation of HO-1 may cause the cytoprotective effect of hemin on osteocyte-like cells. The HO-1 induction could be the effective treatment of glucocorticoid-related ON.

EVALUATION OF ACCURACY AND A LEARNING CURVE OF ACCELEROMETER-BASED COMPUTER NAVIGATION IN TOTAL KNEE ARTHROPLASTY

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The KneeAlign2 (OrthAlign,Inc., Aliso Viejo, CA) is a portable accelerometer-based navigation device for use in performing the distal femoral resection in total knee arthroplasty (TKA). The aim of this study was to investigate the accuracy in positioning the femoral component and the presence of a learning curve in conducting TKA using this device.

60 knees underwent a primary TKA using the KneeAlign2. These TKAs were divided in two groups. Group1: operated by surgeon of experience using the KneeAlign2 more than 30 cases. Group2: operated by surgeons of experience using the KneeAlign2 less than 30 cases. Standing AP hip-to-ankle radiographs were obtained postoperatively. Positioning of the femoral component was measured by the radiographs. Outlier in coronal alignment were defined as >3°. The radiographic results and operation time were compared between the groups. Students t-test was performed to assess the statistical analysis ($p<0.05$).

There was no outlier and all patients had an alignment within 90±3°to the femoral mechanical axis in the coronal plane in both groups. The mean deviation (absolute values) from the neutral alignment of the femoral component were 1.5±0.5 in group1 and1.2±0.7 in group2. There was no statistical significance between the groups. Average operation time was 106.2 minutes in group1 and 108.5 minutes in group2. There was no statistical significance between the groups.

The KeeAlign2 is highly accurate in positioning the femoral component. As the learning curve does not be observed, this portable navigation is easy to handle even for beginner users.

A REGISTRATION METHOD TO ASSESS TIBIAL BONE MINERAL DENSITY IN THREE DIMENSION USING CT SCAN

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Alterations of bone mineral density (BMD) are a common hallmark to both osteoarthritis and osteoporosis. BMD is usually measured using DXA. This imaging technique is however two-dimensional, prohibiting comprehensive spatial analysis of BMD. Three-dimensional imaging techniques, such as computed tomography (CT), exist, however they require statistical methods to derive anatomical correspondences among samples and thus allow analyses despite variations in bone shapes. More recently, successful computational anatomy methods were proposed to establish anatomical correspondences among bones. Nevertheless, there is a paucity of such methods for the proximal tibia, specifically when only a portion of the tibia is imaged. The objective of this study was to develop a method for three-dimensional analysis of BMD in the proximal tibia.

The anatomical correspondence between tibia models, obtained by segmentation of the CT images, was established following a three-step mapping procedure. Specifically, the mapping was determined based on a rigid alignment of the tibias, followed by a non-rigid registration of the transverse bone section areas and a non-rigid registration of the models. This method was used to map 23 healthy knees onto a reference tibia and to calculate the three-dimensional distribution of BMD inside the tibia. This procedure reported excellent reproducibility (ICC of 0.964±0.01), and identified a common pattern of BMD in the tibias.

In the future, it could be used to quantify BMD alterations inside the tibia in three-dimension notably in case of osteoarthritis or osteoporosis. The presented method could also be used with other three-dimensional imaging techniques and applied to other pathologies.

STANDARDISED HISTOPATHOLOGIC SCORING SYSTEM TO ASSESS TENDON HEALING

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Superficial digital flexor tendinopathy is a common and potentially devastating injury in all equine athletes. Regenerative medicine and cell-based therapy have shown promising results in the treatment of tendinopathy. The aim of this project was to develop and validate a specific histological scoring system dedicated to the assessment of equine tendon lesions treated by regenerative medicine.

We have developed a semi-quantitative histopathologic scoring system based on commonly used scoring methods reported in the literature, which aims to improve over previous systems to focus on key parameters related to tendon regeneration that is easily assessable on longitudinal H&E sections by both inexperienced and specialized pathologists. The parameters include tenocyte density and morphology, leukocytes, neovascularization, interfascicular matrix density and collagen fibre organisation and crimp. Histological slides were blindly scored with bright field microscopy to determine morphology and cellularity and with polarized light microscopy to evaluate the collagen crimp.

The scoring system was compared with the previously published systems using tendon samples from unaffected horses and horses with surgically induced core lesion of the superficial digital flexor tendon treated by regenerative medicine. The new system better reflected re-establishment of normal morphology.

TOPOGRAPHY-INDUCED MECHANOTRANSDUCTION IS A CONTEXT-DEPENDENT REGULATOR OF STEM CELL DIFFERENTIATION TOWARDS THE TENOGENIC LINEAGE

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Tenocytes, the main cell type of the tendon, require mechanical stimulation for their proper function. *In vitro*, it is known that micro-topographies provide biomechanical cues and guide cell fate. In light of this, we previously found that micro-topographies promote the expression of mechanosensitive transcription factors and tendon related matrix proteins on tenocytes. In this study, we investigated if micro-topographies can elicit a similar effect on human adipose-derived mesenchymal stem cells (AD-hMSCs) and can guide differentiation towards the tenogenic lineage.

By utilizing the TopoChip, a platform containing 2176 unique micro-topographies, we identified an optimal *in vitro* niche by screening for Scleraxis (SCX) expression, a tenogenic differentiation marker. Through machine learning algorithms, we associated SCX levels with morphological characteristics and topographical design parameters. Large surface fabrication of micro-topographies inducing significant higher SCX levels allowed studying the dynamics of tenogenic marker expression and the pathways involved in their regulation.

Through gene expression studies, we found that micro-topographies elicited an early activation of the mechanosensitive transcription factors EGR-1, SCX, and MKX, followed by a late upregulation of the tendon related matrix proteins COL-I, COL-III, BGN, and DEC. Of interest, we found a synergistic effect on SCX levels when combining micro-topographies with TGF-β2, indicating a topography-induced sensitization towards this signaling pathway.

Further investigation found an upregulation of the TGF-β receptor and inhibitor experiments confirmed the importance of TGF-β signaling in topography-induced mechanotransduction. The knowledge gained from these studies will be essential for creating a new generation of culture platforms where surface architectures guide cell fate.

GRADED IMPLANTS FOR ROTATOR CUFF REPAIR – SPECIFIC ANIMAL MODELS IN THE SELECTION PROCESS

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Chronic rotator cuff tears are a well-known problem in shoulder surgery. Due to tendon contraction and fatty muscle degeneration, implant material is necessary for surgical treatment. Due to different tissue requirements (tendon, cartilage, bone) in the enthesis region, graded implant materials with special adaption to the respective demand are developed and first tested *in vitro*. Prior to clinical use, preclinical testing in animal models is necessary. Therefore, different small and large animal models are used in the selection process of new materials.

For first angiogenesis and biocompatibility testing dorsal skin and femur chamber models in mice and rats are used. With these models, capillary density and leucocyte infiltration can be observed *in vivo* in the postoperative time period of up to 21 days at different selected time points additional to histological evaluations. With these models a first selection of promising materials is possible. A chronic rat tendon defect model is the next step, where a defect of the M. infraspinatus is created and refixated four weeks later with selected materials. After eight weeks, biomechanical testing of the defect area is performed.

Differences in biomechanical stability can further specify suitable materials. At the end of the selection process, the material is implemented in a chronic tendon defect in a sheep, with a situation most similar to humans.

These selection steps lead to a fast feedback to the production processes and offer the opportunities for specified adaptions in the material composition and therewith improvement prior to expensive and time-consuming large animal studies.

GLYCOSAMINOGLYCAN DISSACHARIDES CHANGES DURING CHONDROGENIC DIFFERENTIATION OF HUMAN BONE MARROW/SYNOVIAL-DERIVED MESENCHYMAL STEM CELLS UNDER DIFFERENT OXYGEN TENSIONS

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Glycosaminoglycans (GAGs) are major components of cartilage extracellular matrix, which play an important role in tissue homeostasis not only in providing mechanical resistance to compressive loads, but also as signalling mediators of cell adhesion, migration, proliferation and differentiation. GAGs are linear, highly charged, acidic carbohydrates with a repeating disaccharide unit. Specific GAG types as well as their disaccharide sulfation patterns can be predictive of the tissue maturation level but also of disease and degeneration states.

In this work, we used a highly sensitive liquid chromatography-mass spectrometry (LC-MS) method to perform a comparative study in terms of GAG type, amount, disaccharide composition and sulfation patterns between chondrogenic micromass tissues generated from human bone marrow- and synovial membrane-derived mesenchymal stem/stromal cells (hBMSC/hSMSC). The effect of oxygen tension on GAG composition and disaccharide patterns was also evaluated by the analysis of chondrogenic cultures performed under normoxia (21%O2) and hypoxia (5%O2).

Prior to LC-MS analysis, the chondrogenic differentiation of hBMSC/hSMSC cultured under different oxygen tensions was assessed by micromass average size, total collagen and GAG content as well as by histological and immunofluorescence stainings. Afterwards, chondrogenic micromasses were lysed using a commercial surfactant reagent, sonicated and digested with GAG lyases. The resulting disaccharides were recovered by centrifugal filtration, labelled and analysed by LC-MS. The GAG profiles obtained were compared with undifferentiated cells and human articular chondrocytes.

In overall, the obtained GAG profiles may provide new insights to characterize the quality of MSC-generated chondrocytes from different cell sources and obtained under distinct culture conditions.

EXTRACELLULAR MATRIX DECORATED POROUS POLYCAPROLACTONE SCAFFOLDS FOR BONE TISSUE ENGINEERING

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Synthetic polymer-based materials, such as polycaprolactone (PCL), have been widely applied as scaffolds and used commercially in bone tissue engineering (TE). However, their ability to promote osteogenesis is generally limited by sub-optimal cell-material interactions resulting from the lack of biological active sites. The extracellular matrix (ECM) is a three-dimensional (3D) network of structural and functional molecules, which provide an appropriate microenvironment for cell adhesion, migration, proliferation and differentiation. Therefore, the decoration of synthetic scaffolds with decellularized ECM has received considerable interest as a strategy to enhance their biological performance.

Herein, we developed an extrusion-based 3D porous PCL scaffold with controlled architecture, porosity and high interconnectivity which was decorated with human mesenchymal stem/stromal cell (hMSC)-derived ECM by culturing hMSC in PCL scaffolds for 14 days, allowing them to adhere, proliferate and secrete ECM. Afterwards, the resulting constructs were decellularized and hMSC-derived ECM decorated PCL scaffolds were obtained. Scaffold morphology and ECM presence were confirmed by scanning electron microscopy (SEM)/Energy dispersive X-ray (EDS) analysis and immunofluorescence stainings. The ability of hMSC-derived ECM-decorated PCL scaffolds to promote MSC proliferation and osteogenic differentiation was assessed and compared to the untreated scaffolds.

After 21 days under osteogenic induction, ALP activity levels, mineralization deposition and mRNA levels of osteogenic markers (COLI / Runx2 / ALP / OPN / OC) were evaluated. In overall, we described a method to fabricate hMSC-derived ECM-decorated PCL scaffolds with high interconnectivity and enhanced biological performance, which are promising for bone TE applications, as demonstrated by the beneficial effect on hMSC proliferation and osteogenic differentiation.

TRAPEZIOMETACARPAL JOINT STABILITY: LATERAL PINCH VS POWER GRIP

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Cases of trapeziometacarpal (TM) joint arthritis present clinically with some degree of dorsal subluxation. Therefore, a dorsally directed force may have a role in disease development. Herein, we endeavored to understand forces inducing dorsal subluxation and determine if they result from key pinch or power grip.

Five non-arthritic cadaveric specimens were prepared by stabilizing the wrist, fixing the 2nd through 5th metacarpal-phalangeal joints in 60º flexion, and mounting the forearm onto a frame. Extrinsic and intrinsic tendons were prepared for weight suspension. Specimens were loaded into power grip and key pinch configurations, then all TM ligaments were resected in order to record their effect on joint stability. Stability was evaluated statically and dynamically in power grip and key pinch. The TM joint was statically and dynamically stable after resection of all supporting ligaments in the key pinch configuration. Conversely, in the power grip configuration, 3 specimens dislocated and 2 subluxed prior to a dynamic challenge (statically), and all 5 specimens dislocated when dynamically challenged.

We demonstrated that the forces induced on the TM joint during pinch do not generate a shearing component requiring ligament restraint to maintain stability; the forces induced during grip do. Therefore, dorsal subluxation and resulting arthrosis may be the result of a dorsal shearing force generated during gripping in the presence of incompetent TM ligaments. Power grip generates shear forces that may promote or exacerbate TM osteoarthritis, while pinch does not.

This may have relevance in conceiving rehabilitation protocols, surgical techniques and designing prosthetic joints.

THE PARALLELOGRAM EFFECT: HOW CENTRAL BAND FAILURE CAN CAUSE ULNAR IMPACTION SYNDROME

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Ulnar impaction syndrome is a degenerative wrist condition caused by increased loads of the ulnar head onto the carpal bones (carpal abutment). We hypothesize that elongation of the central band of the forearm interosseous ligaments may change longitudinal radial-ulnar relationships resulting in an ulnar positive wrist and therefore carpal abutment.

Six cadaveric, human forearms were used to measure relative displacement of the ulna during axial loading of the radius. The IOL complex, TFCC, radio-ulnar joints and the elbow collateral ligaments were preserved. The ulnar shaft was oriented vertically and rigidly fixed to an adjacent vertical beam. We applied axial loads onto the lunate facet of the distal radius. Radial heights were measured in supination and pronation under a 5lbF preload. Gradual axial loads were applies up to 50lbF and the resultant axial displacement was measured. All measurements were evaluated with the IOL intact and repeated with the central band cut.

Due to a parallelogram effect, the radius shifted proximally under a 5lbF preload, creating an ulnar positive wrist relationship. Dynamic loading of the forearm after ligament excision resulted in increased ulnar variance, suggesting dynamic impaction often observed clinically. In supination, the radius displaced 2.1x further after the central band was cut (3.00mm). In pronation, the radius displaced 1.8x further when the central band was cut (2.84mm).

In summary, our study demonstrates that the central band plays a role in maintaining longitudinal stability and therefore ulnar variance.

ALTERED WALKING AND MUSCLE PATTERNS REDUCE HIP CONTACT FORCES IN INDIVIDUALS WITH SYMPTOMATIC CAM FAI

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Cam-type femoroacetabular impingement (FAI) is a causative factor for hip pain and osteoarthritis. It is still unclear what role muscle forces play and how they affect the hip joint loading, therefore the purpose was to examine muscle contributions and hip contact forces in individuals with symptomatic cam FAI during level walking.

Gait kinematics and kinetics of 18 symptomatic patients (FAI) and 18 control participants (CON) were recorded using a motion capture system (Vicon MX-13) and force plates (Bertec FP4060-08). Muscle and hip contact forces were subsequently computed using a musculoskeletal modelling program (OpenSim 3.1). The FAI group walked slower and with shorter steps, showing reduced psoas major (Median = 1.1, IQR = 1.0–1.5 N/BW) and iliacus forces (Median = 1.2, IQR = 1.0–1.6 N/BW), compared to the CON group (Median = 1.6, IQR = 1.3–1.6 N/BW, $p = 0.004$; and Median = 1.5, IQR = 1.3–1.6 N/BW, $p = 0.03$, respectively).

The FAI group altered their walking mechanics to reduce their psoas major and iliacus muscle forces. This can be interpreted as a protective mechanism, which ultimately resulted in lower hip contact forces to the anterosuperior acetabulum ($p < 0.05$). Limited hip mobility is not only attributed to bone-on-bone impingement, caused by the cam morphology, but could be attributed to musculature as well. Athletic conditioning could further strengthen core muscles for improved hip mobility and pelvic balance.

Thus, these findings can help guide nonsurgical management as well as postoperative protocols for the treatment of symptomatic FAI.

TOTAL COST OF TREATMENT: ASSESSING THE KEY FACTORS IN HIP FRACTURE

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Several authors have reported on time to surgery (TTS), length of stay (LOS) and total cost. Anecdotal evidence from our trauma service suggests that all hip fractures are not created equal. We decided to investigate this suspicion and captured data on a retrospective cohort of 400 neck of femur (NOF) performed at Mayo University Hospital.

We analysed this hip fracture population and show how patient demographics and operative features may directly impact LOS and cost of treatment. While 8 patients required major optimisation pre-op, 229 (89%) reached theatre within 24 hrs of admission. 55% underwent hemiarthroplasty while 45% received fixation. Mean LOO varied significantly from 1:22 [0:23 to 5:08] depending on surgery performed. Hemiarthroplasty took 1:19 while fixation took 0:05 longer.

LOS did not correlate to age or to operation performed. LOS was significantly shorter for patients discharged Home (12 days, same hemiarthroplasty/fixation ratio). Mean total cost is €22,155 with implant, theatre and ward costs €1,045, €2,555 and €18,555 respectively. LOS is significantly less for patients discharged Home ($p < 0.001$): they are 5-years younger than the ⅓ discharged to Nursing Home or District Hospital. Total cost of DHS (€21,758) is 23% less than that of IM Nailing (€28,385); PCCP is ½ the cost of DHS or IM Nail ($p < 0.05$). The cost of an orthopaedic bed (€750/day) is still the most critical factor; €18,555, or 84% of €22,155.

ARTHROSCOPIC PARTIAL MENISCECTOMY: SYSTEMATIC REVIEW AND META-ANALYSIS

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25% of adults aged over 50 experience frequent knee pain from degenerative knee disease. Today it is common practice to treat concomitant meniscal tears with arthroscopic partial meniscectomy (APM). Due to the sheer number of procedures involved annually (100 to 225 per 100,000 patients), we review the published evidence base.

Literature search identified 10 RCTs (level 1 evidence) which compare APM to conservative treatment for degenerative meniscal tears in middle-aged patients. Of the 10 trials included in our meta-analysis, 90% do not report any long term benefit in terms of reduced knee pain over conservative management. When we analyse the 8 RCTs which report knee pain at 3-months, we find a statistically significant reduction in pain of -0.24 (95% CI -0.37 to -0.10, $p < 0.001$, $I2 = 0\%$) equivalent to an improvement of only 0.5 points (on a 0 to 10 VAS). 8 RCTs report knee pain at 1-year follow-up: meta-analysis shows that there is absolutely no benefit for knee arthroscopy compared to conservative management (SMD = 0.00, $p = 0.96$). In 2017 the Canadian AAC wrote that ‘arthroscopic debridement is not indicated as primary treatment in the management of osteoarthritis of the knee.

This position echos guidelines published by the Australian AKS, American AAOS, German DGOU, French HAdS and British BOA. Meta-analysis shows a benefit at 3-months corresponding to a reduction in pain of 0.5 points (on a 0 to 10 VAS). At 1-year there is no benefit for arthroscopy compared to conservative management.

ENHANCED BONE REGENERATION USING INJECTABLE HYDROGELS CONJUGATED BY OSTEOGENIC PEPTIDES

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Hydrogels have been widely used as potential biomaterials to incorporate bioactive molecules, such as proteins and peptides to improve the bone regeneration. However, the commonly physical mixing and adsorption methods limited their loading efficiency and controlled release.

In this study, we developed a hydrogel that can chemically conjugate peptides and crosslinked in situ, using horseradish peroxidase (HRP)/hydrogen peroxide (H2O2)-catalyzed the reaction between phenol or aniline derivatives. A bioactive calcium accumulating peptide (CAP) containing a collagen binding motif, which can induce osteogenic differentiation, was synthesized. The tyrosine residues in CAP enable the in situ conjugation of peptide into the gelatin-hydroxyphenyl propionic hydrogels through tyrosine-tyrosine conjugation under HRP/H2O2 conditions. The human periodontal ligament stem cells (hDPLSCs) was loaded into the in situ forming gelatin hydrogel conjugated CAP, to evaluate the acceleration of bone formation.

In vitro study demonstrated the bone mineralization and the increase in osteogenic marker expression of CPA/gelatin hydrogels. The remarkable recovery effect after 4 weeks implantation of hydrogels was observed *in vivo*.

These results suggest that injectable hydrogels conjugated CAP are potential as engineered microenvironment to enhance bone regeneration and deliver stem cells in tissue regeneration.

QUANTITATIVE ANALYSIS OF THE OSTEOCYTE SECRETOME FOLLOWING OSCILLATORY FLUID SHEAR STIMULATION

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The osteocyte is the most abundant cell in bone and is an important component of loading-induced bone formation, regulating its secretome in response to mechanical loading to mediate stem cell recruitment and osteogenic differentiation. Although numerous osteocyte secreted factors have been identified, the full secretome of the osteocyte and thus its therapeutic potential remain poorly explored. Therefore, the objective of this study was to identify the secretome of the osteocyte and determine how this is altered in response to mechanical loading, with the aim of identifying novel targets to enhance stem cell contributions to bone formation.

Osteocytes were either cultured statically, or subjected to 2 hours of fluid flow induced shear (1Pa, 1Hz), with migration of human skeletal stem cells (hSSCs) being enhanced over 2-fold towards medium from dynamically cultured cells, as well as displaying increased COX2, OCN, OSX and BMP2 gene expression.

A proteomic analysis of osteocyte conditioned medium (CM) identified over 300 proteins, with 97 of these being significantly upregulated compared to control medium. Further analysis revealed significant enrichment of several “extracellular” and “binding” related gene ontology terms, indicating a key role of the osteocyte secretome in mechanosignaling. Furthermore, 34 proteins were found to be differentially expressed in the secretome of mechanically loaded osteocytes, indicating potential roles in mechanically mediated signaling.

This study highlights the key role of the osteocyte in signaling within bone, and reveals for the first time a complete map of proteins released by the osteocyte which may represent novel therapeutic targets for bone regeneration.

CALCIUM PHOSPHATE, CHITOSAN AND HYALURONIC ACID - BIOMIMETIC SUBSTRATE MODULATES MONOCYTE/MACROPHAGE INFLAMMATION

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The use of inorganic calcium phosphate supplemented with biopolymers has drawn lots of attention in bone regenerative medicine. While inflammation is required for bone healing, its exacerbation can alter successful tissue regeneration. Owing to their critical role in bone dynamics, investigating the interaction between monocytes/macrophages and bioactive/ osteoinductive calcium phosphate/chitosan/ hyaluronic acid (CaP-CHI-HA) will provide essential information for the rational design of new biomaterials.

CaP-CHI-HA cytocompatibility was monitored by WST-1 assay, DNA quantification and intracellular accumulation of reactive oxygen species (ROS). The low metabolic activities and DNA content of THP-1 on CaP-CHI-HA, in addition to the absence of an increase in ROS intracellular accumulation compared to LPS positive control, confirmed its biocompatibility. On CaP-CHI-HA, THP-1 exhibited a sub-membranous F-actin localization with a prominent distribution of vinculin throughout the cytoplasm and the membrane.

In contrast, with LPS stimulation, F-actin was mostly arranged as spike-like protrusions of the cell membrane with vinculin evenly localized at peri-nuclear region. Exposing monocytes to CaP-CHI-HA resulted in a secretion of pro-healing VEGF and TGF-β growth factors, TNF-α, MCP-1, IL-6 and IL-8 pro-inflammatory mediators, but also IL-10 anti-inflammatory cytokine along with an inflammatory index below 1.5 versus 7.5 following monocytes LPS stimulation. Although CD44 receptor seems not to be involved in the inflammatory index regulation, results suggest a potential role of the chemical composition and calcium release from CaP-CHI-HA, in affecting the intracellular expression of calcium sensing receptors.

Herein, our findings indicate a great potential of CaP-CHI-HA in providing a moderate inflammatory response, suitable for bone regeneration.

LIMITED PENETRATION OF COBALT AND CHROMIUM IONS INTO THE CEREBROSPINAL FLUID FOLLOWING METAL ON METAL ARTHROPLASTY: A CASE-CONTROL CROSS SECTIONAL ANALYSIS

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The aims of this study were to determine whether cobalt (Co) and chromium (Cr) ions were transferred from joint fluid to cerebrospinal fluid (CSF) in patients undergoing metal-on-metal (MoM) hip and knee arthroplasty procedures, and to assess the contribution of implant history and patient factors. An observational, non-randomised cross-sectional study was conducted with 461 patients presenting to a single-surgeon private clinic for treatment of degenerative conditions of the hip and knee.

Blood and fluid samples were collected intraoperatively and analysed for proteins and trace elements. The presence of an implant was associated with significantly higher Co and Cr concentrations in plasma, but not CSF. In absolute terms, <1% of joint fluid metals, and <15% of plasma metals were found in CSF. An association between the ratio of CSF and plasma concentrations, and plasma levels was observed.

Partial least squares regression models revealed different mechanisms of diffusion between Co and Cr to the CSF, with the presence of an implant not associated with ion levels. The presence of MoM implants is associated with significantly higher plasma concentrations of Co and Cr but not CSF, with an apparent influence of plasma metal load on the CSF/plasma ratio.

Co and Cr appear to be transferred to the CSF by different mechanisms, and their concentrations appears dependent on other factors yet to be identified. Although higher levels of plasma ions are associated with above average CSF metal concentrations, the thresholds for neurotoxicity remain unclear and require further study.

EFFICACY OF SHORT-STEM, BONE-PRESERVING HIP RESURFACING FOR OSTEONECROSIS OF THE FEMORAL HEAD: A PROSPECTIVE OBSERVATIONAL COHORT STUDY WITH MINIMUM FIVE-YEAR FOLLOW-UP

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Published medium-term outcomes of bone conserving metal-on-metal resurfacing as a surgical option for osteonecrosis of the femoral head (OFNH) remain sparse. This study reports the medium-term survival and patient-reported outcomes of bone-preserving hip resurfacing in patients presenting with avascular osteonecrosis treated in an independent clinic.

A series of patients (N=28, 24 males) presenting with hip osteoarthritis associated with OFNH (Ficat-Acet stage >2) underwent hip resurfacing with a mid-head resection device. Patients were followed up with serial radiographs and patient-reported outcomes (Veteran's Rand-36, Harris Hip Score, Western Ontario and McMaster Universities Osteoarthritis Index, Tegner Activity Scale). A survivorship analysis was performed with the Australian National Joint Replacement Registry.

Latest follow-up was a median of 6.5 years (IQR 5.5 - 8.0), with one revision detected (96.7% cumulative survival) and significant ($P<0.001$) improvements overall, exceeding minimally clinically important improvements in patient-reported outcomes. A high incidence of lucency was observed around the cup (85.7%) and stem (74.1%), with neck narrowing exceeding 10% of initial neck width in 27.8% of the sample. Hip resurfacing with a mid-head resection device provided excellent outcomes in younger patients with ONFH at medium-term follow up.

Future studies should compare its performance against alternative options (hip resurfacing, total hip arthroplasty) for this indication in a larger sample.

GENERATION OF INDUCED PLURIPOTENT STEM CELLS FROM A PATIENT WITH AUTOSOMAL RECESSIVE OSTEOPETROSIS

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Autosomal recessive osteopetrosis (ARO) is a rare heterogeneous disorder, diagnosed by increased bone density in early infancy associated with dysfunctional osteoclasts in bone resorption. Genetic association analysis revealed the relationship between mutations in the SNX10 gene and ARO pathogenesis. It has been shown that this mutation results in dysfunctional osteoclasts by disturbing the formation of ruffled borders in the cells.

In order to further understand the molecular mechanisms and consequences of the SNX10 mutation in ARO development, we generated iPSCs from a 41-year-old female ARO patient, who carries the homozygous c.212 + 1G N T (g.72742G N T) mutation in SXN10. In total, 18 iPSC-like colonies were generated from the patient's dermal fibroblasts using retroviral plasmids containing hOCT4,OX2,C-MYC and hKLF4.

G-banding analysis proved that the selected ARO-iPSC1-11 line carried a normal karyotype. Furthermore, genomic DNA sequencing verified that the disease related mutation (g.72742G N T) was retained in the generated iPSCs. To evaluate the pluripotent state of ARO-iPSC1-11, gene expression analysis con firmed the positive expression of endogenous firmed the positive expression of endogenous pluripotency genes (OCT4, SOX2 and NANOG), but silencing of reprogramming factors expressed by the retroviral transgenes. Immunofluorescent staining demonstrated that ARO-iPSC1-11 also expressed pluripotency markers including TRA1-60 at the protein level.

This ARO patient-specific iPSC line containing the SNX10 mutation provides opportunities to study the pathobiology of SNX10-dependent ARO, and provide a testing platform for screening therapeutic agents in osteopetrosis and metabolic bone diseases.

APPLICATION OF CALCIUM PHOPHATE-BASED BONE SUBSTITUTE ISOLATED AND ASSOCIATED WITH COLLAGEN MEMBRANE IN BONE DEFECTS

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The aim of this study was to evaluate the process of bone regeneration in defects of rabbit tibias using bone cement isolated or associated with collagen membrane. The study was approved by the ethics committee of the Federal University of Campina Grande under number 097/2016.

Twelve adult rabbits of both sexes, divided into two experimental groups bone cement group (GBC) and bone cement group plus collagen membrane (GBCM), were studied. Each group was subdivided into two subgroups, according to the period that these animals were euthanized, 30 and 60 postoperative days. Two bone defects with 2 mm of diameter were performed, one at the proximal tibiae diaphysis and another one on the distal tibiae diaphysis of each pelvic limb. In the right limb (GBC) the defects were filled with bone cement; in the left limb (GBCM) the defects were filled with bone cement plus collagen membrane of bovine origin. Radiographic, histological and Scanning Electron Microscopy (SEM) analysis were performed. Osseointegration of the implants was shown through radiographic evaluation.

Histological results indicated an intense bone neoformation but a progressive degradation of the implants was noticed by SEM. However, no significant differences were observed in relation to the bone regeneration between the experimental groups; nonetheless, it was verified that at 60 postoperative days the bone repair was more pronounced and the bone neoformation was intensified when compared to the 30 days.

According to the results obtained, all the samples were gradually absorbed during the evaluated periods, being replaced by neoformed bone tissue.

PRODUCTION AND CHARACTERIZATION OF UV-CURABLE MATERIALS FOR ENHANCED BONE REGENERATION

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In this work, materials for enhanced bone regeneration after multiple fractures were investigated. In a conventional treatment of a multiple bone fracture, gathering bone fragments can take long time for healing, followed by the fixation of the bone using bone screws and plates. In case of the removal of a larger amount of bone, the metal objects have to stay in the body. Therefore, it would be interesting to be able to apply a material to fix the multiple bone fragments during a surgery, so they can be incorporated in the regrowing bone.

For this purpose, a UV-curing material would be interesting, as portable UV-curing devices are already applied for example in dental treatments. Therefore, in this work, NiPAAm polymer-based composite materials with ceramic additives were synthesized via UV-initiated radical polymerization. The influence of different additives on mechanical properties of the polymer as well as the prepolymer mixture were investigated in order to analyze the suitability of the composites for bone healing applications.

Further, the results were compared with the properties of the polymers in swollen state. It can be stated that it was possible to find mechanically suitable additive to increase applicability of the prepolymer mixture in surgeries. The addition of ceramics to these composites did not decrease their stability drastically and it was even possible to polymerize the monomers using hand-held UV devices. Cytotoxicity tests revealed these samples are non-toxic and slightly increases these values when ceramics additives are incorporated into the polymer matrix.

ESTIMATING JOINT LOADING USING INERTIAL MEASUREMENT UNITS AND GROUND REACTION FORCES

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To calculate joint loading, integrated 3D motion capture and ground reaction force (GRF) measurements in combination with musculoskeletal modelling is typically used, limiting its use to a lab-based environment. Inertial measurement units (IMU) can be used outside the lab to measure kinematics. Relating IMU kinematics to joint loading therefore holds the potential to estimate joint loading in activities of daily living in an ambulatory setting and even in the patients' home environment. The goal of the present study is to determine if IMU kinematics can estimate hip and knee loading or if GRF are additionally required.

Twelve healthy control subjects performed gait while synchronously measuring 3D marker trajectories (Vicon), GRF (AMTI) and IMU kinematics (Xsens). Hip and knee loading were calculated using OpenSim 3.3 using the 3D marker trajectories and GRF.

A multiple regression analysis related peak hip and knee loading to peak sagittal plane IMU lower limb joint angles, linear and angular accelerations and GRF. The minimal number of variables required for a significantly good coefficient of determination ($R2>0.5$) were taken into account ($p<0.1$). Hip loading can be estimated using only IMU kinematics (with 6 variables $R2 = 0.71$). For knee loading the GRF is additionally needed (with 2 variables $R2 = 0.52$).

These results suggest that a combination of multiple IMU kinematics is required to estimate hip loading reliably, whereas the estimation of knee joint loading remains inferior even when including GRF data.

EVALUATION OF CORTICAL BONE IN DIABETIC RATS USING SWIFT

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Diabetes decreases bone strength, possibly because of cortical bone changes. Sweep imaging with Fourier transform (SWIFT) has been reported to be useful for cortical bone evaluation. The Purpose of this study was to evaluate cortical bone changes in diabetic rats using SWIFT, assess the usefulness of this technique through comparisons with conventional MRI, and clarify the mechanism underlying cortical bone changes using histomorphometry.

8-week-old male Wistar/ST rats (N = 36) were divided into diabetes (induced by streptozotocin injection) and control groups. 6 animals from each group were sacrificed at 2, 4, and 8 weeks after injection. Tibial bones were extracted and evaluated using MRI. Proton density-weighted imaging (PDWI) and SWIFT were performed. The signal-to-noise ratio (SNR) was calculated for each acquisition. The bone formation rate was evaluated using histomorphometry. Findings at each time point were compared using Mann–Whitney U tests.

At all time points, PDWI-SNR showed no significant differences between groups ($P = 0.59$, 0.70, and 0.82 at 2, 4, and 8 weeks, respectively), SWIFT-SNR was significantly lower in the diabetes group than in the control group ($P < 0.05$ at 2 and 4 weeks and $P < 0.01$ at 8 weeks), and the bone formation rate was significantly lower in the diabetes group than in the control group ($P < 0.01$ for all).

Our results suggest that SWIFT can detect cortical bone changes in diabetic rats earlier and more sensitively than conventional MRI. Thus, it may be a useful tool for evaluation of the bone turnover and bone quality, which will aid in the diagnosis of osteoporosis, in patients with diabetes.

WHAT IS THE BENEFIT OF USING AMNIOTIC MEMBRANE IN ORAL SURGERY? AN EXHAUSTIVE REVIEW OF CLINICAL STUDIES

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Since its first use for the reconstruction of tissue defects in the oral cavity in 1985, human amniotic membrane (hAM) has been widely studied in the field of oral surgery. However, there is no systematic review concerning its clinical applications and relevance for soft and hard tissue reconstruction in the oral cavity. The aim of this review is to provide a thorough understanding of the potential use of hAM in oral surgery.

A systematic electronic and a manual literature search of the MEDLINE-PubMed database and Scopus database was realized. Patient, Intervention, Comparison and Outcomes (PICO) technique was used to select the relevant articles to meet the objective. Studies using hAM for oral reconstruction, and conducted on human subjects, were included in this survey.

A total of 22 articles were analyzed, and five potential clinical applications were identified: periodontal surgery, cleft palate and tumor reconstruction, prosthodontics and peri-implant surgery. Periodontal surgery was the only area to assess the efficacy of hAM with randomized clinical trials. A wide variability of the preservation methods of hAM and the lack of objective measurements were observed. Much studies now supports the use of hAM in the field of oral surgery, but, they consisted mostly in retrospective case series.

Thanks to its biological and mechanical properties, hAM is promising as a treatment for wound healing in various areas of oral reconstruction. However, further randomized clinical trials are needed to confirm these preliminary results.

TRANSLATION OF CHONDROGENESIS FROM *IN VITRO* TO *IN VIVO*: ROLE OF MATRIX MECHANICAL PROPERTIES AND DEGRADATION

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Despite the tremendous progress in the past decade in translating biomaterials in cartilage regenerative medicine from *in vitro* studies to *in vivo* applications, there is still a lack of complete appreciation of the interplay between degradation and mechanical properties of biomaterials on cell fate decisions. While engineering cartilage tissue *in vitro* (*ex vivo*) is well established, the fate of such engineered tissue upon implantation remains less investigated. Recently, tissue engineered nasal chondrocyte constructs have been successfully used in knee articular surface arthroplasty and in facial reconstruction following tumour resection. However, maintenance of chondrogenic phenotype in constructs derived from articular chondrocytes following transplantation has proven rather challenging.

Using 3D architectured hydrogels (ArcGels) derived by crosslinking gelatin using ethyl lysine diisocyanate (LDI) as a model system, we investigated the impact of mechanical properties and ArcGel degradation on the retention of the cartilage matrix following implantation to identify conditions that could rescue the chondrogenic phenotype in human articular chondrocytes (HAC). By comparing the fate of *ex vivo* engineered cartilaginous constructs with the de novo formation of cartilaginous tissue, in HAC laden ArcGels in an ectopic nude mouse model, we have identified that mechanical properties are more important in dictating fate of HAC *in vitro*. However, *in vivo*, chondrogenesis is governed by a subtle interplay between degradation and biomaterial mechanics.

Our findings show that development of maintenance of cartilaginous tissue by human articular chondrocytes (HC) are governed by different variables and this highlights the importance for establishing translational correlation in cartilage tissue engineering.

MECHANOREGULATIVE COMPARISON OF CONVENTIONAL AND 3D-PRINTED TITANIUM

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There is a growing trend of use of 3D printed prostheses made of metallic materials such as titanium alloys. It is also known that the microstructure and topology of porous layers are different from similar conventional materials made by sintering or powder spraying technology. In this way local fluid permeability and respectively nutrients transport are also varied, This affects expected mechano-regulative signalling to cells when fluid mass and momentum transfer are caused by the material deformation and not by some external perfusion (alike in bioreactors).

Here we are analysing mechano-regulative index variations for different titanium specimens during representative loading scenarios. We show that under three-point free bending conditions it is possible to create zones in the specimen favouring bone, cartilage or fibrous tissue formation in one specimen. However, for physiologically relevant tissue formation conditions (~1 Hz, 300-1000 microstrains) conventional materials lead to mechanoregulation highly dominated by fluid velocity rather than mechanical strain. For 3D printed titanium with the same specimen geometry it is possible to tailor porous permeability to combine mechanical strain and local fluid flow matching the expected values *in vivo* (such as for 20-100 μm micromotions).

The outputs of in silico modelling of these cases and their potential translation to implants are discussed.

CLINICAL AND RADIOLOGICAL OUTCOMES OF HOOK PLATE FIXATION IN THE ACROMIOCLAVICULAR JOINT DISLOCATION

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The purpose of this study was to evaluate the shapes of subacromial erosions and their effect on underlying rotator cuff after hook plate removal. In addition, we evaluate the clinical and radiological outcomes after hook plate fixation for AC dislocation.

We evaluated the 20 patients with AC dislocations treated with hook plate fixations, who could follow up at least 2 years. The clinical outcomes were evaluated using the Constant-Murley score (CMS), Visual Analog Score (VAS) for pain, and Korean Shoulder score (KSS) at final follow-up. Coracoclavicular distance (CCD) was measured to evaluate the maintenance of reduction and computed tomography (3D-CT) was checked on all patients after hook plate removal. In addition, all patients performed musculoskeletal ultrasonography (US) to evaluate the presence of rotator cuff lesions which might be related with subacromial erosion at last follow up.

The mean CMS, VAS for pain, and KSS were 94.56 ± 10.3, 1.5 ± 0.8, 94.6 ± 11.1, respectively. The mean CCD was not statistically different from the contralateral unaffected shoulder (8.99 mm ± 1.49 mm vs. 8.00 mm ± 1.37 mm, p=0.152). In 3D-CT, various types of depressed subacromial erosions were observed in 14 patients (70%) and did not show any marginal inferior protrusion of subacromial erosion. Also, there were no rotator cuff lesions such as partial tear in US. Hook plate fixation for the AC dislocation resulted in good clinical and radiological results. And, subacromial erosion did not influence on the underlying rotator cuff after hook plate removal.

GAIT BIOMECHANICS DURING DIFFERENT PHASES OF GAIT: IS FOOT CENTRE OF PRESSURE SUPERIOR?

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Foot centre of pressure (COP), knee adduction angles (KAA) and knee adduction moments (KAM) are important in the development, and potentially useful in the identification of knee osteoarthritis (OA). This study aimed to characterise and compare these measures in healthy and osteoarthritic groups in each phase of gait and determine whether COP is superior to KAA in identifying osteoarthritic patients.

108 subjects were recruited; 84 had no known pathology; 18 had medial and 6 lateral knee OA. Gait analysis was performed using motion capture and force plates. The normalized COP, KAA and KAM were measured during early, mid and late gait phases.

The first phase of gait demonstrated significant differences between groups for all measures: KAA in all phases, COP in phase one and three and KAM in phase one only. Healthy subjects had a lateral COP for early and mid-stance and medial for late stance (mean (SD): 17 (22), 11 (19) and -1 (14) mm respectively). Medial OA subjects had lateral pressure positions similar to healthy subjects for all phases, whereas for lateral osteoarthritis subjects this shifted medially for early stance.

The largest mechanical changes are seen in the first phase of gait in osteoarthritic patients. Although not a substitute for KAA, COP can be helpful in identifying osteoarthritic patients and evaluating surgical and non-surgical interventions in this phase. Measuring COP is easier than measuring other biomechanical factors. As such it is a potential simple assessment tool for orthopaedic interventions.

CHEMOPROPHYLAXIS IN LOWER LIMB IMMOBILISATION: IS THERE A ROLE FOR NOACs?

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Deep vein thrombosis (DVT) is a common complication following lower limb immobilization. A systematic review and meta-analysis were performed to review the effectiveness of low molecular weight heparin (LMWH) and novel oral anticoagulants (NOACs) for thromboprophylaxis in trauma patients treated non-operatively with lower limb immobilisation.

All randomized controlled trials (RCTs) comparing thromboprophylaxis (either LMWH or novel oral anticoagulant) to no prophylaxis or standard for prevention of VTE in patients with lower limb trauma treated with immobilisation were included in the data analysis. Eight studies totaling 3190 patients were included.

The overall incidence of thromboembolic events in the control group ranged from 2.3% to 40% (137/871) and from 0% to 37% (77/884) in the LMWH group (RR 0.57; 95% CI = 0.45 to 0.73), $P < 0.00001$. There was no significant difference in bleeding. No RCTs comparing NOACs with placebo or no treatment were found. One cohort study demonstrated equivalence of NOACs in VTE rate to LMWH with another demonstrating a significant reduction in VTE rates.

Our results demonstrate that LWMH is an effective agent in reducing DVT in these patients with an acceptable safety profile. Although studies evaluating NOACs such as rivaroxaban as a thromboprophylactic agent in patients with lower-limb immobilisation are limited, there appears to be a potential for this regimen. Further randomised controlled trials are needed to assess this.

PREVENTING BACKFLOW LEAKAGE OF STEM CELLS INJECTED INTO ATROPHIC NON-UNION FRACTURE MODEL USING THE Z-TRACK METHOD

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Atrophic non-union is a major clinical problem. Treatment is usually prolonged, over years, and commonly leads to permanent disability. Replacement of biological factors by stem cells is of growing interest. A minimally invasive technique is used to deliver stem cells into the fracture site via percutaneous injection, however, this technique is significantly affected by a backflow leakage following injection, this occurs through the injection tract into the skin, subsequently the net number of injected cells might be reduced and their therapeutic privilege is affected.The Z-track method is currently being used in the clinical practice for intramuscular injections, it has been proved to be effective in sealing the injected materials and to prevent backflow leakage. Therefore, it could be used for the percutaneous injection in non-union models.

Using rat's cadaver (n=3), a mixture of toluene blue stain and contrast material was used as an injection material into the fracture site to allow visual and radiological detection of possible leaks. Ante grade nailing of tibia via tibial tuberosity was done, then tibia bone was fractured using 3-point close technique to keep intact skin and overlying soft tissue. Injection was performed into the fracture gap by pulling skin over the shin of tibia towards the ankle and injection of the stain into the fracture gap. The needle was then partially pulled, the skin was returned to its normal position and a complete extraction of the needle was followed.

Observation at the injection site revealed no blue stain could be detected over the skin, the injected material initially formed a palpable mass around tibia and that was located away from the injection site. The mass looked sealed with no occurrence of leakage on mild compression. X-rays revealed a localized radiopaque area around the tibia with no material escape noticed.

In summary, the z-track method is an effective way to prevent fluid backflow escape after injection. It can ensure delivering and sealing of the injected material into the targeted area. Therefore, the therapeutic privilege of stem cells injection could be preserved and their efficacy can be optimised.

OBTAINING RELIABLE X-RAY VIEWS OF THE LEG IN A MODEL OF ATROPHIC NON-UNION

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Appropriate *in vivo* models can be used to understand atrophic non-union pathophysiology. In these models, X-ray assessment is essential and a reliable good quality images are vital in order to detect any hidden callus formation or deficiency. However, the radiographic results are often variable and highly dependent on rotation and positioning from the detector/film. Therefore, standardised A-P and lateral x-ray views are essential for providing a full radiological picture and for reliably assessing the degree of fracture union.

We established and evaluated a method for standardised imaging of the lower limb and for reliably obtaining two perpendicular views (e.g. true A-P and true lateral views). The normal position of fibula in murine models is posterolateral to the tibia, therefore, a proper technique must show fibula in both views. In order to obtain the correct position, the knee joint and ankle joints were flexed to 90 degrees and the foot was placed in a perpendicular direction with the x-ray film.

To achieve this, a leg holder was made and used to hold the foot and the knee while the body was in the supine position. Lateral views were obtained by putting the foot parallel to the x-ray film. Adult Wister rat cadavers were used and serial x-rays were taken. A-P view in supine position showed the upper part of the fibula clearly, however, there was an unavoidable degree of external rotation in the whole lower limb, and the lower part of the fibula appeared behind the tibia. Therefore, a true A-P view whilst the body was in the supine position was difficult. To overcome this, a P-A view of the leg was performed with the body prone position, this allowed both upper and lower parts of the fibula to appear clearly in both views.

This method provides two true perpendicular views (P-A and lateral) and helped to optimise radiological assessment.

ACUTE OPEN CHARCOT FOOT

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Charcot foot is a form of chronic progressive destructive arthropathy affecting the bones and soft tissue of the foot. It is an important entity although rare, affecting only 0.12 – 0.3% of diabetics per year. It has a high associated patient morbidity and healthcare cost the classic presentation is the patient with acute onset red, swollen foot with poorly defined pain.

In this case we report a case of a lady who presented to the emergency department with an acute open charcot foot, with extrusion of the navicular bone. This was atraumatic, resulting from normal weightbearing. The patient was managed with excision of the navicular and skin closure and after prolonged wound care healed and maintains a stable foot. Charcot foot significantly alters the normal operative treatment for open fracture-dislocations.

Here the mainstay of treatment is offloading and soft tissue protection to avoid ulceration, which can lead to amputation. However where surgery is required corrective procedures should focus not on restoration of the normal foot anatomy but in establishing a weightbearing plantigrade foot with soft tissue cover.

Here we demonstrate that good results can be minimising surgical intervention even in apparently limb-threatening presentations.

LONGITUDINAL ASSESSMENT OF PATELLAR TENDON MORPHOLOGY ON IMAGING (MRI AND ULTRASOUND) AND VISA-P SCORES IN COLLEGIATE BASKTEBALL PLAYERS ACROSS A SINGLE SEASON

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This study of male collegiate basketball players aims to 1) assess for change in patella tendon (PT) morphology on MRI and US across a single season; 2) to correlate patella tendinopathy grade on imaging to VISA-P scores; 3) characterize non-PT related knee pathology seen on MRI.

In eleven male collegiate basketball players (mean age 19, age range 18-21), PT ultrasound and MRI of both knees were performed at pre-season and post-season time points, and players reported their VISA-P scores throughout the season. Patella tendinopathy was graded on MRI and US. Non-PT related pathology visible on knee MRI were recorded. Spearman coefficients correlated patella tendinopathy grade to VISA-P.

Imaging findings: 6 of 11 players (54.5%) had baseline patella tendinopathy on MRI and US. At post-season, progression of patella tendinopathy was seen in 1 of 6 players on MRI and 4 of 6 players on US. Post-season change in MRI and US patella tendinopathy grades were not statistically significant. New, non-PT related pathology on post-season MRI included gastrocnemius strains, medial meniscal tear, and iliotibial band friction syndrome. VISA-P: The mean change in VISA-P score was 15.18 (+/- 8.55). VISA-P scores decreased $\geq$10 points in 9 out of 11 players (81.8%). Neither MRI or US grades of tendinopathy correlated with VISA-P.

MRI and US detected changes in patella tendinopathy grade in collegiate male basketball players across a single season, although not statistically significant. Players demonstrated varied non-patella related pathology. Neither MRI nor US grades of patella tendinopathy correlated with VISA-P.

EVALUATION OF EQUINE OSTEOARTHRITIS USING VISCOELASTIC PROPERTIES OF SYNOVIAL FLUID. VARIATION BETWEEN NORMAL AND PATHOLOGICAL METACARPOPHALANGEAL SYNOVIAL FLUID

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The viscoelastic properties of synovial fluid (SF) are crucial to the performance of joint function. Lameness due to joint injury is the most prevalent cause of diminished athletic function and wastage in athletic horses. The aim of the present research was to detect the possible variation in the viscoelastic character of equine SF from normal and diseased metacarpophalangeal joints.

For this purpose, SF was aspirated by aseptic arthrocentesis from 20 Thoroughbred horses and 20 Warmblood horses and subjected to routine cytological analysis. For determining hyaluronic acid (HA) concentrations in equine SF samples, a commercially available ELISA kit was used. Moreover, full rheological sample characterization was performed in order to measure the elastic G' and viscous G'' moduli respectively, at horse's body (37.5 ºC) temperature.

The ANOVA findings indicated statistically significant main effects ($p < 0.001$) for radiographic diagnosis and breed on the mean values of HA measurements. Generally, we can observe that subjects with positive radiographic diagnosis seem to present lower HA measurements compared to the reference category (normal horses). A statistically significant main effect of radiographic osteoarthritis on the mean values of logG" ($p < 0.001$) and logG'($p = 0.004$) measurements was also noted. Horses with positive radiographic diagnosis seemed to present lower logG'' and logG' measurements compared to the reference category (normal horses).

In conclusion, values of viscoelastic properties and HA concentration of diseased metacarpophalangeal joints of Warmblood and Thoroughbred horses seem to be significantly lower compared to the ones obtained from healthy subjects.

ANATOMIC PREDICTORS OF CARTILAGE DEGENERATION USING T1ρ MAGNETIC RESONANCE IMAGING IN ASYMPTOMATIC HIPS WITH CAM MORPHOLOGY

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This study aims to determine 1. If asymptomatic hips with cam morphology are at risk of further cartilage degeneration (as evaluated by T1ρ) over time, 2. Whether T1Rho changes are predictive of symptom-onset 3. Whether bony morphological parameters are associated with T1ρ signal changes.

In a prospective, longitudinal, IRB-approved study, seventeen asymptomatic volunteers/hips [16 males; 32.9±6.0 years] with cam morphology underwent two T1ρ MRI scan and functional assessment (WOMAC) at recruitment and at 3.9 years (range: 2.2–6.3). Images were acquired and analyzed using a validated technique. The differences in T1ρ values (ΔT1ρ) and relative differences (%ΔT1ρ) were calculated as: ΔT1ρ=T1ρFollowUp–T1ρInitial and %ΔT1ρ= ΔT1ρ/T1ρInitial. A %ΔT1ρgreater than 17.6% was considered significant. Using CT data, femoral- acetabular- and spino-pelvic parameters were measured.

The global T1ρ remained unchanged between initial (mean:34.8±4.7ms) and follow-up scans (mean:33.9±3.3ms) (p=0.46). Similar T1ρ values were seen initially between the anterolateral and posterolateral (33.7ms Vs. 33.0ms) regions (p=0.7); at follow-up T1 values were significantly higher posterolaterally (35.5ms Vs. 32.4ms) (p=0.03). Two volunteers reported lower WOMAC, one of which exhibited a significant increase in %ΔT1ρ (-26.2%). The degree of acetabular coverage correlated with %ΔT1ρ (rho=0.59–0.61, p=0.002).

Although, signs of joint degeneration posterolaterally were detected, these were not on the whole associated with symptoms and only one of the 2 volunteers with the onset of symptoms had significant changes. Therefore, further study is required to define the use of T1ρ in clinical practice. Reduced acetabular coverage should be considered when stratifying hips at risk.

AN EVALUATION OF THE EFFECTIVENESS AND SAFETY OF TOTAL HIP ARTHROPLASTY AS AN OUTPATIENT PROCEDURE

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Outpatient hip arthroplasty is being performed more routinely, however safety remains a concern. The purpose of this study was to compare the adverse events rate of outpatient total hip arthroplasty (THA), and assess barriers to discharge.

We examined 136 patients who underwent unilateral THA by one surgeon and were discharged on the same day of surgery. Using propensity matching, 136 inpatients who received the same procedure, and were discharged on post-operative day one or later, were identified. For each cohort, 90-day occurrence of adverse events, readmissions, and ER visits were recorded and compared. Adverse events were graded using the Ortho-SAVES tool. A secondary objective was to assess potential barriers to same day discharge.

Within 90 days post-operatively, 12 outpatients (8.82%) and 14 inpatients (10.29%) developed an adverse event. There were no significant differences between rate or severity of adverse events between the two groups, and no serious adverse events in either group. In the outpatient group there was a correlation between the dosage of spinal anesthetic (bupivacaine) given and time required to stay in PACU post-operatively. When comparing the two groups, there were no differences in adverse events at 90 days.

At our center, in the correct patient population, outpatient THA is a safe and cost effective option. A potential barrier to mobility post-operatively, and successful same day discharge is the time required to stay in PACU post-operatively, which was significantly correlated with an increased dose of spinal anesthetic given in our outpatient cohort.

IN VIVO WEAR RATE OF HIGHLY CROSSLINKED POLYETHYLENE COMPARING RE-MELTED TO ANNEALED MANUFACTURING

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The production of highly crosslinked polyethylene (HXLPE) can be done by either a re-melting or annealing thermal treatment processes with different implications in regards to performance. The aim of this study was to evaluate *in vivo* wear and clinical performance of HXLPE liners manufactured using these processes.

Linear and volumetric wear was assessed using Martell Hip Analysis Suite, and clinical performance was assessed through patient reported outcome measures and rate of revision surgeries. Eighty re-melted and 53 annealed liners were included in the wear analysis due to radiological follow up and software-based exclusions, mean of patients was 66.

At a mean follow-up of 3.3 years, there was no significant difference (p=0.10) in total wear rate between linear wear for re-melted (0.04mm/yr) and annealed liners (0.01mm/yr). There was no significant difference (p=0.30) in annual volumetric wear between re-melted (43.01mm^3/year) and annealed liners (46.95mm^3/yr). No hips were revised due to liner related complications and patient reported outcome measures were comparable between groups.

Results from this study suggest that both thermal processes are valid options for improving the longevity of total hip replacements.

THE EFFECT OF SURGICAL RESECTION OF HIP IMPINGEMENT DEFORMITIES: A WITHIN-PATIENT EXPERIENCE

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Femoracetabular impingement (FAI) involves abnormal contact in the hip due to deformities and is associated with osteoarthritis. Bone mineral density (BMD) in the acetabulum is higher in subjects with convex femoral (cam) FAI deformities compared to control subjects. The objective of this study was to assess post-operative changes of BMD with and without surgical correction of the cam deformity.

Thirteen patients with bilateral cam deformities underwent pre-operative and follow-up CT scans of both hips. The deformity was surgically removed from the symptomatic hip. BMD was measured in regions of interest around the superior acetabulum from CT scans at both time points. The contralateral untreated hip was used as a within-patient control. Changes in BMD were assessed by two-way repeated measures ANOVA (side, time) and paired t-tests.

A greater BMD decrease was seen in the treated compared to the untreated hip ($p<0.02$). BMD within the superior acetabulum decreased by 7.1% on the treated side ($p<0.0001$) but only 3.2% ($p=0.04$) in the untreated contralateral hip. In the antero-superior rim where impingement primarily occurs, the decrease was -7.5% in the treated hip ($p=0.0002$) and -2.7% ($p=0.1$) in the untreated hip. BMD decreased in the treated hip, suggesting a positive effect of surgical correction in relieving stresses within the hip joint.

Longer term follow-up is required to assess the ultimate fate of the articular cartilage within the joint. This study showed that surgical correction of the cam deformity in patients with FAI may alter the pathological biomechanics within the joint.

ESTABLIHING 'THE REASONABLE PATIENT'S' EXPECTATION OF 'MATERIAL RISKS' TO BE DISCLOSED WHEN CONSENTING FOR TOTAL HIP ARTHROPLASTY

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'*Montgomery v Lanarkshire Health Board*' is the current landmark legal trial introducing a profound shift from a 'reasonable doctor' approach to an emphasis on 'the reasonable patient' when determining sufficient risk disclosure during the consent process'. A critical component of valid consent is disclosure of 'material risks' to the patient regarding the procedure. This study aims to establish 'the reasonable patient's' expectation of 'material risks' to be disclosed when consenting for total hip arthroplasty (THA).

A questionnaire conveying the risks and incidence of undergoing a THA was distributed to patients undergoing THA to complete to establish which risks they felt were 'material'. Patients were asked their preference about how these risks should be communicated. 60 patients met inclusion criteria. The median patient age was 71(range 42-84). 82% of patients lacked third level education.

No statistically significant correlation was found between educational level, religion or income and specific 'material risks'. 87% of patients chose discussion with their surgeon as their preferred method of risk information. The remainder preferred a leaflet or to attend a day at 'joint school'. 12% of patients would rather not be made aware of any risk prior to surgery while 55% wished to know all risks. 84% of patients determined 1 in 100 risk as the ceiling to which they would wish for risks to be disclosed.

This patient cohort demonstrates gross heterogeneity in what patients determine as 'material risk'. We recommend disclosure of all risks known to the surgeon to each patient to account for such heterogeneity.

PERIPROSTHETIC FRACTURE FOLLOWING FIRST METATARSOPHALANGEAL JOINT ARTHRODESIS IN PATIENTS WITH OSTEOPAENIA

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First metatarsophalangeal (MTPJ) arthrodesis is an effective treatment for hallux valgus with arthritis with success rates of 77-100%. The incidence of peri-prosthetic fracture following first MTPJ arthrodesis is largely unknown. These are the among the first documented cases of peri-prosthetic fracture following first MTPJ arthrodesis to the best of our knowledge.

We present three patients on long term steroid therapy for systemic disease with hallux valgus and first MTPJ arthritis who underwent first MTPJ fusion using a dorsal anchorage plate and screws™, and a plantar fixos lag screw™. All patients who developed a peri-prosthetic fracture post-operatively had reduced bone quality noted intra-operatively. The fractures appear to be related to a stress riser effect given their pattern and location. The fractures healed uneventfully and both patients have had a subsequent uneventful post-operative course at a minimum of one year follow up. Ultimately we feel caution is appropriate when treating this patient cohort.

Pre-operative pharmacotherapy optimization with the rheumatologist should be considered. Bone health should be assessed and optimized. It can be surmised that using a longer dorsal plate to increase the load sharing of the construct may decrease the incidence of this complication. Alternative surgical interventions such as first MTPJ resection arthroplasty could be considered. Other considerations include adjusting the weight-bearing regimen post-operatively, allowing earlier unrestricted weight-bearing or more gradual increments to full weight-bearing.

More research is required to ascertain the most appropriate fixation method and weight-bearing regimen for patients with systemic disease and decreased bone quality with hallux valgus and first MTPJ arthritis.

ADDITIVELY MANUFACTURED BIODEGRADABLE POROUS IRON

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Topologically ordered, porous additively manufactured (AM), metallic biomaterials with proper biodegradation profile offer a rare combination of properties ideal for bone regeneration: an interconnected porous structure, bone-mimicking mechanical properties, and the potential to fully regenerate bony defects. While the majority of such biomaterials is based on magnesium, and thus degrading fast, we used Direct Metal Printing (DMP) to generate topologically ordered porous iron scaffolds based on a repetitive diamond unit cell.

Our full-scale study comprises *in vitro* biodegradation behavior (up to 28 days), electrochemical performance, time-dependent mechanical properties, and biocompatibility of such scaffolds. Mechanical properties of AM porous iron (E = 1600-1800 MPa) fell within the range of values reported for trabecular bone even after 4 weeks of biodegradation.

Electrochemical tests showed up to ≈12 times higher rates of biodegradation for porous iron as compared to cold-rolled (CR) iron. Only 3.1% of weight loss was measured after 4 weeks in immersion tests, while biodegradation mechanisms were found to be topology-dependent and different between periphery and central parts of the scaffolds. Cytotoxicity according to ISO 10993, was evaluated in static MG-63 culture and compared to Ti-6Al-4V, for up to 72 h.

Our study shows that DMP holds potential to increase the surface area and decrease grain sizes of topologically ordered porous iron, a metal that usually is considered to degrade too slowly. Our approach thus paves the way for developing novel biodegradable biomaterials.

TREATMENT OF KNEE OSTEOARTHRITIS WITH CONCENTRATED ADIPOSE TISSUE INFUSION: CLINICAL RESULTS AND HISTOLOGICAL OBSERVATIONS

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Osteoarthritis (OA) is characterized by articular cartilage degeneration and subchondral bone sclerosis. Early OA begins as a focal damage; thus, its repair is envisioned to spare the joints from further degeneration and resume pain free movement. OA may benefit from non-surgical treatments based on articular infusions of adipose tissue derived-Stromal Vascular Fraction (SVF) or -mesenchymal stem cells (ASCs).

Since both cultured-expanded ASCs and collagenase-isolated SVF need manipulation in laboratory setting, we investigated the possibility to reduce lipoaspirate manipulation using autologous concentrated adipose tissue, injected intra-articularly in the knee. The infusion of concentrated adipose tissue resulted safe, and all patients reported an improvement in term of pain reduction and function increase (VAS and WOMAC scores), even though the MRI evaluation was unable to detect augment in the thickness of cartilage.

SVF and ASCs isolated from adipose tissue samples were cultured *in vitro* in standard conditions and plated on a composite bone scaffold, showing capabilities to differentiate into osteoblasts and chondrocytes upon stimulation. Immunohistochemistry performed both on bone scaffold and on knee joint intra-operative biopsies of patients, who underwent joint prosthesis, showed new tissue formation close to the osteochondral lesions.

Overall our data indicate that concentrated adipose tissue infusion can stimulate tissue regeneration and might be considered an innovative and safe treatment for knee osteoarthritis, to place side by side to arthroscopy.

IS OSTEOARTHRITIS A VASCULAR DISEASE?

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OA pathophysiology has a vascular component consisting of venous stasis resulting in intraosseous hypertension and hypoxia. In response, osteoblasts change their cytokine expression, accelerating bone remodelling and cartilage breakdown consistent with OA.

We have characterized circulatory kinetics in OA bone in animal models with dynamic contrast enhanced MRI (DCE-MRI) and ^{18}F PET and have demonstrated venous stasis and reduced perfusion that temporally precede and spatially coincide with OA lesions.

Osteoblast uptake of ^{18}F is consistent with abnormal perfusion, bone remodelling, and severity of OA. Circulatory kinetics with DCE-MRI in humans with OA of the knee exhibit similar venous outflow obstruction. Venous stasis is associated with hypoxia in subchondral bone. As an example of the effects of hypoxia on OA osteoblasts, we have described upregulation of fibrinolytic peptides, but a deficiency in the upregulation of PAI-1, leading to the generation of plasmin by human OA osteoblasts exposed to hypoxia *in vitro*. Plasmin is a serine protease that has been shown to degrade cartilage in OA. Abnormal circulatory kinetics by DCE-MRI may be an imaging biomarker of OA.

Pharmacologic modulation of venous stasis would have a salutary effect on the physicochemical microcirculation of subchondral osteoblasts and the pathophysiology of OA.

THE EFFECTS OF TREADMILL EXERCISE AT A SINGLE TIME ON KNEE ARTICULAR CARTILAGE *IN VIVO*

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The purpose of this study was to investigate the metabolism of articular cartilage in knees of rat treadmill exercise at a single time and to elucidate the role of HIF-1,2α in exercise.

Twelve-week-old male Wistar rats ran on a treadmill at 12 m/min or 20 m/min for 45-mins at a single time. Rats in control group were kept sedentarily. All were sacrificed after running. Total RNA was extracted from right knee cartilage. We analyzed gene expressions regarding cartilage metabolism with quantitative RT-PCR. Left knee of each group was stained with immunostaining for HIF-1,2α.

Almost all gene expression in the 12 m/min group didn't change compared with control group. Gene expressions of sox9 and ADAM-TS5 in the 20 m/min group was increased. In immunostaining, HIF-1α was more strongly stained in the 12 m/min group than in the control group. HIF-2α was more strongly stained in the 20 m/min group than in the control group, but weakly stained in the 12 m/min group. Twelve m/min running on treadmill at a single time did not adversely affect the gene expression of homeostasis on articular cartilage except for production of HIF-1α. On the other hand, the results of 20 m/min group show that cartilage metabolism was activated from the early stage with excessive exercise. Moreover, HIF-1,2α production in articular cartilage was changed according to running speed.

These results indicate that HIF-1α and HIF-2αmay regulate in the balance of cartilage metabolism on exercise.

FINANCIAL IMPACT AND EFFECT ON THE OUTCOME OF PREOPERATIVE TESTS FOR AT-RISK OLDER HIP FRACTURE PATIENTS

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Older patients with proximal femoral fractures often undergo preoperative tests due to coexisting morbidities. Our aim was to evaluate these tests and their impact on patient outcome and medical expenses.

This retrospective study includes data on head computed tomography, carotid ultrasound, echocardiography and pulmonary functional tests calculated according to the type of surgery (osteosynthesis or hip arthroplasty) carried out on 2798 patients. Time-to-surgery, test repeated postoperatively, American Society of Anesthesiology Physical Status score, additional procedures, hospitalization time, 30-day mortality and associated medical expenses were evaluated. A total of 921 preoperative tests were carried out in 780 (28%) patients, and 375 postoperative tests were carried out in 329 (12%) patients ($P < 0.001$). A total of 23 procedures were carried out after surgery, none related to the originally carried out tests.

Significant group differences were found for American Society of Anesthesiology Physical Status score, days to surgery, hospitalization time (days) and mortality rates. The medical expenses of these tests were 1.3% of the average income per case, and 0.6% of the average study group income.

Non-routine preoperative tests prolong time-to-surgery, increased hospitalization time and contribute to 30-day mortality. No postoperative procedure was related to preoperative test findings. The financial cost for these tests does not burden the medical expenses per procedure.

ELECTROSPINNING-BASED MODULAR CONSTRUCTS FOR TENDON AND CARTILAGE TISSUE ENGINEERING

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Tissue engineering holds a great potential in tendon and cartilage regenerative medicine strategies, since the traditional methods of repair for injuries of these tissues have disadvantages that can deter their long-term effects. To achieve production of tendinous or cartilaginous tissue, scaffolds must provide a desirable 3D environment. where tenocytes and chondrocytes respectively will deposit their tissue-specific extracellular matrix. The electrospinning process has been used to produce nanofibrous scaffolds for various musculoskeletal tissues including cartilage tendon and ligament.

In this work two commercially available polymer materials, a) BIOSYN®: poly (glycolide -co- dioxanone -co- trimethylene carbonate) and b) MAXON®: poly (glycolide-trimethylene carbonate) were used to fabricate electrospun scaffolds. The structural, mechanical and thermal properties were assessed with electronic microscopy, uniaxial mechanical testing and differential scanning calorimetry (DSC) respectively.

Human chondrocytes and tenocytes were expanded up to passage 3 in DMEM media, supplemented with 10% fetal bovine serum and 1% penicillin / streptomycin. 50,000 cells / cm^2 were subsequently cultured for up to 14 days. Cell viability and metabolic activity was assessed using Live/Dead® and alamarBlue® assays respectively. Cell morphometric analysis was carried out using DAPI and Rhodamine conjugated Phalloidin and subsequent image analysis (ImageJ). Extracellular matrix deposition was assessed with immunocytochemistry.

A MINIMUM OF 10-YEARS FOLLOW-UP OF FEMORAL REVISION WITH THE WAGNER TAPERED STEM

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Reconstruction of severely deficient femoral bone stock is a critical issue in hip revision surgery. The present study evaluates retrospectively the long-term clinical and radiographic outcome of the cementless Wagner Self-Locking (SL) stem. From September 1992 to March 1998, 68 hips (66 patients) with extended femoral bone loss underwent revision using the Wagner SL stem.

Twenty-six patients died of unrelated causes without additional surgery. Forty hips were available for clinical and radiographic follow-up evaluation at a mean follow-up of 13.9 years (range, 10.4-15.8) after surgery. There were 11 male and 29 female patients, with an average age of 61 years (range, 29-80). In 31 hips a transfemoral approach was performed. In 5 cases stem revision was required because of infection (2), progressive subsidence (2), and recurrent dislocation (1). Complications included dislocations (3) and subsidence ≥ 10 mm (8).

The mean Harris hip score improved from 33.0 points preoperatively to 73.3 points at follow-up ($p < 0.001$). In 32 stems (91.4%) radiological signs of stable bone fixation were assessed. The cumulative survival rates at 15.8 years with femoral revision for any reason and for stem failure as the end points were 92.0% and 96.6%, respectively.

Revision of severe proximal femoral bone loss is a technically demanding procedure because of the difficulty in obtaining the primary stability of the new prosthesis. The tapered and fluted Wagner SL stem, by means of a stable distal fixation, enables restoration of periprosthetic bone stock ensuring highly successful long-term outcomes.

A MINIMUM OF 10-YEARS FOLLOW-UP OF FEMORAL REVISION WITH THE WAGNER TAPERED STEM

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Hip resurfacing has conventionally been undertaken through a posterior approach, but recent investigations expressed concerns with the damage of capsular blood supply. To date, few papers have reported only preliminary outcomes of surface arthroplasty performed through alternative approaches. This retrospective study evaluates the mid-term clinical and radiographic results of current generation metal-on-metal resurfacing prostheses performed using an anterolateral Watson-Jones approach.

Fifty-seven hips in 52 patients underwent metal-on-metal resurfacing arthroplasty. Two patients died from unrelated causes, leaving 55 hips in 35 males (3 bilateral) and 15 females (2 bilateral), with a mean age of 56 years (range, 27-70). Clinical and radiographic follow-up was carried out in all the cases. The cumulative survival rate was determined according to Kaplan-Meier. At a mean follow-up of 5.2 years (range, 2-9.2), 2 hips required revision because of early aseptic loosening of the acetabular component and were successfully converted to conventional arthroplasty.

Average Harris hip score improved significantly from 59.8 points (range, 30.4-90.6) preoperatively to 93.7 points (range, 53-100) at the latest examination. Neck narrowing showed an average of 3.27%, but it never exceeded 10%. Nonprogressive acetabular radiolucencies and osteolysis were detected both in 2 hips. The cumulative survival rate at 9.2 years with revision for any reason as the end point was 93.0%.

Medium-term clinical and radiographic results of modern metal-on-metal hip resurfacing performed through an anterolateral approach are promising, but longer-term evaluation is necessary. A rigorous patient selection is essential to minimize the risk of complications and prevent early failure.

DOCUMENTED DIFFERENCES IN PRE-OPERATIVE PAIN SUBTYPES AND OUTCOME EFFECTS IN KNEE REPLACEMENT PATIENTS

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The main indication for knee replacement surgery is pain in an arthritic knee. Various factors such as anxiety and depression have been noted as predictors of poor outcome in knee replacement surgery, and overall post-surgical pain is the most common problem affecting the knee replacement patient population. The primary focus of industry and surgeons has been centred on implant design and morphology. Our clinical observation suggested patient related pre-operative factors may be as important, and we therefore created a pain diary to identify pain sub-types and track how these patients faired post-surgery. A consecutive series of patients were counselled about the pain diary at pre-operative assessment as asked to complete it. From a patient group of 148, we obtained 85 completed pain diaries, who's data we analysed. Within this group the mean age was 67 and there was a 2.3 female to 1 male ratio. Sixty three patients had a total knee, 22 a partial unicompartmental replacement. The somewhat startling finding was that 1/3 of patients in both the total and partial knee groups had some form of atypical neuropathic pain, anxiety, depression or some combination, pre-operatively. We found differences within these sub-groups eg more isolated neuropathic pain in the partial knee group and more combined anxiety, depression and neuropathic pain in the total knee groups. These differences produced subtle differences in 6 month knee score outcomes when compared to the typical pain group, but none in the atypical group attained the highest knee scores of over 90% of normal. The risk of having neuropathic pain post-operatively was also higher in this group. We conclude that routine mapping and qualification of pain subtypes pre-operatively is important for patients and surgeons, and patients should be counselled as to their expectations based on this. It also confirms that there is diagnostic complexity in what has been previously considered a straightforward diagnosis, such that some patients with painful knee replacements are having unnecessary or non-useful surgery.

APPLICATION OF COMPLEXITY SCIENCE PRINCIPLES TO CLINICAL ORTHOPAEDIC PRACTICE. THE SWINDON COMPLEXITY SCORE

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Complexity science is based around the study of the interaction of factors to predict potentially unpredictable, so-called emergent events. Other features of complexity and complex adaptive systems include non-linearity, feedbacks, self-similarity and scalability. This is in contra-distinction to Newtonian, deterministic models of behaviour often focusing on one agent or factor, and reliance on an average parameter, of which the medical model is an example. Use of fractal analysis has transformed the understanding of natural science subjects, and in medicine has thus far centred on cardiac and cancer basic science studies.

Over the past 10 years we have undertaken a number of clinical assessments based on clinical complexity and the interaction of just 2 factors namely local and systemic complexity, generating a 4 part classification, in a 2x2 matrix. We have undertaken such studies for both elective and trauma conditions and found statistically significant differences between the most complex groups and straightforward patients in a variety of parameters ranging from complication and mortality rates, speed and degree of recovery and ability of more junior surgeons to undertake complex case surgery. We specifically present our results in total knee replacement surgery, which also shows a statistically significant difference between the most straightforward and most complex cases at 1 year. Additionally our observations of complexity have also highlighted differences in patient presentation, which we would describe as diagnostic complexity.

The summation of our results suggests we look more closely at the principles of complexity science, as this may provide an alternative methodology and be more accurate than present modelling of healthcare outcomes and delivery and at the same time demonstrating which additional data we need to collect. Stratification of clinical complexity of a single diagnosis or index operation using this methodology seems so far to have almost universal applicability and may help us to define and deliver optimal, efficient and tailored high-quality healthcare into the future. It is also likely to explain the present mis-match between current data and expected costs and delivery targets and is likely to be applicable to analysis of entire departments and entire organisations. Analysis based on complexity theory will lead to a paradigm shift in how we map healthcare into the future

CONFIRMATION OF HLA-B27 TRANSGENIC RATS AS A SPONDYLOARTHRITIS MODEL

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The spondyloarthritis (SpA) are inflammatory diseases of the eye, intestinal tract, genitalia and skin. Taurog *et al*. developed HLA-B27-Transgenic rats mating with human β2-microglobulin as a SpA model. The final goal of our research is to develop more effective therapy for SpA. Based on the previous paper by Taurong *et al*., we established transgenic rats by crossbreeding between 21-3 rat transgenic line (with 20 transgene copies of HLA-B27 and 15 transgene copies of human β2-microglobulin: hemizygous) and 283-2 rat transgenic line (with 35 transgene copies of $h\beta_2m$: homozygous).

We identified that 34 rats out of 54 rats has transgene successfully (with 20 transgene copies of HLA-B27 and 50 transgene copies of human β2-microglobulin), analyzed by genotyping technique. The male rat with HLA-B27/$h\beta_2m$ transgenes (21-3 x 283-2) began to exhibit SpA like phenotype (Epididymoorchitis, Arthritis, or Spondylitis) from 100 days after birth.

We scored and classified the phenotypic severity based on paw thickness, tail swelling and size of epididymis every 4 weeks from 100 days to 250 days. Finally, scoring evaluation, X-ray and immunohistological analysis suggested that male HLA-B27/$h\beta_2m$ transgenic rats (21-3 x 283-2) had severe arthritic phenotype. In conclusion, we established the model rat exhibiting strong SpA-related phenotypes by cross-bleeding transgenic rat with transgenes HLA-B27 and $h\beta_2m$ for further experimental utilization.

CLINICAL RESULTS OF AN INDIVIDUALISED MINI-METAL IMPLANT FOR FOCALCARTILAGE LESIONS IN THE KNEE

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We report prospective detailed results of patients undergoing treatment for chondral defects using a patient specific 2nd generation individualized mini-metal implant. Prospective analysis of sequential patients from 11 surgeons. Detailed specific MRI data was used to manufacture patient specific implants and guide instruments by a CAD/CAM process, to fit the unique anatomy of each individual knee.

Implants were uncemented and made of chrome-cobalt, double coated with hydroxyapatite on top of Titanium. Demographic, operative and clinical scores (VAS and KOOS) were collected preop and at 6 months, 1 and 2 years postoperatively. 92 patients (46 men, 46 women) with focal cartilage lesions ICRS grade 3 or 4 underwent partial resurfacing, 75 on medial condyle, 6 lateral condyle and 11 on trochlea. Mean age 49 (27-69) years, mean BMI 29 (21-41). 30% had failed previous cartilage surgery. 2 patients (4.5%) underwent revision (at 9 months for infection and at 30 months for progression of arthritis). All mean KOOS domain scores were significantly improved at 1 and 2 years ($p<0.05$). Mean preoperative aggregated KOOS (38) improved to 62 at 12 months and 60 at 24 months ($p<0.05$). Mean VAS score improved from 62 preoperatively to 37 at 24 months.

The study shows excellent early clinical results in the treatment of focal full thickness symptomatic cartilage lesions on the femoral condyles or trochlea with a second-generation patient specific metal implant and cutting guides. Adherence to strict indications has allowed for high patient reported scores and low early revision rate.

THE EVALUATION OF RELIABILITY IN QUADRANT METHOD FOR THE EVALUATION OF FEMORAL TUNNEL POSITION AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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The Quadrant method is frequently used the evaluation for femoral tunnel position after ACL reconstruction. It was drawn a line along Blumensaat's line. But Blumensaat's line was known it was not straight. The purpose of this study was to be defined a line on 3DCT for each variation of Blumensaat's line and evaluated the Quadrant method for the femoral tunnel position.

40 patients underwent anatomical double bundle ACL reconstruction using out-side -in technique. 3D-CT photographed within 2 weeks after surgery and we observed the intercondylar lateral wall. We classified it as straight type (ST), large hill type (LA), small hill type (SM) according to the classification of Iriuchishima. Then we defined the Blumensaat 's line, which becomes the reference line, as the S-line matching the line ahead of the condyle. It was also defined as H-line matching the tangent at the apex of Hill. In ST, only S-line was used. In each case, femoral tunnel positions of anterior medial bundles (AMB) and posterior lateral bundles (PLB) was evaluated.

In the shallow-deep directions, there was no significant difference between the 3 groups on the S-line and H-line. In the high-low directions, there was no significant difference between the 3 groups on the S-line. But in the high-low directions, a significant difference was observed between ST and LA and ST and SM in the H line. Quadrant method showed a difference in the value due to the difference in the definition of the Blemensaat 's line which is the reference line.

INTRAMEDULLARY PIN STABILITY AFFECTS THE PATTERN OF FRACTURE HEALING IN MICE WITH DIFFERENT SIZE MARROW CANALS

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Mouse models have been created with genetic deficiencies to imitate human inherited bone diseases and are used to examine molecular mechanisms of bone repair. Despite the well documented importance of the mechanical environment during bone healing, hypodermic needles are currently used to stabilize fractures that do not provide appropriate mechanical stability. Although inserting one of these devices is technically easy, their mechanical stability is very poor.

This is particularly important when age, genetic background, or gene alterations result in differently sized marrow canals. For instance, a hypodermic needle implanted in a mouse that has a bigger marrow canal will result in an unstable fixation and will heal with greater callus formation, whereas bones with a smaller canal will result in a more stable fixation and therefore smaller callus size. Regrettably, numerous studies can be found using various mouse models that have attributed a different pattern of fracture healing to the function of the specific gene or genetic variation, when in fact it is highly probable that the fixation stability played a more important role.

The latest findings will be presented to demonstrate the effect of fixation stability on the healing of closed fractures in mice with different sized marrow canals.

EFFECTS OF ACETABULAR ABNORMALITIES ON THE FRACTURE SITE OF NON-TRAUMATIC SUBCHONDRAL FRACTURE OF THE FEMORAL HEAD

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Based on the hypothesis that mechanical stress induced by acetabular abnormalities may affect non-traumatic subchondral fracture of the femoral head (SF), we compared fracture sites in non-traumatic SF between acetabular dysplasia and retroversion.

We examined 13 consecutive non-traumatic SF patients with dysplasia and 14 patients with retroversion. Dysplasia was evaluated by the presence of a lateral center-edge angle of <20° on radiographs. Retroversion was evaluated by the presence of a crossover sign or posterior wall sign on radiographs. Both mediolateral and anteroposterior location and extent of SF were evaluated by measuring each edge of low-intensity bands on all coronal-slices of T1-weighted MRI. Stress distribution on femoral head cartilage was evaluated in contralateral unaffected hips with same acetabular abnormality using finite element modeling.

Medial edge of SF in retroversion was medially located compared to that in dysplasia, while there was no significant difference in locations of both lateral and anteroposterior edges of SF between the two groups. Mediolateral extent of SF in retroversion was significantly larger than that in dysplasia, while there was no significant difference in anteroposterior extent of SF between the two groups. Contact stress in retroversion was widely distributed from lateral edge of acetabular rim to medial region, while that in dysplasia was concentrated on lateral edge of acetabular rim.

This study demonstrated that both the mediolateral location and extent of SF differ between hips with acetabular dysplasia and retroversion due to different stress distribution, suggesting that acetabular morphology can affect the fracture site of non-traumatic SF.

HISTOLOGICAL EVALUATION OF TREADMILL RUNNING ON KNEE JOINT OF RAT ARTHRITIS MODEL

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Exercise therapy is widely used and effective against various diseases. However, the indication for rheumatoid arthritis (RA) is unclear because the progression of synovitis and cartilage degeneration are concerned. The purpose of this study is to evaluate the effects of treadmill running on the knee joint in the rat arthritis model histologically.

Collagen-induced arthritis (CIA) rat was prepared using 8-week old male DA rat as arthritis model and divided into 4 groups: control (CIA -, treadmill -), treadmill (CIA -, treadmill +), CIA (CIA +, treadmill -), and CIA treadmill (CIA +, treadmill +) group. Each rat in treadmill and CIA treadmill group was forced running at 12m/min and 30 min/day from 10-week old and sacrificed 4 weeks later. Both knees were extracted. The right side was stained with safranin O, and the left was immunostained by connexin (Cx) 43.

The safranin O staining was lower in the CIA and CIA treadmill groups and was the lowest in the CIA treadmill group. Immunohistochemical staining for Cx43 increased in the synovium of CIA group but decreased in the CIA treadmill group. Although the treadmill running at 12m/min has chondroprotective effects in normal rats, degeneration has progressed in CIA rats.

The mechanism of cartilage degeneration in CIA rats may differ from in normal rats. Moreover, treadmill running may suppressed synovitis, based on the results of Cx43 immunostaining. Appropriate intensity exercise should control synovitis and cartilage degeneration simultaneously.

INFECTIONS ARE INCREASED AS THE CAUSE OF REVISION TOTAL HIP ARTHROPLASTIES IN THE SUPER-AGING AREA IN NORTHERN JAPAN

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Northern part of Japan is a head of the super-aging society, and the rate of it already reached 30.8% in 2016. Along with aging society, rapid increase of revision total hip arthroplasties (THAs) with primary THA has been predicted. The aim of this study is to estimate the trend of revision THAs in our super-aging area in Northern Japan.

Trend on number and rate of primary and revision THA in one of the local area of leading super-aging society were surveyed in the last decade using the database of diagnostic procedure and surgical records from 2004 to 2015. The cause of revision THA was analysed in 2004-2009 versus in 2010-2015. Spearman's rank-correlation coefficient and student's t-tests were performed using the PASW 25 software.

The data revealed 24,822 cases of orthopaedic surgery, including 3,905 primary and 405 revision THA from 2004 to 2015. All THA increased from 282 cases in 2004 to 450 in 2015 year by year. The revision contained 300 aseptic loosening, 69 infections and 36 dislocations. The value of infections and dislocations as cause of revision THA in the latest six years (2010-15) was larger compared to the value in the former six years (2004-09) (2.0 and 1.6 times, $p<0.05$).

The number and rate of revision THA with primary THA increased annually, because of expansion of elderly people in the super-aging society. The number of revision THA due to infections or dislocation may be still increasing year by year.