# ROUNDUP360

## Research

*For other Roundups in this issue that cross-reference with Research see: Hip & Pelvis Roundup 8; Spine Roundup 5; and Trauma Roundup 2.*

### Demineralised bone matrix not as good as we thought?

**x-ref Spine, Trauma**

There is controversy surrounding biologic agents in the achievement of bone fusions and treatment of bony defects. The increase in popularity of the BMPs and other biologic agents has given rise to some difficult decision making, balancing the potential therapeutic benefit against a relatively poorly described side-effect profile and increased costs associated with each agent. There are a range of products that act as BMP substitutes, many of which are processed allografts rather than recombinant products. One of the difficulties associated with decision making surrounding biologic agents in bone substitutes is that there are few comparative clinical or pre-clinical studies examining the various agents available. A basic science research team from **Farmington (USA)** have shed some light on this potentially awkward topic with their recent study.[1] They designed a simple science study with the intention of evaluating the osteoprogenitor cell response to both to rhBMP-2 and demineralised bone matrix (DBM). The research team selected a transgenic mouse model with a critical-sized defect and evaluated the effects of the two bone graft substitutes using a combination of pre-osteoblastic (Col3.6GFP topaz), osteoblastic (Col2.3GFP emerald) and a marker of myofibroblast activity (α-SMA-Cherry). In addition to the tissue expression markers, the investigators used radiographic and histologic studies of bone defect healing. The study consisted of 90 mice (30 DBX, 30 rh-BMP2, 30 controls) with the headline result being that in the rh-BMP-2 model all defects were found to heal while just 10% in the DBX group (n = 3/30) and 7% (n = 2/30) in the control group healed. Quantification of the osteogenic activity in both groups of mice demonstrated an osteogenic response at seven days in the rhBMP-2 group only. This study reported a very limited osteogenic response in the control group and DBM group with no visible radiographic or histologic healing of the defect in the majority of cases. This is in contrast to the BMP group where all healed and there were significant differences in the elicited osteogenic response with the rhBMP-2 group outperforming the other two groups. This has implications for bone graft substitutes.

### Trunk control following ACL reconstruction

**x-ref Knee**

One of the potentially unresolved and interesting issues surrounding ACL reconstruction is the potential ramifications for proximal joints. There is a focus on outcomes surrounding the knee, but the abnormal hip and trunk kinematics are also seen in patients with knee instability. Surgeons in **Lexington (USA)** have looked at ACL reconstruction from this different and interesting angle of assessing resolution (or otherwise) of proximal joint abnormalities.[2] The study group performed a comparative case study between 20 women who had undergone ACL reconstruction and 20 healthy individuals. The study team assessed their outcomes using kinematic measures of abduction and external rotation strength, a trunk control test, and instrumented gait evaluation during running. There were no differences in any of the comprehensive kinematic analyses undertaken by the study team, aside from the increased ipsilateral trunk lean, forward lean and higher errors on the trunk stability test, however, hip strength was equal between both groups. Although there are no significant differences in the gross overall function, it is disappointing to find that there are persistent changes in trunk stability following ACL reconstruction that do not appear to be addressed by the standard post-operative rehabilitation programmes – perhaps physiotherapy regimes should be altered to address this in line with the findings of this study.

### Subclinical thyroid dysfunction: not quite subclinical?

**x-ref Hip & Pelvis, Trauma**

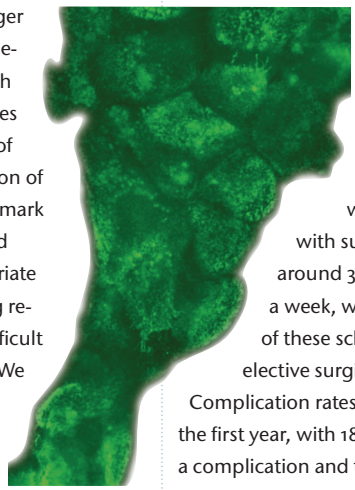
The interest in improving outcomes in treatment of predisposing pathology and future prevention of fragility fractures is at an all-time high. The comprehensive joint care pathways have reduced mortality following hip fracture, and bone health assessments have a significant impact on long-term patient outcomes. Taking a more holistic view to these fragile patients has yielded renewed interest in vitamin D supplementation and other bone health interventions. A research group in **Lausanne (Switzerland)** has added further momentum to the osteoporosis prevention bandwagon.[3] They set out to ascertain if there was an establishable association between subclinical thyroid dysfunction and fractures. They conducted a large review of over 50 years of published papers indexed on Medline and EMBASE. Their search strategy identified just seven papers that included data on thyroid function and fracture outcomes, however, these seven papers were large population-based cohort studies and, as a result, the review article includes the results of 50 245 patients. Although the study populations were heterogeneous the population did include 1966 hip and 3281 non-spinal fractures. The analysis included a random-effects model and the patients' surgeons were able to include five higher quality studies in this which estimated the pooled adjusted hazards ratio of fracture in those with 'subclinical hyperthyroidism' as 1.38 for hip fractures and 1.20 for non-spinal fractures, although the confidence limits for both of these estimates crossed. When considering the wider population of all seven studies and excluding those patients who were receiving thyroxine replacement, the hazards ratios

jumped to 2.16 and 1.43, respectively. While it is impossible to account for the difficulties with selective reporting, heterogeneous study populations and adjust for all the potential confounders, there is enough evidence out there to suggest that it is more likely than not that subclinical hypothyroidism is associated with an increased fracture risk and, as such, treating clinicians should be aware of this potential cause of increased risk for fragility fractures in their patient populations.

### Establishing musculoskeletal function in mucopolysaccharidosis

x-ref Children's orthopaedics

There is very little known concerning the longer-term and baseline musculoskeletal function in patients presenting with mucopolysaccharidosis (MPS), and given the rarity of the condition a lack of baseline data can considerably hamper research efforts into potential interventions to maximise function – randomised controlled trials or even comparative cohort studies are not feasible nor ethical in many situations and then investigators must rely on baseline population functional data to establish their outcomes. The problem with MPS is there aren't any! Researchers in **Seattle (USA)** have given MPS research a boost by setting up a baseline functional outcomes study with the intention of establishing baseline functional data using the Pediatric Outcomes Data Collection Instrument (PODCI).[4] Unlike the majority of conditions, due to the rarity of MPS, this series consists of 25 patients (a large sample for MPS) with a spread of subtypes; four Hurlers, seven Hunters, four Morquios and one Maroteaux-Lamy. The differences in PODCI were estimated between the groups and compared with normal children, demonstrating impairments in all domains in the MPS subgroups (bar upper limb function in Maroteaux-Lamy syndrome). There were significant differences between the groups with regard to upper extremity and physical function scales, the highest scores being achieved by the Maroteaux-Lamy patient with the Hurler group outperforming the Hunter syndrome children. This is the first paper to investigate at all the functional impairment with regard to MPS syndromes and the effects in the longer term on musculoskeletal function. Although only a small case series this paper is worthy of inclusion in this edition of *360* as it sets a benchmark for these children and illustrates an appropriate approach for starting research in rare and difficult to study conditions. We applaud the authors for their thoughtful and careful approach to this complex problem.



### Starting out: a first year in consultant practice under the spotlight

x-ref Hip & Pelvis, Knee, Foot & Ankle, Wrist & Hand, Shoulder & Elbow, Spine, Trauma, Oncology, Children's orthopaedics

Like many things in life, starting as a consultant (or attending) doctor can be a daunting and challenging time, particularly in subspecialty practice. It is reasonable to suppose that the average surgeon increases the complexity of cases they do during their first year, and that their complication rates fall and outcomes improve. Despite all the changes to and emphasis on safety and modernising surgical training, there is surprisingly little known about how surgeons (and their patients) fare during this first year. Using paediatric orthopaedics as a model, a research team in **Atlanta (USA)** studied the transition from fellowship to practice in five paediatric orthopaedic surgeons in the US.[5] The surgeons were all fellowship trained and the study team undertook a retrospective of their first year in practice, paying particular attention to clinical volume, surgical cases, complications and healthcare provider. The five surgeons in the study performed a total of 1172 cases (an average of 234/year or 19.5/month). As would be expected in the first year of practice almost half (42.3%) of patients were government insured or uninsured. Clinic workload was significant, with surgeons seeing around 30 new patients a week, with just 10% of these scheduled for an elective surgical procedure. Complication rates were high in the first year, with 18% sustaining a complication and the majority being minor (19% of complications were major). The vast majority of the workload during this first formative year consisted of fracture care and management of infection with very few elective surgical interventions. This paper highlights the difficulties faced by senior surgeons starting in consultant practice, even when they have undertaken fellowship training. With few elective cases on their workload and the majority of cases being the result of emergency presentations, perhaps how surgeons start in their practice and are supported by their peers may need some re-examination. In the days of increased surgical safety and post "Getting it right first time", we wouldn't be surprised if more starting young consultants ended up with a more gradual emergence in specialist practice.

### How soon is too soon? Stroke and elective surgery

x-ref Hip & Pelvis, Knee, Foot & Ankle, Wrist & Hand, Shoulder & Elbow, Spine, Trauma, Oncology, Children's orthopaedics

The timing of elective surgery following patients experiencing an ischaemic stroke is critical. During the peri-event period patients are more susceptible to significant complications including death. Although there are some major studies quantifying the risk in patients who have suffered a myocardial event, the proximity of an ischaemic stroke to elective surgery and the risk that poses is still not fully understood. Using a nationwide cohort, researchers in **Copenhagen (Denmark)** set out to establish what the prevalence of complications in non-cardiac surgery was, and how that was affected by a previous ischaemic stroke.[6] They included all elective non-cardiac surgery in the adult population of Denmark over a five-year period (a whopping 481 183 operations) and sought to relate the time elapsed between ischaemic stroke and the risk of complications including major adverse cardiac events and all-cause 30-day mortality. The cohort included 7137 patients with a prior stroke and the crude incidence rates of major cardiac events were massively different between the two groups at 54.4 and 4.1 per 1000, respectively. The study team went on to calculate odds ratios and produce multivariant logistic regression models. Remarkably, patients who had an ischaemic stroke were 14.23 times more likely to suffer a major adverse cardiac event when the ischaemic stroke was within three months of the surgical procedure. This risk dropped steadily to 2.47 if the stroke occurred nine months or more before surgery. There was a similar (and obviously related) pattern seen for 30-day mortality with odds ratios falling from 3 (within three months) to 1.47 when the stroke had occurred more than nine months previously. While it is not possible to reduce the risk following stroke to normal levels for elective surgery, we would agree with the authors that, given that the risk decreases for both mortality and major cardiac event over a nine-month period then levels off, it seems sensible to avoid any planned elective surgery within nine months of an ischaemic stroke if at all possible.

## Sepsis and clots

Thromboembolic events are big news and big business with pharmaceutical companies generating millions of dollars of income each year from revenue generated by thromboprophylaxis. The difficulties of establishing any 'facts' in what is a serious, relatively rare and both politically and commercially sensitive area are well known (and well covered in these pages). Studies like this one from **Bern (Switzerland)** are hard to come by: a well-designed impartial study with enough patients to shed some real light and insight onto the problem.[7] The research team aimed to establish if sepsis increases the risk of arterial and venous thrombosis in a large prospective study using the National Surgical Quality Improvement Program database of the American College of Surgeons (ACS-NSQIP). The research team included data from 374 hospitals of all types across the USA and included results from 2 305 380 surgical procedures performed in adults during the duration of the study. Data were collated on comorbidities and potential risk factors for thromboembolic events as well as information on outcomes in terms of venous or arterial embolus. Overall, patients were around three times more likely to suffer from a thromboembolic event if they had any type of pre-operative sepsis. This had a more profound effect on venous thrombosis (OR 2.7 vs 3.3) and, surprisingly, patients with sepsis alone were more likely to develop a thrombosis with a diagnosis of sepsis than systemic inflammatory response syndrome (OR 3.3 vs 5.7). The increased risk of thrombosis in patients with sepsis should be taken into consideration when patients are risk scored in the peri-operative period. In light of this paper we will be lowering our threshold for thromboprophylaxis in patients with sepsis or other sequelae of infection.

## Hip geometry and arthritis incidence

In perhaps one of the more ambitious studies investigating the incidence of osteoarthritis, researchers from **Oxford (UK)** have reported on the MOST (Multicentre Osteoarthritis Study).[8] This large case controlled study reports on 1328 hips and knees in 664 patients as an ancillary study to the MOST study. The study was designed to establish the association (or otherwise) of tibiofemoral osteoarthritis with hip geometry. Reasoning that lateral compartment disease is less common than medial compartment disease overall, but more common in women, they set out to establish if there is any association with hip geometry. Of the 1328 hip/knee pairs, there were 219 with lateral compartment osteoarthritis and 260 with the medial compartment disease. All patients underwent full limb radiographs and a range of geometric measurements were taken in order to establish the overall limb and joint-specific geometry. Potential covariates were adjusted for and then means compared between both genders and patients with lateral *versus* medial compartmental OA. As would be expected, there were a number of geometric differences between genders, with women having reduced femoral offset (40.9 mm vs 45.9 mm) and more valgus hips (neck shaft angle 128.4 vs 125.9). Interestingly, looking at things the other way round lateral compartment OA was associated with reduced femoral offset, high hip centres, and a more valgus hip as well as an increased abductor angle. While establishing causation is nigh on impossible when studying phenotypic traits, this paper goes a long way towards establishing that certain geometric traits are associated with patterns of OA prevalence and that these traits are to a certain extent linked to gender. There is also an interesting implication here that inferences can be drawn as to the contribution of mechanical 'wear and tear' to osteoarthritis.

## Theatre discipline and infection

In these liberated times of tie-less doctors and a friendly, open, patient-centred approach to healthcare delivery, there is a risk of informality creeping into all aspects of healthcare. For centuries operating theatres have been places of formality and discipline with generations of senior theatre sisters ensuring that standards are maintained. There is a risk that modern approaches to healthcare delivery will undermine this discipline. The question posed by a review team in **Minneapolis (USA)** is how much of 'traditional' theatre discipline is actually evidence-based?[9] They reviewed the research supporting every part of theatre discipline. Their review concluded that although scrubs, masks and theatre hats do reduce bacterial counts in the operating theatre, there is little evidence that this translates to a reduction in the incidence of surgical site infection. There is unsurprisingly strong evidence, however, for the use of gloves and gowns and how they contribute to the risk of infection. With regard to the theatre design and sterility there is some evidence surrounding ventilation systems, and good evidence that room traffic increases bacterial counts within the room and on the operating sets. A worthwhile read and succinct summary of the available evidence, we would recommend this review to *360* readers.

## REFERENCES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