ROUNDUP360

Research

When is the 'residency cake' done?

With the evolution or regression (depending on your political standpoint) of not only educational theory but also working practice legislation throughout the world, the thorny issue of 'completion of training' has become increasingly difficult to define. Within the UK and Europe the implementation of the European Working Time Directive (EWTD) and the subsequent knock-on effects in lack of training time (junior and trainee doctors are now limited to a 48-hour working week), the craft-based specialties including orthopaedics have been moving increasingly towards competency-based assessment where not all trainees move through the training programme at the same rate. This problem has also started to impact in the US. A very interesting series of editorials from Joseph Bernstein **Philadelphia (USA)** makes a timely and insightful commentary on training in the new era in North America. Dr Bernstein draws parallels between baking a cake "375 degrees for 45 minutes" and orthopaedic residency programmes. Cooks won't take the cake out of the oven until it's done, even if it takes 75 minutes, so why do we rarely allow trainee surgeons extra time? Surely like the cake, the trainee should be allowed to graduate "when they are done".[1] Here at *360*, we wholeheartedly agree with Dr Bernstein that the difficulty with this kind of surgery is the assessment of the cooking. Identifying when a resident is sufficiently trained to operate independently is difficult to know, not only from a technical standpoint, but also in the more challenging skills of outpatient management and decision making, which are, in our opinion at *360*, much more difficult to teach and assess. How does one teach competency?

Steroids, stem cells and tendons

Having fully acquainted ourselves with stem cell technologies in last month's *360*, we couldn't help but notice this interesting article from **Pittsburgh (USA)**. So many of our patients have diagnoses that may be helped with steroid treatments, but the use of steroids carries with it the risks of infection and tendon/ligament rupture. This is brought more sharply into focus in the case of tendinopathy, where the anti-inflammatory properties of steroids can treat the tendinopathy, but are also implicated in rupture. The authors used *in vivo* and *in vitro* techniques to investigate the effects of dexamethasone on the ability of tenocytes to both proliferate and differentiate. They established that stem cells treated with low doses of dexamethasone were stimulated to proliferate at low concentrations (< 1000 nM). However, at higher concentrations a number of other less positive changes were observed. Higher doses of steroids inhibited proliferation and the researchers observed a change in cell shape suggestive of non-tenocyte type differentiation of the stem cells. They measured an almost complete suppression of collagen type I expression, and a synchronous upregulation of non-tenocyte related genes when higher concentrations (>10 nM) of dexamethasone were used. Subsequent implantation of dexamethasone-treated tendon stem cells resulted in the extensive formation of a range of tissues (fat, cartilage and bone) but no tendon formation. The researchers hypothesise that the use of dexamethasone in clinics may have a paradoxical effect, and that although the anti-inflammatory effect improves the patient's symptoms, the inhibition of tenocyte formation and move down a 'non-tenocyte' differentiation pathway may in fact cause the patient's symptoms to worsen in the longer term, one would presume leading to tendon rupture.[2] For those orthopaedic surgeons who do not favour direct tendon injections with steroids, there are some significant data to avoid the practice. Perhaps the best future clinical and scientific direction would be in investigating the dose/response relationship observed by these authors. It may well be that with direct steroid injections less is more. After all, if these results are to be believed, low-dose steroids not only have an anti-inflammatory effect but actively promote tenocyte differentiation.

What exactly is osteoarthritis?

Despite years of research and millions of pounds invested in a range of research projects, the cellular mechanisms of osteoarthritis continue to evade even the boffins here at *360* HQ. Although it is likely that osteoarthritis is in fact a constellation of conditions, all with a similar presentation, some significant headway has been made recently in understanding the causes and mechanism of disease (essential if any early biological intervention is to be effectively developed). There have, despite the enormity of the task, been great strides in understanding of the biology of the disease in recent years, particularly in understanding what the drivers and cellular markers of disease are. Researchers in **Berlin (Germany)** hypothesised that cartilage degradation and erosion are important disease processes in both osteoarthritis (OA) and rheumatoid arthritis (RA), and aimed to investigate the effects of synovial fluid from both diseases on human chondrocytes. They designed a basic study where tissue cultures of primary human chondrocytes were exposed to synovial fluid aspirates from patients with RA and OA. The cellular responses were quantified with a combination of histology, cell counting and quantification chemokine and cytokine expression (multiplex suspension array method).[3] The researchers established that exposure to rheumatoid synovial fluid resulted in altered chondrocyte morphology and small cells when compared with the osteoarthritis group. In addition, there were lower numbers of cells in the chondrocytes treated with RA synovial fluid. Interestingly, the researchers found increased cytokine and chemokine production in both groups, and although the picture was marginally

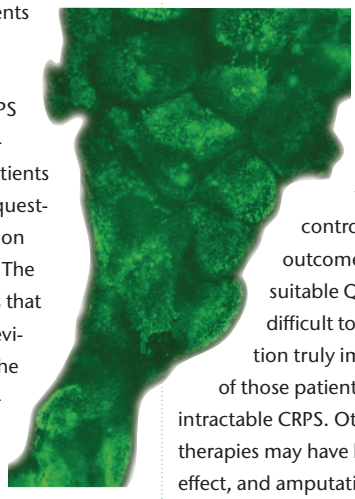
different (with VEG-F predominating in the OA group), the findings of this study support the gradual shift towards the understanding of OA as an active inflammatory disease.

Platelet-rich plasma: not the cuff panacea

Clinicians in **Sacramento (USA)** have been successfully treating cuff tears using a standard arthroscopic technique for some time. However, despite high rates of patient satisfaction they, like many others, noted higher than desirable rates of anatomic, if not clinical, failures. Reasoning that biological augmentation may offer a potential solution to this failure they embarked on a randomised controlled trail to test their hunch. Selecting platelet-rich fibrin matrix (PRFM), a biological augment consisting of a fibrin matrix with high concentrations of viable platelets, the authors devised a randomised controlled trial to establish the relative merit of the PRFM-augmented cuff repair. Following a power analysis and selecting pain score as the primary outcome measure, a series of 60 patients were enrolled in the study (which was powered to detect a 20% difference in pain scores). Patients were assessed with clinical evaluation (range of movement), outcome scores (American Shoulder and Elbow Surgeons (ASES), UCLA and Simple Shoulder Test (SST)) and pain scores. Surgery was undertaken in a standardised arthroscopic manner using a single-row rotator cuff repair. Patients were randomised to the use of a commercially available PRFM. Follow-up was at regular intervals to one year. The study team did not note any adverse events and the randomisation successfully produced two comparable cohorts. As would be expected, the PRFM arm took an average of ten minutes longer due to the implantation of the fibrin matrix. Throughout the study the teams were unable to identify any differences in pain scores, opioid use, range of movement, SST or ASES scores. However, in the secondary outcome measure of UCLA activity scores, the results were different (PRFM = 27.94 ± 4.98 *versus* 29.59 ± 1.68), although the confidence intervals overlapped and the measured difference was clinically irrelevant.[4] Based on the results of this well conducted randomised controlled trial there does not appear to us here at *360* to be any compelling argument to support the use of PFRM as an augment to arthroscopic cuff repair.

CRPS: to chop or not to chop?

Complex regional pain syndrome (CRPS) is not an easy syndrome to treat, and over the years a form of multimodal pain management has proven in the majority of cases the most effective method of treatment. Perhaps the most difficult patients to treat and indeed get through the consultation in a timely manner are those with resistant CRPS. For some patients the combination of pain and disability associated with a CRPS results in a non-functional limb. These patients will often present requesting further intervention or even amputation. The difficulty, however, is that there is a paucity of evidence surrounding the outcomes, complications and recurrence rates of CRPS post-amputation. Researchers in **Groningen (The Netherlands)** have set out to fill this void in the literature. They undertook a prospective review of a retrospective case series (Level IV evidence) with the aim of establishing the outcome of primary amputation for CRPS. They reviewed the notes and medical records of 21 patients who underwent amputation for long-standing therapy-resistant type 1 CRPS over an eight-year period. The majority (15) had undergone lower limb amputation, with six having undergone upper limb amputations. Patients had a mean age of 46 and had CRPS for a median of six years at the time of amputation. The investigators conducted a semi-structured review with examination of the residual limb. While there was no group for comparison and the authors did not have pairwise tests for analysis, the patients reported improvement in their quality of life (95%), pain levels (90%), mobility (81%), and sleep (67%). Perhaps most tellingly of those patients asked, the majority (18) would undergo amputation again. However, although encouraging results, nearly 25% of the patients had a recurrence of their CRPS (14% in the residual limb and 10% in the ipsilateral limb). The authors conclude that amputation may improve the lives of patients with intractable CRPS.[5] This is a fascinating paper that challenges the widely held belief that CRPS is not amenable to treatment with amputation. We are slightly concerned, however, that without a control group, paired outcome measures or suitable QALY analysis, it is difficult to say if amputation truly improved the lives of those patients affected by intractable CRPS. Other multimodal therapies may have had a similar effect, and amputation is, after all, a final treatment.



d-Dimer for DVT?

d-Dimer is a cross-linked fibrin degradation product, which, while highly sensitive for prothrombotic events, is unfortunately very non-specific. Researchers in **Ontario (Canada)** reasoned that revisiting the indications and threshold for testing may improve or maintain the value of d-Dimer testing while reducing the number of unnecessary duplex tests. The authors aimed to evaluate a selective d-Dimer testing strategy based on clinical pre-test probability for DVT. They tested their hypothesis with a randomised controlled trial. Patients with their first suspected episode of DVT were randomised to either selective testing or uniform testing. The selective group only underwent d-Dimer testing when the C-PTP risk was moderate or low (< 1.0 µg/mL [low C-PTP]), and then duplex scanning if the d-Dimer was raised (< 0.5 µg/mL [high C-PTP]). The uniform testing group all underwent duplex Doppler scanning. The primary outcome measure was the proportion of missed symptomatic DVT during the three-month follow-up of the study. There was no difference in the primary outcome of incidence of symptomatic venous thromboembolism between the two groups (0.5% in both). However, the selective testing group had lower rates of d-Dimer testing (21.8%, 95% CI 19.1 to 24.8) and ultrasonography (7.6% overall; 21% in low C-PTP group).[6] The investigators conclude that based on even event rates in both groups and significantly lower investigation rates, the selective d-Dimer testing offered advantages and few disadvantages. Although not strictly an orthopaedic study, this investigation provides valuable information relevant to all orthopaedic surgeons. In a healthcare environment where DVT and symptomatic thromboembolic events are under the spotlight, an evidenced based approach to screening for DVT is more than welcome.

Reducing bacterial adhesion

There is some evidence that selection of closure method has an effect on post-operative infection rates, and there are compelling data that bacterial adhesion may be modified by surface coatings and suture types. A number of recent meta-analyses have demonstrated that monofilament suture closure has lower infection rates than other forms of closure, particularly in the fractured neck of femur population. Researchers in **Pittsburgh (USA)** have conducted an experimental study to establish where the newer types of barbed monofilament suture may fit into our current

understanding of likely infection associated with the selection of suture type. The authors conducted a tissue culture study designed to establish the adherence of bacteria to a range of commonly used suture types (Vicryl™, Vicryl™ Plus, PDS™, PDS™ Plus, and Quill™). They aimed to establish the adherence characteristics of bacteria to each suture, the adhesion characteristics (ability to culture viable bacteria after washing) and the pattern of adherence. Using a standardised contaminated wound model and planktonic MRSA cultures, the sutures were exposed to the wound model. After use, a sequential wash method was used to determine the adherence of the bacteria which were then plated to establish bacterial growth potential. Finally, the contaminated suture material was examined under a confocal microscope to determine the adherence patterns of the bacteria. While one might expect the barbed suture to exhibit similar adherence characteristics to the braided sutures, in fact the Quill™ suture exhibited the lowest observed bacterial adherence of all three suture types. The monofilament sutures (either barbed or regular) exhibited comparable but lower rates of bacterial growth on agar plates post-inoculation than the braided sutures. The best performance was seen with the antibacterial sutures (both braided and monofilament) that showed no significant growth despite delayed cultures. These results were mirrored in the confocal microscopy results where the bacteria were seen to be more adherent to the braided than non-braided sutures.[7] Given the low event rates of wound infection, and the small effect size seen in previous *in vitro* studies examining wound infection rates and suture types, it may be some time before a clinical study of sufficient power emerges to support the use of the Quill™ suture. However, this study is a thorough examination of the microbiological properties of the Quill™ suture and based on this data, it seems reasonable to expect no rash of superficial infections following adoption of a barbed monofillament type suture.

Fin or limb?

One of the most difficult to research concepts in evolutionary biology is the transition from sea to land thought to have occurred during the Paleozoic era and was certainly well established 540 million years ago when the earliest fossil record of a footprint is thought to have originated. How then did we get from fins to limbs to make the footprint? While not strictly orthopaedic research, this superb review article from **Sendai (Japan)** traces the current understanding of the fin-to-limb transition as well as the rise of a new discipline 'Evo-Devo', a fusion of evolutionary and developmental biology, which attempts to explain evolutionary change with reference to developmental biology. Citing a combination of fossil record studies and familiar developmental biology (Zebrafish, HOX genes, Shh and AER signalling), the authors eloquently outline the stages required for fin-to-limb transition and draw parallels between apical fold formation, pattern development, segmentation and ossification, all of which are well described in both fish and mammals.[8] A fascinating article that is well worth a read and draws on previous limb and embryological research to suggest some explanations as to how that first footprint may have been made.

REFERENCES

1. **Bernstein J.** Orthopaedic residency: how do you know when the "cake is done?". *Clin Orthop Relat Res* 2013;471:9-12.
2. **Zhang J, Keenan C, Wang JH.** The effects of dexamethasone on human patellar tendon stem cells: implications for dexamethasone treatment of tendon injury. *J Orthop Res* 2013;31:105-110.
3. **Hoff P, Buttgereit F, Burmester GR, et al.** Osteoarthritis synovial fluid activates pro-inflammatory cytokines in primary human chondrocytes. *Int Orthop* 2013;37:145-151.
4. **Weber SC, Kauffman JI, Parise C, Weber SJ, Katz SD.** Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. *Am J Sports Med* 2013;41:263-270.
5. **Krans-Schreuder HK, Bodde MI, Schrier E, et al.** Amputation for long-standing, therapy-resistant type-I complex regional pain syndrome. *J Bone Joint Surg [Am]* 2012;94-A:2263-2268.
6. **Linkins LA, Bates SM, Lang E, et al.** Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. *Ann Intern Med* 2013;158:93-100.
7. **Fowler JR, Perkins TA, Buttaro BA, Truant AL.** Bacteria adhere less to barbed monofilament than braided sutures in a contaminated wound model. *Clin Orthop Relat Res* 2013;471:665-671.
8. **Yano T, Tamura K.** The making of differences between fins and limbs. *J Anat* 2013;222:100-113.