ROUNDUP360

Research

Bearing surfaces

The literature has been filled with publications on the adverse effects of metal-on-metal bearings over the past few years. However, only limited information is available on the potential risk to the human frame of degradation products from these bearings. Researchers from **Jiangsu (China)** studied this by investigating the cytotoxicity and genotoxicity of orthopaedic-related nanoparticles on human T cells *in vitro*. They found that cobalt nanoparticles and cobalt ions could inhibit cell viability and enhance lactate dehydrogenase release in a concentration- and time-dependent manner. Cobalt nanoparticles could also induce primary DNA damage. These findings suggested that cobalt nanoparticles could indeed generate potential risks to the T cells of patients after metal-on-metal hip arthroplasty.[1] Dear, oh dear, thinks *360*. Yet another nail in the metal-on-metal coffin, when so many patients still do so well after a metal-on-metal hip arthroplasty.

Arthroplasty surgeons try hard to reduce the degree of wear experienced by the bearing surfaces they implant. The use of highly cross-linked polyethylene (HXLPE) is one way to try and achieve this. However, some studies do still report wear and osteolysis associated with the material. As this is such an important area of practice, *360* was pleased to find the work published by researchers from **Philadelphia (USA)**, who undertook a systematic review of the issue. They identified 391 studies, of which 28 met the inclusion criteria for a weighted-averages analysis of two-dimensional femoral head penetration rates. It seems that HXLPE liner studies consistently report lower femoral head penetration and an 87% lower risk of osteolysis. However, a reduction in femoral head penetration or osteolysis risk is not established for large-diameter (> 32 mm) metallic femoral heads or ceramic ones of any size. In addition, there is very little evidence on the results of HXLPE in knees.[2]

Bioactive ceramics and osseointegration

Full osseointegration is a Holy Grail sought by many. Bioactive ceramics used as a coating for implants have certainly been shown to improve implant osseointegration but the effect of these coatings on the osseointegration of screws is not known. Researchers from **Seoul (Korea)** have investigated this after coating titanium alloy screws with calcium pyrophosphate (CPP), CaO-SiO2-B2O3 glass-ceramics (CSG), apatite-wollastonite 1:3 glass-ceramics (W3G) and CaO-SiO2-P2O5-B2O3 glass-ceramics (BGS-7). Coated and uncoated screws were inserted into dogs and the torque values of the screws measured at the time of insertion and at removal eight weeks later. There was little difference in insertion torque between coated and uncoated screws. However, those coated with CPP and BGS-7 showed significantly higher torque values at removal. It thus seems that such coatings are valuable and will improve osseointegration even within cancellous bone.[3]

Noninferiority – a new approach to comparative trials

For cost-effective care to be provided in orthopaedics, controlled trials are essential. Typically, comparative trials are based on superiority testing, using statistical tests that lead to a p value. However, as an author from **Boston (USA)** writes, superiority becomes more difficult to show and less important as margins of improvement shrink to clinically irrelevant levels. Alternative methods to compare groups in controlled trials are noninferiority and equivalence. An understanding of these concepts is key, so *360* welcomes this article, which goes a long way to explain the use of noninferiority and equivalence. Noninferiority testing also allows for inclusion of superiority testing in the same study without adjusting the statistical methods. Although such testing has been endorsed by the Food and Drug Administration and European Medicines Agency, one weakness is the potential to flood the market with 'me too' procedures and products that may be noninferior yet simply do not add value.[4] There are other issues, too. However, *360* found this paper eminently readable and fascinating and a must for any aspiring researcher.

Mesenchymal stem cells

Stem cells are big news at the moment and there is unquestionably an unmet need for a supply of autologous, patient-specific stem cells for a variety of regenerative therapies. Researchers from **Glasgow** and **Southampton (UK)**, and **Riyadh (Saudi Arabia)** highlight that one of the major problems of mesenchymal stem cells (MSCs) is their propensity to spontaneously differentiate, with the loss of multi-lineage potential when grown on standard tissue culture plastics *in vitro*. The MSC population typically undergoes rapid diminution as spontaneous differentiation occurs. This differentiation can be driven by the material/cell interface, an observation that suggests a possibility of manipulating stem cells without employing complex soluble chemistries or cellular reprogramming. In this publication the authors identify a nanostructured surface that retains stem-cell phenotype and growth over an eight-week period. This finding highlights well the potential of surfaces as non-invasive tools in this rapidly developing stem-cell era in which we all now practise.[5]

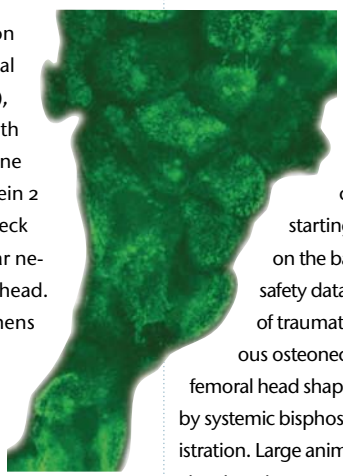
Tranexamic acid after trauma

Multicentre trials are generally to be recommended. However, sometimes they are so big that it is almost impossible for *360* to grasp the number of authors involved. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage – 2) trial into the effects of early administration of tranexamic acid on death, vascular occlusive events and blood transfusion in trauma patients is a good example of this. This was a randomised controlled trial undertaken in 274 hospitals in 40 countries and involved 20 211 adult trauma patients with, or at risk of, significant bleeding. Patients were randomly assigned within eight hours of injury to either

tranexamic acid or matching placebo. The primary outcome measure was death in hospital within four weeks of injury. All-cause mortality was significantly reduced with tranexamic acid and, specifically, the risk of death from bleeding was also significantly reduced. However, there was strong evidence that the effect of tranexamic acid was greatest if given as early as possible after injury. Treatment given more than three hours after injury seemed to actually increase the risk of death from bleeding.[6] *360* notes that tranexamic acid, if it is to be used, should be administered as soon as possible after injury. If given late it could actually be harmful.

Avascular necrosis

■ In some countries, avascular necrosis (AVN) of the femoral head is a huge problem. Anything that might help us understand its pathogenesis is clearly to be welcomed. Consequently, work from **Shandong (China)** is of interest, where researchers studied the expression of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and bone morphogenetic protein 2 (BMP-2) in femoral neck fracture and avascular necrosis of the femoral head. Femoral head specimens were obtained from 59 donors undergoing total hip replacement, the bone mineral density being measured in the weight-bearing area of the femoral head by means of dual energy X-ray absorptiometry. Pathological changes were observed through microscopy (optical and scanning electron) and the expressions of VEGF, bFGF and BMP-2 mRNA were detected through an *in situ* hybridisation technique. Patients were divided into three groups: A, with traumatic AVN; B, with non-traumatic AVN; C, with a fresh femoral neck fracture. Interestingly, bone mineral density was lower in groups A and B than in group C. Meanwhile, in group C the percentage of empty bone lacunae was significantly higher and the percentage of trabecular bone area was significantly lower. Expressions of VEGF, bFGF and BMP-2 mRNA were significantly lower in groups A and B than group C. It appeared that the repair capacity of the femoral head in traumatic AVN is greater than for non-traumatic AVN. Meanwhile, the expressions of VEGF, bFGF and BMP-2 mRNA decline in both varieties of the disease.[7]



Perthes' disease and bisphosphonates

■ One damaging feature of Legg-Calvé-Perthes' disease is the development of femoral head deformity. This is said to relate to bone resorption that, in turn, leads quickly to the hypothesis that antiresorptive agents may be a useful adjunctive therapy in this condition. So write two workers from **Westmead (Australia)**. Multiple animal studies support the further investigation of bisphosphonates in this scenario with clinical data only now starting to be gathered on the basis of animal and safety data. Rodent studies of traumatic and spontaneous osteonecrosis confirm that femoral head shape can be preserved by systemic bisphosphonate administration. Large animal piglet studies also show better preservation of the femoral head shape with systemic and local bisphosphonate administration. Timing of effective dosing is likely to be very important. If the goal of treatment is to prevent deformity, then the window of therapy may be limited to an early stage of the disease before any significant collapse of the head.[8] *360* agrees entirely with the authors. This is exciting work, particularly if deformity of the femoral head can be prevented in Legg-Calvé-Perthes' disease. Further basic science and clinical studies are certainly needed.

Antipsychotics and bone resorption

■ Second generation antipsychotics have been linked to metabolic and bone disorders in clinical studies although the mechanisms remain unclear. Work from **Scarborough (USA)** is thus of interest. Using *in vivo* and *in vitro* techniques, a research group examined the effects of risperidone, a commonly prescribed antipsychotic, on the bone of mice. Not only did risperidone reduce trabecular number but trabecular histomorphometry demonstrated increased resorption parameters. It also altered adipose tissue distribution such that white adipose tissue mass was reduced and the liver had significantly higher lipid infiltration. The number of osteoclasts was significantly increased by the addition *in vitro* of risperidone while osteoblast differentiation was not altered. These studies indicate that risperidone treatment can have adverse skeletal consequences by direct activation of osteoclast activity.[9] The *360* view? Proceed carefully at present if you intend to use risperidone. More work is clearly needed.

Do impact factors truly reflect clinical utility? A *360* experiment.

■ Finally, for this section, a word about dreaded impact factors. We seem to chase increased impact factors like headless chickens, yet how useful are these measurements in reality? Enter at this point a *360* experiment ably pioneered by one of our Editorial Board, Professor David Wood from **Perth (Australia)**. Rather than seeking a number of individual and recommended publications, he asked his team to look at a single issue of an established musculoskeletal journal, in this case the September 2011 issue of *Clinical Orthopaedics and Related Research*. Let it be known that none of the major musculoskeletal journals will escape *360*'s attention over the years. The reviewers were asked to score each section of each paper on the basis of quality of the Abstract, Introduction, Hypothesis, Method, Results, Statistics, Novelty and Clinical Significance. Scoring was 0 to 4, with 0 equating to useless and 4 being outstanding. Review articles were harder to score and were more subjectively judged. However, having read each paper, the team decided that only one could be recommended for inclusion in *360*, that by Vavken[4] on superiority, noninferiority and equivalence in the design of orthopaedic trials. It will be interesting to see how the official impact figures relate to how we, as surgeons, see the utility of a particular publication on the clinical front line. Time will no doubt tell.

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