ROUNDUP360

Research

Rheumatoid factor is not just a 'quick test'

Rheumatoid factor (RhF), the autoantibody to the Fc portion of IgG, as we all learned at medical school, is highly sensitive but not specific for a diagnosis of rheumatoid arthritis. It is usually used in the setting of an acute arthropathy to define the type of rheumatological disease. Despite the day-to-day use of RhF, relatively little is known about the long-term prognostic value of raised RhF in the normal population. Researchers in **Copenhagen (Denmark)** examined blood samples taken as part of a previous prospective cohort study 20 years ago. The cohort of 9712 individuals from the general population did not have any autoimmune disease diagnosed at the time of obtaining the blood sample. The study population was observed for a truly staggering 187 659 person years, during which time 183 patients developed rheumatoid arthritis. In healthy individuals, doubling levels of RhF was associated with a three-fold increased risk of developing rheumatoid arthritis. Researchers noted a similar association with other autoimmune diseases. The authors performed a fairly comprehensive risk factor modeling which identified risk factors to include female gender, age between 50 and 69 years, smokers, and rheumatoid factor levels > 100 IU/mL. When all these risk factors are combined, this paper suggests that one third of the cohort were at risk of developing rheumatoid arthritis. This study confirms that elevated rheumatoid factor in normal individuals gives up to a 26-fold risk of developing rheumatoid arthritis, equivalent to a 32% ten-year absolute risk of rheumatoid arthritis.[1] While we at *360* are used to reading high-quality rheumatology-based research into musculoskeletal disease, we were struck by this particular study, and not just because of its novel findings. It underlined to us the power of patient registries. While our own orthopaedic patient registries are a well utilised resource it set us thinking: how much more useful would they be with accompanying tissue samples or genetic material? Registries are the future, but we must strive to include much more useful information in them. This is one area where we are firmly ahead of our colleagues from other specialties.

Osteonecrosis common in smokers

Cigarette smokers are not the most popular patient demographic with doctors as a whole, and the list of their sins in orthopaedics continues to grow. Not beloved of trauma surgeons due to the nonunion-inducing side effects of smoking, researchers from **Osaka (Japan)** have put one more nail in smoking's coffin. They performed a multicentre matched prospective cohort study (Level II evidence) with the aim of establishing the effects of smoking on the risk of osteonecrosis of the femoral head. They were expanding on previous work, this time paying particular attention to any interaction with corticosteroid use. The researchers designed a matched study in which patients with osteonecrosis were gender-, age- and ethnicity-matched to two controls. The study team then used a logistic regression model to calculate odds ratios for the 72 cases and 244 matched controls included in the study. They calculated an odds ratio of 3.89 (95 % CI 1.46 to 10.4) for smokers, rising to 4.26 (1.32 to 13.7) for those with at least a 26 pack per year history, and 3.11 (0.92 to 11.5) for those with a smoking history of 29 years or more. The study team identified an OR of 10.3 among smokers without corticosteroids and 1.56 among corticosteroid users. There was a significant interaction between smoking and corticosteroid use. Amazingly, smoking had the most pronounced effect in non-corticosteroid users.[2] This is the second unexpected counterintuitive interaction that caused some scratching of heads here at the *360* headquarters. We had just got over the shock that tranexamic acid in trauma gives a lower rate of adverse thrombotic event when we came across this. How could smoking and corticosteroid use, two risk factors for osteonecrosis, not have cumulative effects? Some further research is definitely required; it is differential interactions that lead to scientific breakthroughs.

Pasteurisation is effective for bone reconstruction

There have never before been as many commercially available bone grafts, bone substitutes and biological augments as are currently available throughout the world. With renewed interest in bone substitutes in trauma, reconstruction and tumour work, we agree wholeheartedly with a study team in **Tokyo (Japan)** who believe it is high time we revisit the old technology of bone pasteurisation. Pasteurisation, similar to irradiation, has a tumour-killing effect and maintains the mechanical strength, but not the biological viability of the graft bone. Despite these promising characteristics of autologous bone treated with this technique, we at *360* have come across surprisingly few reports in the orthopaedic literature. The study team identified 27 cases in which bulk autograft had been used after treatment with pasteurisation. Of these 27, 12 died and one was lost to follow-up during the impressive period of over 12 years. Patients were treated with a variety of different surgical methods including osteoarticular graft, composite graft and intercalary grafting. The authors report a five- and ten-year survival of 78.6% and 47.6% respectively. Three of the six osteoarticular cases failed because of late-onset resorption or infection of the pasteurised bone.[3] Based on the results of this study pasteurised bone appears safe to use with good long-term outcomes.

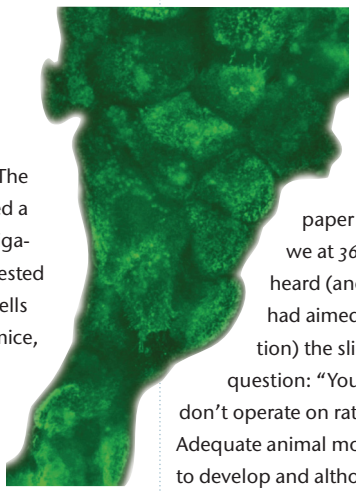
Venous thromboembolism risk greater in rheumatoids

There have been some preliminary reports in the scientific literature that rheumatoid arthritis (RA) may be associated with a higher risk of venous thromboembolism (VTE). There has never been more interest

in the literature surrounding the risks of, strategies to prevent, and the sequelae of VTE. Here at *360* almost every conference we have attended recently has a symposium, talk, or invitational session on the topic. We were curious to read this article, as the current trend is one of increased interest in risk assessment and individualised patient treatments. A team from **Stockholm (Sweden)** undertook a prospective population cohort study using a population-based registry, rather than hospital admission records. They aimed to establish if RA was an independent risk factor for VTE, without introducing other confounders. They included an RA prevalent cohort (n = 37 856), an RA incident cohort (n = 7904), and matched general population comparison cohorts. All patients were from Sweden and were followed up for 13 years. The authors established that the cohort with prevalent RA had a greater than two-fold increased risk of VTE (6/1000 person years *versus* 2.8/1000 person years). They noticed no increase in VTE rate in these same patients prior to diagnosis of RA. However, after the onset of rheumatoid symptoms there was an increased risk of VTE, but this did not increase year on year. The authors could find no interaction between hospitalisation and RA as risk factors for VTE which appeared to be independent. The study team concluded that when compared with the general population, Swedish patients with RA had an elevated risk of VTE.[4] Population-based studies of this kind are particularly welcome here at *360*. Establishing risk factors within the background population for VTE is essential in continuing to provide patients with safer surgery. We applaud the research team for a well-conducted high-quality study, establishing RA as an independent risk factor for VTE.

Stem cells may reverse age-related osteopenia

The global interest in biological bone-healing augmentation continues apace. The dizzying array of augments from growth factors to stimulators to platelets continues to expand, many without a significant evidence base. Mesenchymal stem cells have started to find their first clinical application in orthopaedics, and interest in the potential for cartilage regeneration and bone healing of these pluripotent cells continues. Researchers in **Montreal (Canada)** aimed to establish the potential for clinical application of mesenchymal stem cells in osteopenic mice. The research team aimed to establish if the decline in osteogenic precursor cells in the long bone marrow was associated with impaired bone formation and whether this could be corrected by stem cell transplantation. The researchers conducted a murine model investigation where they harvested mesenchymal stem cells from healthy donor mice, differentiated them to osteoblasts and cultured them on titanium rods. These were then implanted into the femoral canals of osteopenic mice as a model of total hip femoral component integration. The researchers used microCT to examine the bony architecture surrounding the implants and established that there was a higher quality and greater volume of bony integration in the rods surrounded by the mesenchymal stem cells as compared with those that were not. The authors conclude that their research establishes the principle that differentiated mesenchymal stem cells could be used to promote osseointegration of implants.[5] We were excited at *360* to read this fascinating report on the development of a 'biological' implant. Arthroplasty surgeons have long talked about the biological integration seen in uncemented components, but this technology provides a tantalising glimpse of the future. We may soon see implants that not only osseointegrate, but come ready-coated with all the biological components required to establish a firm fix, even in poor bone.



Running is bad for rat knees

One of the difficulties faced by the modern orthopaedic clinical scientist is that of translating research into clinical practice. This is often due to the lack of an appropriate animal model. Having identified a novel therapy, signal molecule or therapeutic intervention, this is tested usually in cell culture and then has to go through the tricky animal phase prior to any investigation in man. After a scientific paper at a meeting, we at *360* have often heard (and sometimes had aimed in our direction) the slightly trite question: "You do realise we don't operate on rats don't you?" Adequate animal models are difficult to develop and although not linked directly to significant findings we feel the model developed by the research team in **St Louis (USA)** is an excellent one. They aimed to develop a realistic model of cartilage degeneration using osteoarthritic rats on a running regimen. The investigators used the Wistar rat model of OA, and divided the rats into two groups. The running rats used a motorised treadmill to run 30Km in three weeks or 55km in six weeks. Each week the investigators analysed the stride length and step angle using a paw print method. The rats were killed at three and six weeks for cartilage analysis. The knees demonstrated typical osteoarthritic cartilage changes, decreased proteoglycan content, uneven type II collagen deposition, expanded calcified zone and increased MMP-13 levels. The gait analysis results demonstrated an inverse relationship between paw angle and OA progression.[6] Wow, we thought at *360*! 55km is long way for a rat on a treadmill, and it certainly shows in their knees. What we have here is an excellent physiological model of joint disease, which we are sure will yield many interesting results in the future.

Rapid rat healing with ultrasound

Bone is a unique tissue, healing without scar, but it can take a long time, or falter and fail to heal at all. The number of patients now attending our clinics here at *360*, clutching a crumpled piece of newspaper and asking for one of a variety of bone-healing machines seems to have increased exponentially in the last few years. While there is little clinical data, and a Cochrane meta-analysis yielding no evidence for efficacy, the interest in the potential to speed up bone healing is still intense at the basic science and clinical level. Researchers from **Hong Kong (China)** have weighed into the argument by designing a study to investigate if sensory innovation has a role to play in the effect of ultrasound on bone healing. The researchers used a rat model of tibial fracture with the study group consisting of 112 rats divided into four groups. Each rat had a standardised tibial shaft fracture generated, which was fixed with an intramedullary rod. The rats then had either division of their sciatic nerve or patellar tendon and pulsed ultrasound, or not. Outcome measures were radiographs, CT and histomorphology. The researchers found that in the daily ultrasound group the rate of union and volume of bone was significantly higher in the neuronally intact rats, but absent in the neurectomised group. There was faster callus maturation seen on the histomorphology studies in the ultrasound group compared with the controls. The researchers curiously found that this benefit was lost in neurectomised rats leading to the hypothesis that sensory innervation may be responsible for the observed results.[7] We have to admit,

here at *360*, to being a little sceptical about bone-healing devices, but we are fascinated by the results of this study. The authors' conclusion that sensory innovation may be key in the observed response seems a reasonable one, but it is important to remember that limping rats are different from aneural rats, and there are a number of other plausible explanations. However, this is a very interesting result, and one that merits further study.

Magnetic stem cells

Now we move from ultrasound to magnets, but the rats are still the subject of experimentation. Researchers in **Hiroshima (Japan)** present some fascinating work that has really made our ears prick up here at *360* HQ. We have always wondered how, if stem cell therapy is to be effective, one would get the stem cells to the area of interest, keep them there, and tell them what they need to do. Part of this puzzle may have now been solved. The researchers developed a method of delivering magnetically-labelled mesenchymal stromal cells directly to the site of a nonunion in a rat. The boffins in Hiroshima labelled the stromal cells with ferucarbotran and transplanted luciferase positive cells into the fracture site. They then applied a magnetic field and were able to track the fortunes of the stem cells using bioluminescence to track the luciferase label. Amazingly, the use of the magnetic field induced accumulation of the observed photons at the fracture site and persistent mesenchymal cell presence from the third day to a month. The researchers were also able to demonstrate improved callus formation and enchondral ossification.[8] To say we are impressed at *360* is an understatement. Ineffective delivery systems have been the blight of more than one biotherapy in musculoskeletal medicine. To be able to demonstrate a viable delivery and targeting system for cell therapies is nothing short of a huge step towards viable biotherapy in musculoskeletal medicine. We commend the authors for their groundbreaking research.

Surgery may not be as safe as we thought

It is extremely difficult to perform large population studies, and even some simple questions – the answers to which are taken for granted – are not in fact known. An international collaborative based in **London (UK)** aimed to establish outcomes after non-cardiac surgery at a national and international level. The researchers hypothesise that there is known to be heterogeneity between hospitals, nations and healthcare systems and that there is the potential to improve outcomes for patients if the determinants are understood. The European Surgical Outcomes Study was set up and has now reported its initial findings of a seven-day cohort study across Europe. The study team identified 46 539 patients over the age of 18 who underwent surgery within that period, and patients were followed up for 60 days. The study team reported outcomes in 498 hospitals situated in 28 different European nations, and assessed surgical outcomes using the surrogate markers of mortality and ITU stay. The raw mortality was 4% with 8% of patients requiring admission to critical care after surgery for a median of two days. Worryingly, the authors identified that the majority of patients who died (73%) were not admitted to critical care post-surgery. Surgical safety measured by mortality varied dramatically between countries (from 1.2% in Iceland to 21.5% in Latvia). The authors adjusted for confounders and standardised mortality to the United Kingdom, however, large discrepancies still occurred with a range between 0.44 for Finland (95% CI 0.19 to 1.05) and 6.92 for Poland (2.37 to 20.27).[9] In a century when the World Health Organization has identified surgical safety as one of the key factors in improving global health and outcomes, it is encouraging to see these studies being performed, but here at *360* we were slightly worried to see the major variations in mortality between developed healthcare systems.

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