ROUNDUP360

Research

You cannot escape your genes

It is difficult to escape your genes. *360* sometimes feels we would be better off without them, as a recent study by **arcOGEN (UK)** has produced some fascinating work in the field of genetics and osteoarthritis (OA). arcOGEN, for those who may be unfamiliar with it, is a UK-wide consortium funded by Arthritis Research UK, whose aim is to identify the genetic determinants of OA by carrying out a large-scale genome-wide association scan. It comprises 16 investigators from 11 centres in the UK. The authors acknowledge that OA is the most common form of arthritis worldwide and is a major cause of pain and disability in elderly people. The health economic burden created by it is increasing commensurate with the prevalence of obesity and longevity. There is a strong genetic component to OA but the success of previous genetic studies has been restricted by insufficient sample sizes and phenotype heterogeneity. Consequently, the researchers undertook a large genome-wide association study in 7410 unrelated and retrospectively and prospectively selected patients with severe OA, 80% of whom had undergone total joint replacement, and 11 009 unrelated controls from the UK. They then replicated the most promising signals in an independent set of up to 7473 cases and 42 938 controls, from studies in Iceland, Estonia, The Netherlands, and the UK. All patients and controls were of European descent. The researchers identified five genome-wide significant loci for association with OA and three loci just below this threshold. The strongest association was on chromosome 3 with rs6976, which is in perfect linkage disequilibrium with rs11177. This single nucleotide polymorphism encodes a missense polymorphism within the nucleostemin-encoding gene GNL3. Levels of nucleostemin were raised in chondrocytes from patients with OA in functional studies. Other significant loci were on chromosome 9 close to ASTN2, chromosome 6 between FILIP1 and SENP6, chromosome 12 close to KLHDC5 and PTHLH, and in another region of chromosome 12 close to CHST11. One of the signals close to genome-wide significance was within the FTO gene, which is involved in regulation of bodyweight - a strong risk factor for osteoarthritis. All risk variants were common in frequency and exerted small effects.[1] *360* was very excited by this work and can only support the authors' own conclusions, as they have provided an insight into the genetics of arthritis that can only help to identify new pathways that might be amenable to future therapeutic intervention. We suspect there will be much more to follow.

Oral prophylaxis for DVT?

We have long struggled to reduce or abolish the chances of a deep-vein thrombosis (DVT) occurring after surgery, and the choice of regimes is huge, particularly with the arrival of a number of newer oral medication options. Researchers from **Madrid (Spain)** have looked at a number of these in order to assess their clinical outcomes for prophylaxis against venous thromboembolism after total hip or knee replacement. This was a systematic review, meta-analysis, and indirect treatment comparison using Medline and CENTRAL (up to April 2011), clinical trial registers, conference proceedings, and websites of regulatory agencies as data sources. The authors looked at randomised controlled trials of rivaroxaban, dabigatran, or apixaban compared with enoxaparin for prophylaxis against venous thromboembolism after total hip or knee replacement. Two investigators independently extracted data. Relative risks of symptomatic venous thromboembolism, clinically relevant bleeding, deaths, and a net clinical endpoint (composite of symptomatic venous thromboembolism, major bleeding, and death) were estimated using a random effect meta-analysis. The team identified 16 trials in 38 747 patients. Compared with enoxaparin, the risk of symptomatic venous thromboembolism was lower with rivaroxaban but similar with dabigatran and apixaban. Compared with enoxaparin, the relative risk of clinically relevant bleeding was higher with rivaroxaban, similar with dabigatran, and lower with apixaban. The treatments did not differ on the net clinical endpoint in direct or indirect comparisons.[2] So *360* notes the authors' conclusions, that there is a higher efficacy of the newer anticoagulants although this was generally associated with a higher bleeding tendency. The text of this paper is free.

Non-responders and the internet

A small but valuable paper has appeared from **Boston (USA)** in an attempt to solve the eternal problem of patients failing to respond to post-operative questionnaires. This has been a career-long struggle for *360*. Yet in Boston they have simply looked at the use of the internet for this task. As the team says, the internet is available to researchers as a tool for studying long-term outcomes, but no recent research exists on how best to use it. The authors hypothesise that using the internet can be at least 75% effective in locating patients lost to follow-up. With Institutional Review Board approval, the authors searched for 66 patients lost to follow-up after a period of ten years or more with no contact. They also tested an internet-searching protocol that had been developed in 2004 and developed an alternative protocol as a consequence. In all, 74% (49/66) of patients were located by this means.[3] This is good work, we feel at *360*. All being well, the term "lost to follow-up" may soon become a thing of the past. Let us see.

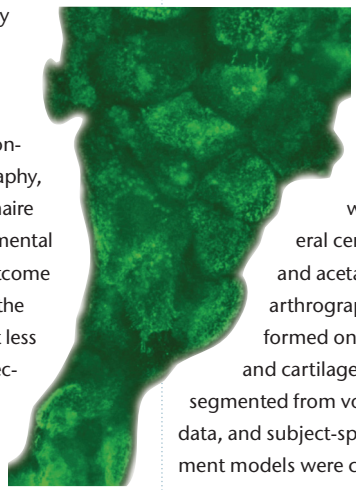
Metal-on-metal, mice and damaged livers

The seemingly endless debate about metal-on-metal continues, this time with a laboratory study from **Guangzhou (China)**. The authors' aim was to explore the effects of chronic exposure to trace chromium as a result of metal-on-metal hip

arthroplasty on oxidative stress in mouse liver cells. They randomly divided 80 mice into four groups and each mouse was given an intraperitoneal injection of CrO_3 at a dose of 0, 5, 10 or 20 mg/kg every other day for 16 weeks. There were five mice from each group that were selected every four weeks for determining the content of chromium in the whole blood and the levels of reactive oxygen species (ROS), malondialdehyde (MDA), eglutathione (GSH), glutathione reductase (GR) activity, and glutamate cysteine ligase (GCL) expression in the liver cells. The ultrastructural changes of the liver cells were also observed using transmission electron microscopy. The team found that an exposure to 5 and 10 mg/kg CrO_3 caused a significantly increased blood chromium concentration and ROS level, which reached its peak level at eight weeks and then stabilised, whereas at a dose of 20 mg/kg, CrO_3 exposure resulted in a progressive, time-dependent increase of blood chromium concentration and ROS level. MDA showed no significant changes in the four groups. With the prolongation of the exposure time, GSH content and GR activity were decreased in these groups. In the 5 and 10 mg/kg CrO_3 groups, GCL expression increased at each measurement time point, but in the 20 mg/kg group, GCL expression decreased gradually with a prolonged exposure. Transmission electron microscopy revealed apoptotic changes of the liver cells in the 20 mg/kg group.[4] So, *360* notes, yet another nail in the coffin of metal-on-metal. This study has demonstrated that the slow accumulation of trace chromium after metal-on-metal hip arthroplasty may cause oxidative stress and changes in the oxidative stress system in the liver cells. If your Chinese is up to the mark then there is a simplified version of this paper available with open access.

Sleeping on the job – an orthopaedic residency study

How often have we heard discussion about hours of work and hours of sleep in many of the professions outside surgery? How about airline pilots or drivers of heavy goods vehicles? Well, the same could easily be said of surgeons, as shown by another study from **Boston (USA)**. Researchers undertook a prospective cohort study with a minimum two-week continuous assessment period. Data on sleep and awake periods were processed using the sleep, activity, fatigue, and task effectiveness model. There were 33 volunteer orthopaedic surgical residents, of whom 27 (82%) completed the study. This represented 65% (33 of 51) of the orthopaedic residency programme. The researchers measured the residents' sleep and awake periods continuously with actigraphy, and a daily questionnaire was used to analyse mental fatigue. The main outcome measures used were the percentage of time at less than 80% mental effectiveness (correlating with an increased risk of error), the percentage of time at less than 70% mental effectiveness (correlating with a blood alcohol level of 0.08%), the mean amount of daily sleep, and the relative risk of medical error compared with chance. The authors found that residents were fatigued during 48%, and impaired during 27%, of their time awake. Among all residents, the mean amount of daily sleep was 5.3 hours. Overall, residents' fatigue levels were predicted to increase the risk of medical error by 22% compared with well-rested, historical control subjects. Night-float residents were even more impaired, with an increased risk of medical error.[5] At *360* we found these data to be quite alarming, although they only really prove what we knew from experience already. Will these findings make any difference to the way healthcare management handle their medical staff? Somehow we doubt it.



Cartilage contact stress in the normal human hip

We are frequently told that too much impact exercise is bad for our joints, so it would be good to have some science attached to such a claim. Consequently, a paper from **Salt Lake City (USA)** caught *360*'s eye. The team's objectives were to determine cartilage contact stress during walking, stair climbing, and descending stairs in a well-defined group of normal volunteers and to assess variations in contact stress and area among subjects and across loading scenarios. They selected ten volunteers with no history of hip pain or disease, and with a normal lateral centre-edge angle and acetabular index. CT arthrography was performed on one hip. Bone and cartilage surfaces were segmented from volumetric image data, and subject-specific finite element models were constructed and analysed using a validated protocol. Acetabular contact stress and area were then determined for seven activities. Peak stress ranged from 7.52 MPa for heel-strike during walking (233% body weight) to 8.66 MPa for heel-strike during descending stairs (261% body weight). The mean contact area across all activities was 34% of the surface area of the acetabular cartilage. The distribution of contact stress was not uniform, and more variability occurred among subjects for a given activity than among activities for a single subject. The magnitude and area of contact stress were consistent between activities, although inter-activity shifts in contact pattern were found as the direction of loading changed. Relatively small incongruencies between the femoral and acetabular cartilage had a large effect on the contact stresses. These effects tended to persist across all simulated activities. These results demonstrate the diversity and trends in cartilage contact stress in healthy hips during activities of daily living, and provide a basis for future comparisons between normal and pathological hips.[6] *360*'s view? Fascinating work. We had not realised what a huge stress passes through our hips during walking and descending stairs. No wonder THR is a growth business.

A perfect reason to subscribe

At *360* we do not officially allow ourselves favourites but forgive us if we once again break our own rule. Try this paper from **Robina (Australia)** where the objective was to estimate the degree of scatter of reports of randomised trials and systematic reviews, and how the scatter differs among medical specialties and subspecialties. This was a cross-sectional analysis for which PubMed was used for all disease-relevant randomised trials and systematic reviews published in 2009. In the event, orthopaedic surgery did not feature but at *360* we did not feel this mattered. The results were very exciting. The scatter across journals varied considerably among specialties and subspecialties: otolaryngology had the least scatter (363 trials across 167 journals) and neurology the most (2770 trials across 896 journals). In only three subspecialties (lung cancer, chronic obstructive pulmonary disease, hearing loss) were ten or fewer journals needed to locate 50% of trials. The scatter was less for systematic reviews: hearing loss had the least scatter (ten reviews across nine journals) and cancer the most (670 reviews across 279 journals). For some specialties and subspecialties the papers were concentrated in specialty journals; whereas for others, few of the top ten journals were a specialty journal for that area. Generally, little overlap occurred between the top ten journals publishing trials and those publishing systematic reviews. The number of journals required to find all trials or reviews was highly correlated (r = 0.97) with the number of papers for each specialty/

subspecialty. Publication rates of specialty-relevant trials vary widely, from one to seven trials per day, and are scattered across hundreds of general and specialty journals. Although systematic reviews reduce the extent of scatter, they are still widely scattered and mostly in different journals to those of randomised trials. Personal subscriptions to journals, which are insufficient for keeping up to date with knowledge, need to be supplemented by other methods such as journal scanning services or systems that cover sufficient journals and filter articles for quality and relevance. Few current systems seem adequate, the authors say.[7] Now, of course, comes the catch. Why is this paper our favourite? Simple. So many papers and so many journals and publications appearing around the globe. No wonder the authors found such a wide scatter. The solution? Subscribe to *360* of course. We can do much of the hard work for you.

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