

ROUNDUP³⁶⁰

Knee

For other Roundups in this issue that cross-reference with Knee see: Hip Roundup 3; Research Roundups 3, 5 and 6.

Conflict of interest and hyaluronic acid

■ We accept in the medical press that the randomised controlled trial (RCT) is beyond reproach, whiter than white, and the jewel in the crown of evidence-based medicine. However, RCTs can be subject to bias like any other study. Methodologically, they are designed to try and reduce these biases, but does this actually work? Researchers in **Ann Arbor (USA)** set out to investigate the bias (or otherwise) associated with RCTs funded by industry. Selecting studies into hyaluronic acid (a controversial intervention at the best of times, with proponents and detractors in equal measure), the investigators set out to establish whether the funding source for an RCT affected eventual outcome. The research team used a previously published systematic review to identify 48 prospective placebo RCTs, all investigating the effects of hyaluronic acid in hip osteoarthritis. They specifically reviewed the literature in light of the publicised funding source. There were three (6.25%) studies with no industry affiliation, 30 (62.5%) were industry funded (or there was a potential other conflict of interest) and the remaining 11 (31.5%) listed no funding sources and no conflicts of interest. All of these studies were designed with similar methodology and end points.

Strikingly, a statistically significant association was observed between financial conflict of interest and the conclusion of the study. All the studies with a reported financial conflict of interest presented favourable conclusions, while the 11 studies with no industry-affiliated contacts concluded there was no benefit of hyaluronic acid over placebo.¹ We are sure, here at 360, that all of the authors in all of the reported studies had the best of intentions and undertook their studies with the highest methodological rigour. However, the conclusions of this review are more than striking. Even when attempting to remove bias through careful study design, it may be that the source of funding is more important than the intervention being tested.

Will time indeed tell in microfracture?

■ The difficulty with the majority of studies concerning biologic and joint preserving surgeries is that these treatments are designed to be effective over decades, and the majority of studies are published over, at best, only a few years of follow-up. It is not, however, completely clear how (if at all) the difference in follow-up time might affect the results. If one therapy has a short-term advantage over another, will this difference converge or diverge at longer-term follow-up? In the case of cartilage preserving surgery, does the advantage of better hyaline-like cartilage confer a long-term advantage over the fibrocartilage seen with traditional microfracture (MF)? Researchers in

Vienna (Austria) designed a fiendishly simple study to try and establish if the benefits seen in some autologous chondrocyte implantation (ACI) studies might have a larger or smaller treatment effect over time. The researchers designed a meta-analysis to test the hypothesis that ACI would have a greater treatment effect than MF with increasing superiority over longer term follow-up. In a statistically comprehensive review centring on a random-effect meta-analysis at one-, two-, and five-year follow-up (combined with assessment of heterogeneity and publication bias), the research team were able to include six study populations (with data from nine papers) reporting the outcomes of just shy of 400 patients. There were no differences in baseline characteristics and, although techniques differed with regards to ACI, the use of MF was standardised. The authors were unable to demonstrate significant superiority of ACI over MF, and although an insignificant advantage of ACI over MF was found, this benefit declined as time went on. When only second and third generation MF techniques were used, there was a significant advantage of ACI over MF. This advantage also declined over time, and by five-year follow-up the authors estimated that any benefit of ACI over MF had declined in entirety.² This interesting meta-analysis highlights the importance of continuing to report studies, even those with apparently significant treatment effects. In this group of patients the treatment benefit of ACI appears to have eroded over time.

Like seemingly all meta-analyses, one conclusion from this study is that there is a need for larger high quality RCTs studying the intervention in greater depth. However, there is much more of use in this study.

Contralateral knee pain and joint replacement outcomes

■ There are many factors that affect the outcomes of joint replacement (and other hospital interventions), with some of the most widely publicised in recent years being the hospital food and parking facilities. However, we sometimes forget what Charnley recognised; that involvement of other joints may determine outcomes as much as the benefit from the joint itself. This is particularly acute in patient-reported outcomes designed to measure functional outcomes and isolate the affected joint as much as possible, where it seems likely that disease in the contralateral knee may play a significant role in the outcomes of the affected joint. Researchers in **Boston (USA)** set out to establish if contralateral knee involvement affects post-arthroplasty outcomes after total knee replacement. The researchers designed a study with the aim of establishing the relationship between pre-operative pain status of the contralateral knee and the risk of a poor post-operative functional outcome in patients who underwent knee replacement. This study included 271 patient participants in the Multicenter Osteoarthritis Study who had undergone replacement since the time of enrolment in the

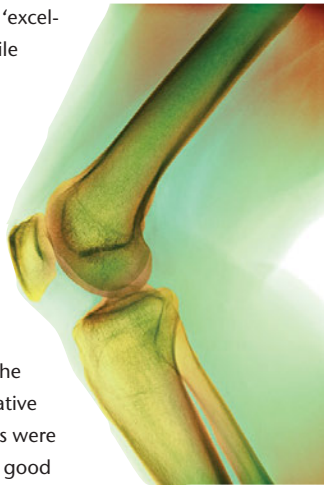
study. All patients had completed Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain scores for both knees at the time of enrolment. Patients were divided according to their contralateral WOMAC knee scores into four categories (0; 1 to 4; 5 to 9; and 10 to 20) and the outcome of arthroplasty of the affected knees assessed using the Patient Acceptable Symptom State (PASS) outcome tool and a clinical performance measure of walking speed. Around a quarter of the patients in the study were unhappy with the results of their arthroplasty (n = 72/264) and failed to attain the PASS threshold score. A slightly higher proportion (just less than a third) had objectively slow walking speed. There was a statistically significant correlation between poor outcomes on these two measures and contralateral pre-operative knee scores. Patients with the poorest pre-operative contralateral knee scores had an over four-fold risk of poor self-reported post-replacement scores. Pre-operative pain in this study was strongly associated with self-reported post-operative outcomes and this should be taken into consideration when interpreting patient outcomes.³

Patient satisfaction and knee replacement: the definitive study?

■ Registry mining is a new phenomenon with large datasets designed to monitor patient safety for new implants, and longevity of older implants being applied to answer as many questions as possible. A research team based in **Newcastle (UK)**, in conjunction with the NJR, set out to establish what could be learned from routinely collated patient data and patient-reported outcome measures. The authors identified 22 798 patients who underwent TKR and had completed nationally collected outcomes data (PROMS) over a two-year period including post-operative satisfaction measures. A surprisingly low proportion of patients, less than one in four,

rated their result as 'excellent' (n = 959), while over 70% identified their symptoms as 'much improved'. The authors used a logistic regression and structural equation, modelling statistical methods to establish which of the pre- and post-operative potential risk factors were best at predicting a good result. The authors were limited in the variables that they were able to include, as is the case with all registry studies. However, they were able to examine the predictive value of a number of pre- and post-operative variables including gender, diagnosis, revision surgery, mental health status, general health status, the Oxford Knee Score and symptom improvement. The chief finding of this impressively large registry study is that pre-operative variables (such as age, knee performance), while contributing to the overall picture, did not completely account for post-operative satisfaction. The authors ascertain that post-operative variables account for this in a more robust manner. The conclusion of the paper is that restricting care based on pre-operative arbitrary variables was unsound.⁴ While we believe in the spirit of the authors' sentiment, we are not sure that their results adequately support the authors' conclusions. The logistic models which these conclusions were based on include the post-operative outcome measures of EQ5-D and the Oxford Knee Score. These validated scores should be dependent variables on satisfaction ratings and, as such, the premise and conclusions of the paper are not only invalid, but misleading.

■ There is a significant incidence (quoted usually as around 5%) of painful knee replacements post-operatively. The scale of the problem is probably higher than this, with



the prevalence of poor outcomes including unrelieved pain following total knee replacement reported elsewhere in this edition of 360 as nearly one in four (see previous Knee Roundup). Here, we roundup two highly complementary papers and although not quite landmark, they

both significantly move our state of understanding about pain in knee replacement forwards.

Hope in the cytokines for painful TKRs?

■ In the first paper, a group of enterprising basic science researchers in **Toronto (Canada)** turned the problem on its head. Reasoning that pain pathways in osteoarthritis are far from understood, they designed an experiment to establish if a pre-existing inflammatory state prior to knee replacement could be responsible for post-operative pain. They enrolled a prospective cohort of 28 patients in a prognostic study (Level II evidence) to establish if inflammatory markers present pre-operatively were related to post-operative outcomes. Patients entering into the study had demographic data and baseline WOMAC scores recorded. Samples of serum and synovial fluid were taken at index operation and levels of a range of inflammatory cytokines characterised. These results were then linked to clinical and pain outcomes at two years with linear regression analysis. The research team identified higher levels of serum and synovial TNF- α , MMP-13 and IL-6 to be independent predictors of poor outcomes (as measured by pain) at two-year follow-up.⁵ The authors venture that there is a potential explanation in a poor inflammatory profile for patients with ongoing pain

following total knee replacement. We have to say that this is one of the most thought-provoking papers we have read in a long time. Perhaps the explanation for this disparity in outcomes lies in subtle differences in the disease process and not in any patient-related or surgeon-related risk factor. If this is indeed the explanation, then it is more interesting that the same disparity in outcomes is not seen in hip replacements.

Pain severity, cytokines and osteoarthritis?

■ In the second paper, researchers in **Tokyo (Japan)** have investigated the potential for differences in perceived pain from knee osteoarthritis based around measured cytokine levels. This study was of a considerably larger number of patients and the researchers were able to recruit 160 female patients with medial compartment osteoarthritis. Patients were assessed clinically, and both pain scores and the Japanese Knee Osteoarthritis Measure (JKOM) were used to assess outcomes. The research team graded 74 patients as having Kellgren-Lawrence grade 2 (early osteoarthritis) and the remaining 96 as severe. The inflammatory status within the joint was assessed using measures of serum interleukin-6 level and high sensitivity C-reactive protein (hs-CRP). Both have previously been shown to be markers of inflammation. The anatomical axis angle (AAA) was also measured with β -coefficient estimation (the authors adjusted this for age and BMI using a multiple linear regression analysis). Multiple linear regression analyses yielded IL-6 levels (but interestingly not AAA) to be associated with higher pain scores in both VAS and JKOM in the early stage of the disease. The counter was true in the more advanced cases of disease, with altered anatomical alignment becoming more important with the AAA, but not IL-6 levels being associated with VAS and JKOM scores.⁶ These researchers have set out to tease out the different potential contribution of mechanical malalignment and inflammatory status in early

and late knee osteoarthritis. We found their results fascinating. They certainly make sense and represent the beginnings of characterisation of the components of what must be a very complex multimodal pain model.

Quadriceps weakness and pain

■ The efficacy of physical therapy in treating osteoarthritis is discussed elsewhere in 360 this issue (see Hip Roundup 3) but not all physiotherapy is the same. In and around the knee, the presence of weakness in the extensor mechanism (particularly in young hypermobile adolescents) is well documented to cause pain and luxation. Improved muscle tone and condition seems likely to result in better knee stability and control, but whether these improved kinematics translate into improved outcomes is far from clear. Researchers in **Iowa City (USA)** have used the Multicenter Osteoarthritis Study (MOST) to establish if physiotherapy really does improve knee pain in adult patients with osteoarthritis of the knee. MOST is a longitudinal study of adults aged 50 to 79 with knee osteoarthritis (OA) or risk factors for knee OA. For the purposes of this study, the researchers used an isokinetic quadriceps strength measurement to establish if quadriceps strength was predictive of knee pain. Their analysis was relatively sophisticated and included measurement of covariates including age, BMI, activity level and history of knee surgery. Outcomes were assessed using the WOMAC score (or the event of requiring a TKR) over the five-year observation period of the study. For the purposes of this study,

4648 knees from 2404 participants were analysed for risk of worsening knee pain. The research team identified that men with lower quadriceps strength did not have a higher risk of worsening knee pain (RR 1.01), however, women in the lowest, compared with the highest, strength tertile had a 28% increased risk of worsening knee pain (RR (95% CI 1.28, 1.08 to 1.52), $p = 0.0052$).⁷ The authors conclude that quadriceps weakness was “associated with an increased risk of worsening of knee pain over five years in women, but not in men”. It certainly seems this way on initial reading of this paper, however, we do have some reservations. The authors have little idea what happened to the patients and, more importantly, the quadriceps strength during the time period of the study. While one interpretation is that there is a cause and effect happening here, another interpretation would be that as knees become more painful, pain inhibition prevents adequate quads function resulting in subsequent loss of muscle tone and function. A better observed prospective interventional study may be required.

Spontaneous osteonecrosis of the knee

■ Spontaneous osteonecrosis of the knee (SPONK) is a relatively common problem, about which we know not a huge amount. Cases are sporadic in nature and result in either resolution or collapse and osteoarthritis development, dependent in the most part by what happens in the subchondral bone. Researchers in **Lund (Sweden)** have designed a

prospective long-term observational study to establish precisely what the natural course of the disease is, and what the long-term consequences are. Impressively, the authors were able to follow 40 consecutive patients diagnosed with SPONK between 1982 and 1988. Patients were followed up clinically and radiologically at regular intervals. At early follow-up (between one and seven years), there were good radiographic outcomes in only 25% of patients (ten patients) with the remaining 30 considered radiographic failures, developing osteoarthritis. By 2012 (minimum 24-year follow-up) all patients were matched to the Swedish Knee Arthroplasty Register (SKAR) and their medical records evaluated, but not specifically clinically reviewed. At final follow up, 33 of the 40 patients had died with a mean follow-up of nine years (1 to 27). Nearly half the patients underwent major knee surgery ($n = 17$) with either arthroplasty ($n = 15$) or osteotomy ($n = 2$). All patients who underwent operative intervention, bar one, had been in the early radiographic failure group. Six of seven patients with large lesions ($> 40\%$ of the AP radiograph) at the time of the diagnosis ended up in the operated group. No patient with a presenting lesion $< 20\%$ underwent operation in the duration of the study.⁸ This is, to our knowledge, the longest follow-up for any patient series with SPONK, demonstrating quite clearly that the size of the osteonecrotic lesion can be used to predict the outcome. Patients demonstrating early osteoarthritic changes or large

osteonecrotic lesions have a high risk of later knee surgery.

REFERENCES

1. **Printz JO, Lee JJ, Knesek M, Urquhart AG.** Conflict of interest in the assessment of hyaluronic Acid injections for osteoarthritis of the knee: an updated systematic review. *J Arthroplasty* 2013;28(Suppl):30-33.
2. **Negrin LL, Vécsei V.** Do meta-analyses reveal time-dependent differences between the clinical outcomes achieved by microfracture and autologous chondrocyte implantation in the treatment of cartilage defects of the knee? *J Orthop Sci* 2013. (Epub ahead of print); PMID: 23934147.
3. **Maxwell J, Niu J, Singh JA, et al.** The influence of the contralateral knee prior to knee arthroplasty on post-arthroplasty function: the multicenter osteoarthritis study. *J Bone Joint Surg [Am]* 2013;95-A:989-993.
4. **Baker PN, Rushton S, Jameson SS, et al.** Patient satisfaction with total knee replacement cannot be predicted from pre-operative variables alone: a cohort study from the National Joint Registry for England and Wales. *Bone Joint J* 2013;95-B:1359-1365.
5. **Gandhi R, Santone D, Takahashi M, Dessouki O, Mahomed NN.** Inflammatory predictors of ongoing pain 2 years following knee replacement surgery. *Knee* 2013;20:316-318.
6. **Shimura Y, Kurosawa H, Sugawara Y, et al.** The factors associated with pain severity in patients with knee osteoarthritis vary according to the radiographic disease severity: a cross-sectional study. *Osteoarthritis Cartilage* 2013;21:1179-1184.
7. **Glass NA, Torner JC, Frey Law LA, et al.** The relationship between quadriceps muscle weakness and worsening of knee pain in the MOST cohort: a 5-year longitudinal study. *Osteoarthritis Cartilage* 2013;21:1154-1159.
8. **Juréus J, Lindstrand A, Geijer M, Robertsson O, Tägil M.** The natural course of spontaneous osteonecrosis of the knee (SPONK). *Acta Orthop* 2013;84:410-414.