Title:

Recent Clinical Trials in Osteoarthritis: What we have learned

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Abstract

Osteoarthritis is a chronic degenerative disease affecting growing numbers of the ageing population. Patients diagnosed with OA place a large burden on access to healthcare services, including primary care, prescription of analgesic drugs, physiotherapy and joint replacement surgery. Not all patients diagnosed with OA will require joint replacement surgery, and therefore avenues for non-surgical treatment for such patients needs to be explored in many cases. In this review we discuss current concepts underlying the pathophysiology of OA. These form a basis to understanding the rationale for new therapies based on recent evidence available from clinical trials in OA. In particular, we discuss the evidence for use of pharmacological treatments, including NSAIDs (non-steroidal anti-inflammatory drugs), chondroitin sulphate and glucosamine, hyaluronan, potential disease-modifying drugs and other interventions such as weight reduction and physiotherapy. Finally, we discuss new developments from trial evidence for joint replacement surgery.

Osteoarthritis – The burden of disease

Osteoarthritis (OA) is an arthropathy affecting predominantly synovial joints that is characterised by cartilage loss and a peri-articular bone response (1). In the early stages of disease, cartilage develops irregularities at the surface where it becomes fibrillated and appears moderately hypercellular (2). As the condition progresses, deep clefts form in the cartilage. There is loss of the main components of cartilage matrix which include the proteoglycan aggrecan and type II collagen. There is also evidence of cell clumping of chondrocytes within cartilage surrounded by regions of intense staining material indicating increased proteoglycan production. As ongoing cartilage damage occurs, the articular joint surface is damaged, leading to loss of joint function. Pathological features observed in the surrounding bone include osteophyte formation, bone sclerosis and joint space narrowing. Recently, evidence has shown that exacerbations of OA can be associated with a synovial reaction and such changes may be amenable to treatment with anti-inflammatory drugs (3, 4, 5). Clinically, subjects with OA can be divided into a number of subsets. These include patients with the following:

1. *Nodal generalised OA*

This is a well-recognised subset, characterised by polyarticular interphalangeal joint involvement of the fingers. There is formation of Heberden's nodes (distal interphalangeal joints) and Bouchard's nodes (proximal interphalangeal joints). In addition, this subset has a female preponderance, a

peak onset in middle age, often good functional outcome, predisposition to OA of the hip, knee and spine with marked familial predisposition (6). In families with hand OA, a greater concordance exists for monozygotic twins than for dizygotic twins (7). There is also an increased incidence of hand OA in first degree relatives (8). Strategies for treatment of this patient group include pharmacological therapies, physiotherapy and risk factor modification. Clinical trial evidence of such therapies will be discussed in further detail below.

2. Large-joint OA

The knee and the hip are the most commonly affected large joints in OA, primarily since they are the main weight-bearing joints in the body. Involvement can often be bilateral, although one side is usually more adversely affected. OA is a multifactorial disease in which genetic predisposition, age, oestrogen status in women and environmental agents all contribute to susceptibility. Changes consistent with OA of the hip and knee are often confirmed on plain radiography, as shown in Figure 1. Typical features include narrowing of the joint space due to loss of cartilage, osteophyte formation, bone sclerosis and bone cysts, which are believed to be responses to persistent mechanical strain on the joint.

In subjects with severe joint space narrowing and loss of function e.g. inability to walk reasonable distances with associated pain, several treatment modalities may be available. These include treatment of risk factors, analgesic therapies, exercise and weight reduction measures. If multidisciplinary approaches fail to control pain and loss of function, total joint replacement in the

large weight bearing joints with a prosthetic hip or knee, depending on the affected joint, is usually considered. Figure 2 shows a femoral head removed at the time of surgery from a patient with severe OA of the hip. Much of the pearly white appearance of normal cartilage has disappeared and the underlying eroded bone is visible (Figure 2). Disability in OA arises from reduced range of movement, diminished control of the affected joint and pain. The pain and functional consequences of OA are responsible for the large burden of morbidity in the community. Severe knee and hip disease contribute to a large financial cost on healthcare services in a generally older and otherwise fitter population. In a study by Lawrence *et al.* (1990), women (but not men) with OA of the knee had higher morbidity and cumulative mortality rates between the ages of 55 to 74 (9). Increased mortality has also been associated with OA of the knee in Sweden (10). To date, apart from joint replacement, few disease modifying therapies exist for the treatment of OA. In comparison, inflammatory arthritis e.g. rheumatoid arthritis and psoriatic arthritis, can be successfully treated with therapies including methotrexate and anti-TNF drugs that inhibit disease progression (11). There is therefore a need to gain a better understanding of the disease process in OA which could help lead to the development of more effective new treatments.

Clinical trials Addressing Risk factors for OA

Obesity

Obesity is associated with an increased risk of OA, especially at the hip, where the risk is higher for women (odds ratio 9.0) than for men (odds ration 4.5) (9). Other studies have shown that significant weight reduction can improve the pain score and function in subjects with OA (12). Furthermore, a study from the Multicenter Osteoarthritis Study reported that obesity was a risk factor for incident knee OA (13). In this study, researchers found that disease progression was affected by obesity particularly in subgroups of knee OA who had neutral or valgus changes, but not varus changes (13). These findings have implications on interventions for treating obesity in patients with OA. A recent clinical trial of 289 patients in the UK utilised an intervention of dietary advice and quadriceps exercises delivered to subjects with knee OA, either in combination, or alone (14). Primary outcome measures included severity of knee pain as assessed by the WOMAC score up to 24 months. The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score is one of the most widely used and validated assessment for subjects with OA (15). In the same study, secondary outcome measures included WOMAC knee physical function and stiffness scores and measures for anxiety and depression. The knee quadriceps exercise group achieved a significant reduction in pain compared with the non-exercise group at 24 months (percentage risk difference 11.61 with 95% confidence intervals 1.81 to 21.41%). By delivering a reduction in calorific intake of 600 kcal per day in the treatment group, the researchers achieved a moderate

sustained weight loss which was associated with reduced depression but this change did not influence pain or function (14). These results suggest that preventing the onset of obesity in the first place may be a better preventative measure for developing OA in weight-bearing joints as opposed to delivering intervention once patients have established OA in the context of also being obese. However, exercise interventions in the obese group of OA subjects certainly appear to be beneficial (16). Other studies are currently underway investigating the role of intensive treatment by exercise and dietary intervention in obese subjects (BMI 27-40.5) with OA, and results of such studies should be available over the next few years (17).

Injury

Major direct injury to a joint is a predisposing cause of OA such as total meniscectomy of the knee (18). Injuries including fractures may also alter mechanical loading and predispose to OA at distant sites, as with fractures of the femoral shaft (hip OA), scaphoid (wrist OA), tibia (ankle OA) or humerus (shoulder OA). Although major direct injuries are predisposing risk factors for OA, alone they are usually insufficient to cause OA. This is bourne out by the observations that not all subjects who undergo meniscectomy develop OA. Subjects who develop OA after direct trauma also have an increased predisposition for OA in other joints (18). However, when surgery has been used to intervene to treat mensical injuries, this has not always resulted in reduction in the progression of OA (19), suggesting that meniscal tears may contribute to

disease progression, but that other degenerative processes in the joint persist even when meniscal tears are repaired.

Pharmacological therapies for the treatment of pain in OA

This is part of the mainstay of treatment for many cases of OA. Treatment with analgesic therapies can be used to treat symptomatic joint pain in OA in a variety of regions, ranging from hand, wrist and shoulder to larger weight-bearing joints such as the hip and knee. Historically, the convention is to use analgesics on the pain ladder, starting with milder agents such as paracetamol, then moving on to NSAIDs and opiates until analgesic effect is achieved. Most recent studies have focused on newer NSAIDs for the treatment of OA and these agents will be discussed in further detail below. Topical therapies including hyaluronan and other agents such as glucosamine, chondroitin sulphate and new emerging drugs such as anti-NGF therapy will also be discussed in this section.

Non-Steroidal Anti-Inflammatory drugs (NSAIDs)

NSAIDs are widely used in the treatment of OA and many clinical trials have been devoted to studying their effects in patients with this condition. NSAIDs have a common mode of action which is to block prostaglandin synthesis through the inhibition of cyclo-oxygenase (COX) which catalyses the synthesis of prostaglandins and thromboxanes from arachidonic acid. There are two isoforms of COX: COX-1 is expressed constitutively in most cell types of the body, whereas COX-2 is induced particularly when inflammatory cells are activated e.g. by the cytokines IL-1 and TNF and it produces the prostaglandin

mediators of inflammation (20). Some of the earliest studies which looked at the efficacy of NSAIDs included agents such as phenylbutazone, mefenamic acid and indomethacin and many of these studies date back to the early 1970s (21, 22). Although several of the agents used initially were effective for their analgesic properties, they often required high doses and were associated with significant side-effects. These included renal, cardiac and gastrointestinal toxicity (23, 24). Over recent decades there has therefore been a pressing need to develop agents that have an improved efficacy profile with fewer side effects. This has led to the emergence of newer agents including diclofenac, naproxen, meloxicam and others that have a better efficacy and side effect profile (25). However, with chronic use drugs may accumulate their toxicity and therefore require further optimisation to limit their side-effect profile. These needs have in part led to the development of other agents such as COX-II selective agents that include etoricoxib and celecoxib that are in clinical use today. These drugs do not appear to inhibit COX-1 at clinical doses and are therefore reported to cause fewer gastroduodenal ulcers at clinical doses. Compared head-to-head, celecoxib and etoricoxib have been shown to be equally effective in improving pain responses in subjects with hip or knee OA (26). One of the major issues regarding prescription of NSAIDs in this population group, whether they are COX-2 selective or not, is their gastrointestinal toxicity and cardiovascular side-effect profile. A Guideline Development Group working for the National Institute for Health and Clinical Excellence recently reported that proton pump inhibitors, which are prescribed in patients taking NSAIDs for their gastroprotective effect, were cost-effective in patients taking conventional NSAIDs or COX-2 inhibitors at

preventing gastroduodenal ulcers (27, 28). More recent trials have focused on looking at reducing cardiovascular side-effect profiles in patients with OA taking NSAIDs and one of the largest studies of this kind was the MEDAL study (29). A meta-analysis of the MEDAL study (Multinational Etoricoxib and Diclofenac Arthritis Long-term) found that etoricoxib was associated with a higher incidence of hypertension in comparison with diclofenac in patients with arthritis (30). The same meta-analysis suggested that treatment of hypertension with calcium-channel blockers and concurrent NSAID use afforded better control of blood pressure in comparison with other anti-hypertensive agents assessed (30). More recently, cyclooxygenase inhibiting nitric oxide donators have been used in clinical trials to assess effects on blood pressure in patients with arthritis. White *et al.* (2009) reported that over 13 weeks of treatment, naproxcinod did not induce as many elevations in blood pressure as in subjects taking naproxen (31). Furthermore, the authors suggested that naproxcinod had similar effects to placebo on the blood pressure of subjects with OA over the time period studied (31).

Hyaluronic acid preparations

Hyaluronan is a normal constituent of the joint which serves functions of withstanding load-bearing and forming a large polymeric structure with the main proteoglycans in cartilage: aggrecan. It contributes to giving cartilage its properties to withstand heavy loads and resist mechanical forces, particularly on large weight-bearing joints including the hip and knee. Several clinical trials have been conducted in recent years proposing hyaluronic acid preparations as

potential treatments for relieving pain in OA. A number of formulations have been subjected to clinical trials, including hylan and hyaluronic acid derivatives (32, 33, 34). Most of the clinical trials have been conducted in subjects with established painful knee OA. The usual protocol for most of these studies has been repeated injections of hyaluronic acid e.g. series of three injections at weekly intervals. The primary outcome measures included assessment of pain and WOMAC (Western Ontario and McMaster Universities osteoarthritis index) scores. One of the earliest studies by Juni *et al.* showed an improvement in pain scores in subjects given three different forms of hyaluronan (32). Of interest, there were more adverse effects in the hyaluronan derived from avian sources in comparison with bacterial sources. In this non-industry conducted study, a therapeutic response to pain was maintained even at 6 months. More recent studies have included placebo arms e.g. with saline treatment to show that the analgesic effect is greater in the hyaluronan treated group (34). More recent trials have compared hyaluronan head-to-head with corticosteroids to obtain good therapeutic effect (35). Furthermore, trials are being reported of efficacy of hyaluronan in smaller joints as well e.g. the hand (36). It has also been suggested that repeated injections of hyaluronan may be effective (37).

Anti-NGF (nerve growth factor) monoclonal antibodies

Due to the side-effect profile associated with NSAIDs and the need to develop alternative therapeutic strategies to treat pain for OA, recent interest has focused on NGF (nerve growth factor) as a potential therapeutic target to treat

pain. In contrast to TNF, NGF acts primarily through a direct action on sensory neurones to induce hyperalgesia (38). NGF injection into animals or healthy volunteers leads to prolonged hyperalgesia and allodynia (39). Increased NGF production has been observed from RA and OA synovial cells and chondrocytes (40). Lane and colleagues recently reported on a clinical trial of tanezumab, an anti-NGF monoclonal antibody as a potential therapeutic target for pain in knee OA (41). They reported that repeated doses of 50 µg/kg tanezumab were generally safe and well tolerated in patients with knee OA and achieved analgesic effect up to 32 weeks. However, the full publication of this study including the side-effect profile, are awaited.

Glucosamine

There is experimental data from *in vitro* work suggesting that glucosamine has chondroprotective effects (42, 43). Various formulations are available, including glucosamine hydrochloride and glucosamine sulphate. A number of formulations of glucosamine have been in clinical use for many years and the early studies of its use date back to the early 1980s (44). It is now widely available as an over-the-counter nutritional supplement worldwide. Glucosamine has been reported to be efficacious in the oral form to relieve pain severity and improve function (45). Reginster *et al.* (2001) reported that long-term oral glucosamine sulphate improved symptoms in older non-obese patients who had primary knee osteoarthritis without inflammation (46). In a larger more recent study, the effect of glucosamine was compared versus placebo, chondroitin sulphate, glucosamine and chondroitin sulphate and celecoxib (47). This clinical

trial found that overall, there was little difference between glucosamine and placebo: the rate of response to glucosamine was 3.9 percentage points higher than placebo (p=0.3), in comparison with celecoxib which was 6.5 percentage points higher (p=0.008). A primary response was defined as a 20% decrease in the summed score for the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (47). Nevertheless, the same study suggested that the combination of glucosamine and chondroitin sulphate may be effective in a subgroup of patients with moderate-to-severe knee pain (ClinicalTrials.gov number, NCT00032890). A Cochrane review on the use of glucosamine has reported it is safe and improved pain more frequently than placebo (http://www.cochrane.org/reviews/en/ab002946.html). In current clinical practice, the use of glucosamine is therefore suggested to be of potential benefit as combination therapy with exercise as part of a multidisciplinary programme for OA management (48, 49).

Chondroitin sulphate

Chondroitin sulphate is a sulphated glycosaminoglycan. It is an important structural component of cartilage that provides cartilage with its ability to withstand compressive loads (50, 51). Chondroitin sulphate, like glucosamine, has become widely available as an over-the-counter nutritional supplement for use in the treatment of OA. In the USA, chondroitin sulphate is regulated as a dietary supplement by the FDA. In Europe, there is an approved formulation of chondroitin sulphate which is considered as a reference product, with evidenced efficacy and safety demonstrated by clinical trials in osteoarthritic patients.

Adebowale *et al*. reported in 2000 that of 32 chondroitin supplements they analysed, only 5 were labeled correctly, and more than half contained less than 40% of the labelled amount (52). In the largest clinical trial using chondroitin sulphate that has been conducted so far, Clegg *et al*. reported that in subjects with knee OA studied over a 24 week period, the rate of response to chondroitin sulphate was 5.3 percentage points higher than placebo (47). Of interest, the combination of glucosamine with chondroitin sulphate was 6.5 percentage points higher than placebo ($p = 0.09$). However, the greatest effect on pain improvement occurred in the celecoxib group overall with 10.0 percentage point rate of response ($p = 0.008$).

Other Potential Disease-Modifying therapy for Osteoarthritis

Some candidate therapies for disease-modifying drugs in OA have surfaced that are reported to inhibit proteolytic enzymes that are implicated in cartilage degradation in OA. These drugs include agents which inhibit MMPs (matrix metalloproteinases) and such agents may prevent collagen degradation in OA.

Work has been previously been conducted using doxycycline in a canine cruciate-defieciency model of OA (53). This study showed that reduced levels of active and total gelatinase and collagenase were found in extracts of of OA cartilage (53). These results have been replicated in human subjects given doxycycline undergoing joint replacement surgery (Smith *et al.* 1998). Other agents such as chemically modified tetracycline have been used in a surgically induced model of OA in rabbits (54). In the largest study of its kind using

doxycycline for potential disease-modifying effect, placebo was compared against doxycycline in women with unilateral knee OA. The trial involved treatment with doxycycline 100 mg twice daily in the treatment arm or placebo, also given twice daily. A total of 431 patients were recruited and showed after 30 months treatment that doxycycline slowed the rate of joint space narrowing in affected knees (55). Of interest, drug intake had no effect on joint space narrowing in the contralateral knee, suggesting that other factors may also be at play. One limitation of this study was that joint space narrowing was measured using plain radiographs, whereas other methods of imaging e.g. MRI may be more sensitive at detecting joint space narrowing, or bone marrow oedema, which has been implicated in the perception of pain in OA (38, 39).

Conservative Non-Pharmacological Management

Increased physical exercise has long been associated with improvement in pain and functional outcome in OA (14). However, there is a paucity of randomized clinical trials investigating specific interventions for the treatment of OA (56, 57). Although there is clear evidence for the use of physiotherapy post-operatively to improve outcome post joint replacement therapy (58), there are only a few studies suggesting the use of exercise as part of a multidisciplinary programme in the management of OA (59, 60). In a Cochrane systematic review for OA of the knee, land-based exercise was assessed (61). The 32 studies included in the analysis up to December 2007 provided data on 3616 participants for knee pain and 3719 participants for self-reported physical function. Meta-analysis showed a beneficial effect of treatment with a standardised mean

difference (SMD) of 0.40 (95% confidence interval (CI) 0.30 to 0.50) for pain; and SMD 0.37 (95% CI 0.25 to 0.49) for physical function (61). The Cochrane review reported platinum level evidence that therapeutic exercise has at least short term benefit in terms of reduced knee pain and improved physical function for people with knee OA. The magnitude of the treatment effect was considered to be small. However, the outcome of physical-based therapies was comparable to estimates reported for non-steroidal anti-inflammatory drugs. Exercise invervention for large weight-bearing OA of the hip and knee should now therefore be considered as part of integrated care for OA (62, 63). Such an integrated rehabilitation package has been shown to be an effective and cost-saving method of managing OA conservatively (64, 65).

Joint replacement surgery for Osteoarthritis

The surgical options for the treatment of arthritic joints include arthrodesis, excision, osteotomy and joint replacement (arthroplasty). In the hip and knee, arthroplasty has become the gold standard treatment and as success rates continue to increase, so the indications continue to widen.

Total hip replacement

In its present form, popularised by Sir John Charnley in the 1960's, total hip replacement is now well established as one of the most successful modes of surgical treatment available in modern healthcare systems (66, 68). Patients can

now expect low rates of complications, relatively short hospital stays, rapid return to function and longevity of fixation. Techniques and materials sciences have been continuously evolving since the 1960's such that the majority of patients now receiving total hip replacement can expect their primary replacement to last their lifetime (70).

Much of our improved understanding regarding the survival of arthroplasty prostheses is due to the development of arthroplasty registers. The forerunner and still world leader in this regard is the Swedish Hip Register. Other large registries also exist, including the Norway and Finland Joint Registries (67, 68) and more recently the Australian and the UK National Joint Registry . All Orthopaedic surgeons recognize the importance of registry data. The key points are that the data reported is surgeon generated, all surgeons should contribute so as to avoid bias from inventors and "experts" and the data can be interrogated by parties with nothing to gain from the results. In the UK we have seen a number of catastrophic implant failures which hopefully will be avoided in the future with the advent of a national joint register. Well compiled registry data can then be used to generate reports making important statements not only about the performance of various implants (68, 69), but also about other aspects of surgical technique and surgeon performance. The latter continues to cause concern in the surgical population, but as long as case mix is borne in mind, valuable information can still be made available both to individual surgeons and to institutions. As large joint registers gain in popularity many challenges still exist, particularly ensuring completeness of data, maintaining timely responsiveness

and keeping the data non-political. Ownership of the data remains one of the biggest concerns from a surgical perspective.

Hip replacements comprise of two basic components – femoral and acetabular. Broadly speaking, these can be divided into cemented and cementless implants. Hip replacements can therefore be cemented, cementless or hybrid (a combination of a cemented and a cementless component). Different survivorship data are available for each of these types of implants. The gold standard hip replacement is still the cemented hip. This is the type of hip that all others must be compared to in order to demonstrate equality or superiority. Data now exists showing that polished tapered femoral stems implanted with cement can survive for more than 30 years (70) . The Achilles heel of the cemented hip replacement remains cup fixation, but with modern cup design and cementing techniques long-term survival and low wear can be expected. Cementless implants gained popularity in the UK and USA as surgeons had concerns about cement and it is true that ossoeintegration can be reliably achieved with cementless implants (71). Although excellent data now exists regarding cementless implants (70), there is no data confirming superiority and these implants are associated with higher rates of fracture, stress shielding and thigh pain. Generally more expensive, cementless prostheses also place a higher burden on health economies than cemented (72).

Fixation to the skeleton, therefore, is no longer a major cause for concern. Much more attention has now been focussed on the bearing surface. Until

relatively recently the great majority of hip replacements have employed Ultra-High Molecular Weight Polyethylene (UHMWPE) as the bearing surface and this has functioned well. However, as fixation has improved so the need for materials with even lower wear rates has increased. Three newer bearing surfaces have been employed; cross-linked polyethylene, ceramics and metal on metal, with other novel surfaces in development.

Sterilising UHMWPE in gamma-irradiation causes chain scission in the long chain molecules and cross-linking. This results in the formation of cross-linked polyethylene and the amount of cross-linking is dependant upon the dose of radiation used. Cross-linked polyethylene has been used in hip replacement prostheses for more than 10 years and very low wear rates have been observed (73, 74). It is important that the cross-linking is performed in an inert environment so as to avoid oxidation which weakens the substrate and to remove any free radicals present at the end of sterilisation so as to limit the amount of oxidation that may occur *in vivo*. Concern also persists about the functional biological activity of any wear particles produced, but this has not yet been confirmed. Third generation cross-linked polyethylenes are now available which retain the mechanical properties of traditional UHMWPE, have extremely low wear rates and which are very much less vulnerable to oxidation processes. With lower wear rates, so the polyethylene can be made available in thinner implants so allowing for larger femoral head size with a greater range of motion and stability.

Ceramics have been available for many years as a bearing surface for hip replacements. Ceramics are extremely hard, well lubricated in the body and demonstrate extremely low wear rates. Difficulty in manufacture, expense and vulnerability to material fracture have limited success until relatively recently. Processes involving high temperature and pressure (HIP) optimises the material properties of ceramic femoral heads and acetabular liners. Risk of fracture is minimized due to a high density of consistently sized particles and additives such as platelets in certain processes. Large head bearing couples are facilitated and the wear rates with modern ceramics are so low, producing inert particles, so that the lifetime of a hip replacement will not be limited (77). Ceramics have not gained universal popularity, however, largely because of expense, persisting concern about fracture and concerns regarding squeaking (75, 76). Due to a combination of transient loss of lubrication, separation of components during gait and unusual forms of surface wear, a significant minority of patients with ceramic bearing surfaces report squeaking during various activities of daily living and this can be a cause for revision surgery in an otherwise well functioning hip replacement.

Ceramic on ceramic

Developed in the 1970's the Mackee-Farrar Hip Replacement demonstrated that extremely low wear rates can be achieved using metal-on-metal articulations (MOM). With accurate machining and appropriate tolerances long-term survival can be expected. MOM bearings can be produced in a relatively non-expensive method and large head couples are facilitated. The

major concern regarding MOM bearings is the biological activity of the wear particles produced. MOM bearings produce a very large number of sub-micron particles, particularly during the “running-in” period (78). Rate of production also varies with implantation technique, implant size and patient activity level. The metal wear particles are biologically active and can excite a local response which can be highly damaging to the tissues (ALVAL). Although not proven concerns also exist regarding propensity to tumour initiation and teratogenic risk.

Hip Resurfacing

As MOM bearings have regained popularity so interest has moved towards “conservative” hip replacement. Fundamental to this philosophy is the tenet that when revision surgery becomes necessary so more bone is available as less has been violated at the primary procedure. Hip Resurfacing has gained popularity in the UK during the last 10 years and has been termed the “high performance” hip amongst other terms. However as concerns regarding MOM bearings have increased (79), particularly local responses such as ALVAL so the popularity of hip resurfacing has dwindled. Femoral neck fracture and loosening have also been reported in certain groups of patients and with certain brands of implants. Hip resurfacing remains a successful implant in relatively young males with normal anatomy, but in other patient groups popularity with surgeons has reduced dramatically. Even in the young male group there is no demonstrable superiority in terms of function or longevity when compared to traditional hip replacements (80). Other conservative hip replacements are in development, but at this stage must be regarded as experimental.

Total Knee Replacement

The results of total knee replacement continue to be less good and less predictable than total hip replacement. Approximately 5% of patients have worse pain following “successful” total knee replacement than prior to surgery and the mechanisms for this are poorly understood. Current research is on-going to try and understand this better and psychological and socio-economic reasons may contribute as well as technical aspects of surgery.

There are many aspects of total knee replacement under investigation but none of them as yet have shown a definite advantage over the condylar, cemented “gold standard” total knee replacement[16]. Patellar resurfacing versus non-resurfacing, posterior cruciate retaining versus sacrificing knee replacement, fixed bearing versus mobile bearing (81), anatomical versus alternative geometry, cemented versus cementless fixation, highly crosslinked polyethylene and novel materials such as trabecular metal are all under evaluation, but persuasive, definitive trials are as yet elusive.

Computer navigation may have a role to play in total knee replacement. Traditional implantation methods employ intra-medullary and extra-medullary alignment rods which are unreliable and risk fat embolism. Use of computer navigation techniques avoid these rods, thus greatly reducing the risk of Fat embolism syndrome and implantation can be performed with a higher degree of

accuracy and reproducibility. As yet, however there has been little if any convincing evidence of clinical benefit to what is a very expensive system (82).

Unicompartmental knee replacement

The treatment of isolated compartment arthritis remains controversial. Medial compartment arthritis and patello-femoral arthritis can now be successfully treated with uni-compartment replacements and lateral compartment replacement is growing in popularity. These procedures rely on intact ligaments and near normal anatomy and are truly bone preserving when performed appropriately. Mobile bearing medial uni-compartment replacement can be associated with extremely good post-operative scores, probably better than the same group of patients receiving total knee replacements and longevity may be also as good (83).

Common to both total hip replacement and total knee replacement has been tremendous improvements in anaesthetic, nursing and rehabilitation techniques. High volume centres employing regional anaesthetic techniques with early discharge planning can achieve lengths of stay of 1 to 5 days following joint replacement (84) and this in the authors view has been the major advance in joint replacement surgery over the last 5 years. Regional anaesthetic techniques allow patients to recover with minimal pain and the incidence of thrombo-embolic complications and blood transfusion is also lower. In the early 21st Century, then, patients can expect minimal pain and a short stay following joint replacement, a major complication rate of approximately 1% and a hip replacement that will

function well for perhaps 30 years and a knee replacement for perhaps 15 (85) years. Further research will bring about only relatively small incremental change. The danger of ill-conceived innovation is recognised mainly through the Joint Registers and very long term follow up studies are now needed to illustrate differences between implants and techniques.

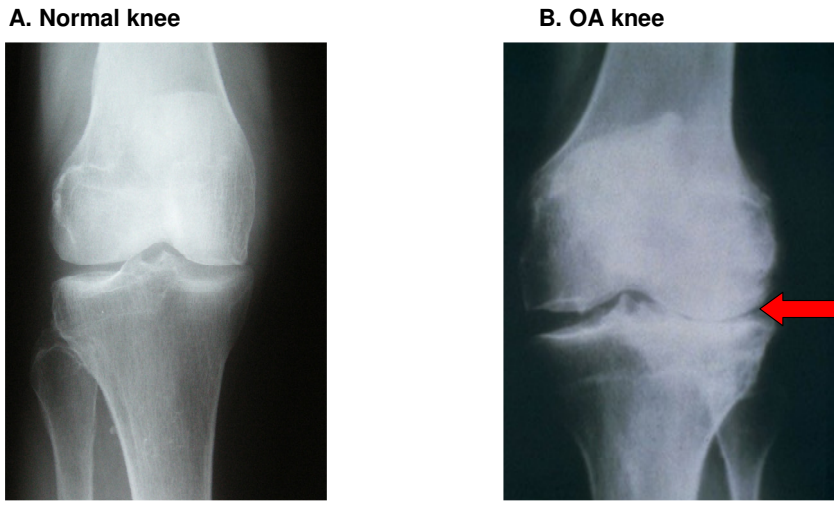
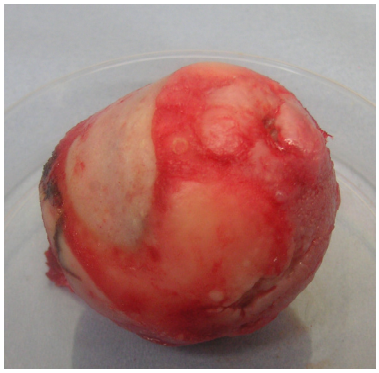


Figure 1.

Panel A. Normal knee joint demonstrated on radiography with even and smooth joint space

Panel B. Joint space narrowing at medial aspect of femoro-tibial knee joint from a patient with osteoarthritis (indicated by arrow)

A.



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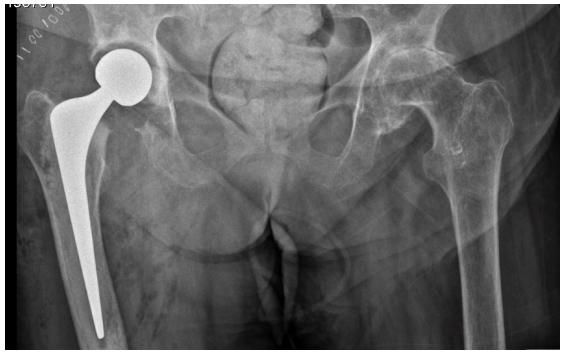

Figure 2. Joint replacement surgery for osteoarthritis

- **A.** Macroscopic appearance of a hip joint from a patient undergoing joint replacement surger. The femoral head removed at the time of hip joint replacement surgery from a patient with severe OA shows destruction of the articular cartilage. The normal pearly white appearance has disappeared to be replaced by denuded cartilage that reveals underlying bone.
- **B.** A prosthetic right hip is demonstrated in situ post hip arthroplasty

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