Arthroplasty options for the young arthritic hip

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Abstract: Total hip arthroplasty (THA) is a successful surgical option for the management of end stage degenerative joint disease allowing. Registry data reveals that the international trend is toward THA in an ever-younger patient population but the long-term outcomes may not be as good in this age group, with a lifetime risk of revision of 35% in patients younger than 55. The mean age at surgery, according to registry data is 68 for males and 70 for females. Patients under the age of 55 are considered young while patients under 30 are considered very young. We present a literature-based discussion of the various THA options available and consider the relative merits of each with regards to longevity, revision rate and overall outcomes in the younger patient. Cost effectiveness is also considered. Metal-on-metal hip resurfacing continues to have a place, but the use of uncemented THA with a ceramic head matched to a highly-crosslinked polyethylene or ceramic liner is safe; and offers excellent results in the majority of cases.

Keywords: Hip replacement; arthroplasty; young patient

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Introduction and background

Total hip arthroplasty (THA) is an immensely successful operation to treat end stage degenerative disease of the hip and can result in pain free motion, return to functional activities and improved quality of life (1). The caveat being it involves introducing a mechanical device of finite lifespan into a biological system; eventually all joint replacements will fail. With the increasing success of THA so have patients' expectations risen. No longer an operation of the elderly, joint replacement surgery is being undertaken on younger patients with the goal to return to high levels of activity (2,3). Younger patients present a challenge to the arthroplasty surgeon in that they are likely to have higher functional expectations, longer life expectancy and greater risk of wear due to higher cyclical load. The consequence of this is greater likelihood of revision surgery in the lifetime of a younger patient with a THA (4). There is a worrying correlation between younger age at initial surgery and lifetime risk of revision. Patients over 70 years have a 5% chance of revision surgery while for patients younger than 55 years, it is 35% (5). Improved bearing surfaces may lead to lower wear, longer lasting prosthetic joints and lower rates of revision. The ideal bearing has yet to be identified.

Age considerations

While modern marketing campaigns the world over drive the by-line that age is just a number, this is at best only partly true. There are numerous age-related physiological changes that occur which have an effect on the patient's course following joint replacement surgery. It is the number of cycles the bearing endures rather than the amount of time elapsed since implantation that determines the longevity of the implant. As activity levels decline by 15–20% per decade, older patients will impart less wear on the

THA bearing surface (6). It is estimated that the demand for arthroplasty in patients under 65 years will increase by 50% over the next 5 years (4). According to the American Joint Replacement Registry (AJRR) the mean age at surgery for THA in 2018 was 65 (±11) years and for hip resurfacing arthroplasty (HRA) it was 53 (±9) years; in total 27% of all hip replacements were in patients under 60 years (7).

The Australian Orthopedic Association National Joint Replacement Registry (AOANJRR) reports a mean age of 68 years with 12% of patients younger than 55 years and 25% between 55 and 64 years (8).

While there is no formal definition of what constitutes a "young" arthroplasty patient, a generalization is accepted as follows.

Young patients are considered in the age range below 55 years. This correlates with 1 standard deviation below the mean age at primary THA surgery.

While primary osteoarthritis is the most common indication for THA in the older patient, in the younger age group degeneration is usually secondary to an underlying condition. Developmental dysplasia of the hip (DDH), femoroacetabular impingement (FAI) and Perthes's disease result in altered joint mechanics, abnormal contact and increased shear forces at the cartilage interface; predisposing the native hip joint to earlier failure (1).

Very young patients are those under 30 years. These patients generally have a different pathological process and present unique challenges. Congenital and developmental anomalies, inflammatory (juvenile) arthritis and infective processes such as bacterial or tuberculous arthritis. Trauma and avascular necrosis (AVN) are some of the more common underlying causes of joint destruction in these patients (9).

Elderly patients (80–90 years) present a separate set of challenges related to medical comorbidities, spinal stiffness, subsequent dislocation risk and poor bone quality which may affect implant fixation or fracture risk.

The goal of arthroplasty surgery has moved from simply alleviating pain to returning patients to normal function. As such higher demands are placed on the mechanical construct. A study by Malcolm and colleagues found that while patients were able to reach the same level of activity after THA as matched controls [University of California at Los Angeles (UCLA) score 6.4 *vs.* 6.6] this was below the level of anticipated function expressed as a recorded desired activity level (7.7); patients expectations exceeded outcome in this group of high demand patients (3).

Failure of THA

Modes of failure in THA include fracture, instability/dislocation, failure of fixation, infection and wear related aseptic loosening.

Fracture may occur intra- or post-operatively and is more common in uncemented femoral components. Instability accounts for 17% of revision THA and may be due to impingement, failure to restore joint biomechanics in vertical and lateral offset, the use of small head sizes that have a decreased jump distance and poor implant positioning (10). Younger, more active patients have a lower dislocation risk (8) than elderly patients due to improved proprioception and muscle tone and better spinopelvic mechanics but changes occur with aging and late dislocations can occur (11). Prosthetic joint infection accounts for up to 15% of revision cases and wear related aseptic loosening accounts for 36% of THA revisions (8).

Aseptic loosening is one of the leading causes of THA failure requiring revision surgery. It is the result of the biological response to polyethylene wear debris and sets up an inflammatory chain reaction (12-15). The immune response is a type of foreign body reaction marked by granulomatous chronic inflammation mediated by osteoclast recruitment via the RANK/RANKL pathway (14,16). In a stepwise manner osteoclastic bone resorption leads to implant loosening, micro-motion and further dissemination of particulate debris within the periprosthetic space. The inflammatory response is dependent on the volume and size of wear particles; the range 0.24–7.2 µm being the most biologically active as they are phagocytosed by macrophages (14). The osteolytic threshold, below which the risk of osteolysis remains low, corresponds to a linear wear rate of less than 0.1 mm/year, a volumetric wear below 80 mm^3/year or a combined total wear volume 670 mm^3 (13). It is believed that a genetic predisposition to osteolysis exists but this has not been well defined (17).

Adverse response to metal debris (ARMD) is an umbrella term used to describe the local inflammatory response to metal wear debris and includes aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL), inflammatory pseudotumor and "Metallosis". ALVAL is a histological diagnosis; a lymphocyte mediated type IV hypersensitivity reaction results in activation of cytotoxic T-cells leading to microvascular changes, inflammatory cell infiltrate and fibrous disorganization (18). Pseudotumor may be asymptomatic in up to 30% of cases or painful and locally destructive—leading to mechanical failure, altered joint mechanics and gait disturbance from abductor dysfunction (19). At a macroscopic level "Metallosis" presents as the accumulation metal debris, synovial thickening, dark colored local tissue staining and sterile effusion and osteolysis. Systemic absorption of ionized cobalt and chromium may cause toxicity; cardiomyopathy, peripheral neuropathy, auditory and taste disturbance have all been described (19,20). Despite theoretical concerns, no studies have been able to show an increased rate of carcinoma in patients with metal-on-metal (MOM) THA and HRA (20). It is advised to avoid MOM bearings in young female patients even though no cases of fetal malformation associated with metal orthopedic implants have been described (19-22).

Ceramic is fully oxidized; biologically inert and wear particles do not exhibit the same propensity to an inflammatory response as polyethylene or metal (23-25). Volumetric wear is extremely low in ceramic-on-ceramic (COC) bearings (26,27). Failure due to fracture results in and third body wear (28-30). Bearing couples are discussed below.

Metal on polyethylene (MOP)

Cobalt-chrome alloy metal heads on "conventional" ultra-high molecular weight polyethylene (UHMWPE) liners, commonly abbreviated as MOP remain the most commonly used bearing combination in THA (23). UHMWPE was first introduced into mainstream orthopedic use by Charnley in the 1970's (1). It is the material with the longest track record, remains the most cost effective, the failure mechanism (osteolysis) is gradual and well understood and systemic consequences of polyethylene wear have not been described (23). MOP has the highest wear rate of any bearing material combinations in common use, reported to be in the range 0.1–0.2 mm/year (31). Fluid film lubrication cannot be achieved *in-vivo* therefore volumetric wear is directly related to head size (10,13). Oxidative failure in UHMWPE liners is also well described. UHMWPE liners stored in air following gamma irradiation sterilization had a linear wear rate of 0.4 mm/year, resulting in early osteolysis and failure (15).

The *in-vitro* volumetric wear rate of a 28-mm MOP bearing is 35–140 mm^3/year (10).

Metal on highly crosslinked polyethylene (MOPx)

Highly-crosslinked polyethylene, abbreviated to Px or XLP, is more resistant to wear than un-crosslinked polyethylene. The manufacturing processes include irradiation in an inert gas, heat annealing and the addition of oxygen scavengers (12,15). Each manufacturer uses proprietary crosslinking techniques and as such we should be careful of considering Px liners as single class, but rather a heterogenous group with similar properties. To date, no registry data prove superiority of any one type of Px over another. The combination of a cobalt-chrome head with Px liner, MOPx, has shown a significant improvement in wear when compared with MOP, with published wear rates being 43–100% lower (12).

The *in-vitro* volumetric wear rate for a 28-mm MOPx bearing is 5–10 mm^3/year (12).

Ceramic on highly-crosslinked polyethylene (COPx)

Ceramic heads have a number of advantages over metal ones when matched with Px liners. Ceramic is hydrophilic (wettable) and as such has better lubrication properties (32). Ceramic is also smoother with a lower co-efficient of friction (25). It is also harder and more resistance to scratching (23). Scratches on a metal head, at a microscopic level, have a sharp ridge on either side of the trough, increasing surface roughness and wear. This is not the case with ceramics, there is only a trough with no ridges (24). Metal heads are prone to developing trunnionosis, ceramic heads are not (33). The reported wear rates of COPx bearings are low, 0.03–0.05 mm/year which is well below the threshold for osteolysis (12).

The rise and fall of metal on metal

Advantages of MOM bearing surface include the absence of polyethylene particles which are known in initiate osteolysis, low volumetric wear, reduced risk of fracture compared to ceramic, ability to use large heads with a subsequent low dislocation risk and greater range of motion than small heads (12). MoM is also currently the only bearing surface available for resurfacing arthroplasty (21).

The initial enthusiasm which lead to the widespread use of MOM (around 20% of all THA during the early 2000's) was based on these advantages but enthusiasm has dwindled due to high revision rates. The low linear wear rate of MOM bearings (0.004 mm/year) and subsequent low volumetric wear, a 28-mm MOM bearing *in-vitro* generates only 1 mm^3 /year of particulate debris which is around 200 times less wear debris than polyethylene bearings (12,25). While the volume of particles is low, the particle size is much smaller and the number of particles generated are thousands of times greater. Corrosion leads to the release of ionized cobalt and chromium which has both local and systemic effects, already discussed. Modular MOM bearings have the potential to generate metal particulate debris from trunnionosis, articular wear, edge loading and backside wear. The all cause revision rate at 10 years for MOM THA is around 3-4 times higher than the equivalent THA with a MOP articulation.

Current guidelines advise ongoing surveillance for patients with a MOM THR or HRA (22). Patients known to be at high risk for ARMD are females, those with a head size smaller than 48 mm, cup position at risk of edge loading (increased inclination or anteversion) and patients known with elevated metal ion levels (19,21,34).

COC

COC bearings are desirable for their excellent wear characteristics (23,26). The fourth-generation or "Delta" ceramic bearing (BIOLOX Delta, Ceram Tec AG, Germany), accounts for 90% of the ceramic components in current use (26). It is a ceramic matrix consisting of alumina (80%), zirconia (17%) and strontium (3%) (12).

The *in-vitro* volumetric wear rate for a modern COC 28 mm bearing is 0.1 mm^3/year (26). With simulated edge loading, micro-separation and increasing the head size to 36 mm, the volumetric wear increased to 0.25 mm^3/year (26). In contrast a MOM bearing under the same conditions has a volumetric wear rate of 2–9 mm^3/year (26). Ceramic, being fully oxidized, is biologically inert and does not result in osteolysis (12,25,27).

The incidence of squeaking is variable, reported to occur in 0.7–20% of COC THA, with a recent large meta-analysis reporting an incidence of 3% (35). Higher rates were noted for head sizes larger than 40 mm, where it was 13% (36). The long-term clinical significance of squeaking is unknown, but there is an association with edge loading, stripe wear, impingement and micro-separation. This instability may account for the higher dislocation rate in these patients (28,36,37). Changes in auditory symptoms, clicking, grinding or new onset of squeaking may be an indicator of ceramic fracture and warrants investigation (28).

While early ceramics were prone to fracture, the rate of catastrophic failure with the new ceramics is significantly reduced, but not completely eliminated (30). The rate of fracture in modern ceramics is very low; in ceramic heads the range is 0.001–0.022% and in liners the range is 0.026–0.038% (38,39). No fractures have been reported in pre-assembled (liner in shell) acetabular components (38). It has been suggested that poor implantation technique, failure to correctly seat the liner, gives rise to the majority of these failures (29), but edge loading, impingement and micro-separation may also be a risk factors for fracture (28,36). Managing ceramic fracture is a challenge. Third body wear caused by hard ceramic particles leads to rapid wear, particularly of softer materials such as metal or polyethylene. Revision for ceramic fracture have a higher rate of failure than revision for other indications, up to 40% re-revision at 5 years (29). It is advised, whenever possible, to use a COC bearing in cases of revision THA following ceramic component fracture. Removal of all ceramic debris is essential, including thorough debridement, irrigation and synovectomy (30,40). The use of MOP and MOM bearing as a revision option is not advised as catastrophic third body wear may lead to high metal ion levels, systemic toxicity and local tissue destruction (41). COPx has reasonable short-term outcomes and may be a suitable option in revision cases where a ceramic liner is not compatible with the acetabular component (40). The disadvantages of COC have been well publicized but failure is rare, squeaking is for the most part benign and wear debris seems to be inert.

Conventional THA

Conventional total hip may be cemented, uncemented or hybrid. Debate regarding the relative merits of cemented and uncemented THA continues. It is reported that cemented cups have a higher failure rate than uncemented, in part due to polymethyl methacrylate (PMMA) cement having a poor ability to resist shear forces (42). Cementation technique (surgical skill and experience) plays an important role in the long-term outcome of cemented THA. This is reflected in registry data, where regions with a historic preference for cemented THA, such as UK and parts of Europe, have 10- and 15-year results in excess of 90% survival (18). In younger, active patients, cemented THA does not perform as well, in Australia the overall risk of revision from cemented implants was 48% higher than that of uncemented implants in patients aged 55 to 64 years (43).

Uncemented THA relies on osseointegration, bony on- or in-growth to the prosthetic component forming a permanent biological bond (42,44). Swedish registry results show that uncemented stems are revised twice as frequently as cemented stems during the first five years and overall cemented stems were ten times less likely to require revision for periprosthetic fracture (45). In young patients the revision rate for uncemented stems is lower than cemented variants; New Zealand joint registry data shows that cemented stems in patients under 55 have a revision rate twice that of uncemented stems. In contrast, patients over 65 with cemented stems have a lower revision rate. Early failure is more common in uncemented THA. The 90-day revision rate of uncemented stems due to fracture and loosening is significantly higher but this trend reverses over time and at 13-year follow-up, if these early failures are excluded, revision rates for uncemented stems are lower than cemented (0.62% *vs.* 0.66%). Late failures due to aseptic loosening are more common in cemented stems. Thigh pain in uncemented stems has been reported but is an uncommon reason for revision (46,47). Modern uncemented acetabular components have excellent long-term results with survival of up to 98.9% at 10 years (44). Hybrid THA, a cemented stem with an uncemented cup, is a reasonable option in all patients and is preferred in older patients (48). The bearing couple also plays an important role. Many of the MOM bearing THA's that were affected by ARMD related failure were coupled with uncemented components; a confounder that may influence registry results (49). The revision rate for uncemented THA on the National Joint Registry (NJR) was 8.25% compared to 3.63% for cemented THA at 11 years, but for COPx uncemented THA over the same period the revision rate was 3.62% (45). While there are many confounding factors within registry data including regional differences in surgical preference and training, disparate patient populations, the effect of bearing combination on wear and stability and threshold for revision surgery; it does appear that there is a slight advantage in the long-term outcome of uncemented THA in young patients.

HRA

The first generation of HRA was introduced in the 1970's and consisted of a metal femoral component paired with an all polyethylene acetabular cup (1). The aim was to preserve femoral bone stock for future revisions and provide a stable arthroplasty option for young, highly active patients; unfortunately, high volumetric wear rates of the polyethylene cup led to early failures. The most important, second-generation HRA, is the MOM bearing Birmingham Hip Resurfacing (Smith and Nephew, Memphis, TN, USA) was introduced by McMinn in 1997. Other designs were released shortly thereafter. Proposed advantages of MOM HRA are lower dislocation rates, more natural joint kinematics, improved gait, preservation of proximal femur bone stock and reduced thigh pain compared to stemmed THA. This results in higher functional activity and return to impact sport post HRA (2,21,50).

The well-publicized failure of some implants has led to much debate around the role of HRA in current orthopedic practice. The withdrawal from the market and recall of the ASR™ (DuPuy Orthopedics Inc., Warsaw, IN, USA) in 2010, affected 93,000 patients world-wide and has resulted a shift away from HRA (51). The Durom Acetabular Component (Zimmer Inc., Warsaw, IN, USA) was voluntarily recalled; the manufacturer deemed the instructions for use and surgical technique inadequate (34). In 2008, 10 different brands of HRA were actively marketed throughout the world, currently only 2 remain. In Australia, according to the AOANJR, in 2017 HRA accounted for only 2.7% of hip replacements (392 recorded cases) a decline of 78% from 2003, while in American current practice HRA accounts for less than 0.5% of hip replacement procedures (7,8).

Treating MOM HRA as a single class of implants is problematic. Design differences between HRA systems account for the different outcomes. Implants with low radial clearance, use of small head sizes and sub-hemispherical cup shape with a low cup articular arc angle (CAAA) result in significantly higher likelihood of edge loading and wear (42,52). Coupled with this, failure to achieve optimal position on implantation causes accelerated wear and subsequently results in a higher prevalence of ARMD and implant failure (12,34,52). A 30% revision at 7 years has been reported in some MOM HRA series (51). This failure, it has been argued, cannot be applied to all HRA implants.

HRA has excellent survival in selected patients; young males with a femoral head bigger than 48 mm, non-dysplastic acetabular morphology and good bone quality (21,50,51). Edge loading can be minimized by accurate cup position. In these patients, registry data shows that implant survival exceeds 95% at 10 years (53). Published series also reveal that when surgery is performed at high volume centers, by experienced arthroplasty surgeons in appropriately selected patients, the results are even better, up to 99.7% implant survival at 10 years (54).

HRA has traditionally been advocated in young, highly active patients; this introduces a significant amount of selection bias into any study focusing on activity levels and return to sport post-surgery. There are numerous, anecdotal, single patient "case series" in the popular media demonstrating return to high level sport following HRA but no randomized control trial to date demonstrates a functional benefit of HRA over THA in any age group. One study found improved gait kinematics in seven HRA patients over seven matched controls with THA while another study found no difference in proprioception between a group of THA patients (n=25) and HRA patients (n=25), with both groups having decreased proprioception when compared with the healthy controls (n=25) (55,56). Activity related thigh pain is more prevalent in young, large male patients with uncemented THA and it is possible that HRA would prevent this (47). In a retrospective review of patients under 55 years who underwent HRA (n=442) and THA (n=327) the HRA group had statistically significant lower complication rate (5.8% *vs.* 20.8%), lower revision rate (2% *vs.* 9.4%) and greater satisfaction (95% *vs.* 88%) than the THA group (50). All the HRA were performed by a single surgeon. In another review, the HRA group (n=124) had a higher patient reported satisfaction, mean UCLA score and less thigh pain than the THA group (n=682) (2). Selection bias cannot be excluded in either of these studies.

Another suggested advantage of HRA is that it is a less invasive and bone preserving procedure. The surgical dissection necessary to access the acetabulum with the femoral neck intact is at least as extensive and often more so than THA, and the acetabular component size is usually larger than matched patients with THA (57).

It has been reported that HRA has a lower all-cause mortality following surgery than THA, controlling for patient age, American Society of Anesthesiologists (ASA) score and medical co-morbidities (58). No satisfactory explanation for this finding has been published.

Revision following failed MOM HRA is not equivalent to a primary THR, with a re-revision rate of up to 26% (59). Revision options following failed MOM HRA vary depending of the indication. Wear related failure and ARMD requires local debridement and synovectomy to remove metal debris and revision of both the acetabular and femoral component (53,60,61).

In cases where the acetabular cup is well fixed and the failure is on the femoral side alone, either due to femoral neck fracture or osteolysis and loosening of the femoral component, revision to a femoral stem and retention of the acetabular cup may be preferable (60). A dual mobility (DM) head paired with a femoral stem is a good option as the use of large metal heads in THA have been associated with high failure rates and are no longer advised. It is important to consider the radial differences between the retained cup and available DM bearings (61).

Alternative bearing HRA, including all-ceramic and ceramic-on-poly HRA's, are currently being evaluated, but to date none are commercially available.

The ideal arthroplasty choice for the young and active patient

After elimination of the poor choices, there is not much evidence in favor of any one arthroplasty solution for the young, active patient; and we are left to consider the relative merits and disadvantages of each.

Despite the fact that internationally registry data supports a low failure rate of cemented femoral stems in young patients, the trend is toward uncemented THA in patients under 65 years. The registry data does not provide an answer as to which design is superior but evidence will probably emerge in time suggesting that anatomical variance should dictate the choice—the optimal uncemented stem will be the one that has the best conformity and bony contact within the patients' native anatomy and technology that enhances this will lead to improved outcomes.

Regarding choice of bearing in the young patient, a prospective randomized trial comparing ceramic-on-polyethylene (COP) (n=28) with COC (n=29) the all cause revision rate at 15-year follow-up was 16% (5 in each group). There were no functional differences noted but the wear rates in COP group were higher; osteolysis accounted for the majority of the revisions in this group while in the COC group there was one head fracture and one acetabular component loosening (62). This study is limited by the small cohort size. COPx is a good, cost effective bearing with a strong track record, has a low wear rate, is not prone to fracture failure and is generally silent. Registry data supports the use of this bearing combination in head sizes up to 36 mm (45).

COC exhibits excellent wear characteristics and the wear particulate debris is inert. The modern ceramic material has a low risk of fracture but if it does occur results of revision are worse due to third body wear (12,30,40,41). Squeaking, while rarely resulting in revision, is another problem that warrants consideration (35,36,63).

While the role of MOM HRA continues to be debated, the results in selected young patients, over a 20-year period, are excellent and in many cases superior to THA (53).

It is difficult to gain consensus, despite millions of data points collected across 24 joint registries in Europe, as well as USA, Australia and New Zealand. There are conflicting opinions due to the variety of prosthesis, surgical approaches and experience, fixation techniques and articulation options. Using revision as an end point introduces a bias as the threshold to intervene surgically may differ based on the difficulty of the procedure, the patients' general medical condition and what revision options remain available. The current generation of THA does not have a 30- or 40-year track record and despite good *in-vitro* data, it is not possible to extrapolate long term survival (26). Many cemented and uncemented stem, cup and articular options meet or exceed the National Institute for Health and Care Excellence (NICE) guideline of 95% 10-year survival and many implants, including MOM HRA, have Orthopaedic Data Evaluation Panel (ODEP) 10A or 13A ratings (7,8,45).

Cost effective THA

Internationally, the health care industry is under financial pressure. The cost of health care in both developed and developing economies is increasing at an alarming rate and the importance of cost containment cannot be overemphasized. It is almost impossible to compare the costs of the various treatments across countries as economies, treatment priorities, health models and access to care is different. The initial cost of an intervention must be offset by prevention of a future cost—if the use of a more expensive implant prevents a revision then it is cost effective. Uncemented implants are generally more expensive than cemented, ceramic is more expensive than metal and highly-crosslinked polyethylene is more expensive than UHMWPE (64,65). HRA is generally more costly than THA (65). The role of additional technology also needs to be considered such as 3-dimensional imaging, patient-specific guides or computer assisted navigation. It is unlikely that future improvements in THA outcomes will be as a result of improvements in material science or manufacturing but rather in improved planning and more accurate execution of this plan.

Conclusions

Current patients with degenerative joint disease are seeking joint replacement surgery at a younger age and have higher expectations than ever before. They are also likely to enjoy longer, more active lives after joint replacement surgery. While early and mid-term results are usually excellent in these patients, the future burden of revision surgery is yet to be realized. There is no single best arthroplasty option for the young patient and a paucity of long-term data on modern implants. A patient specific solution must be sought in order to strike the balance between the relative merits and disadvantages of each bearing and fixation option.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aoj.2020.02.05). AJS reports personal fees, non-financial support and other from Corin, personal fees from Smith&Nephew, personal fees and other from Matortho, outside the submitted work. The other author has no conflicts of interest to declare.

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