How does aseptic loosening occur and how can we prevent it?

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Abstract

Aseptic loosening is the loosening of a prosthesis from bone in the absence of infection or trauma. It is the most common cause for failure and revision surgery after primary total joint arthroplasty. The number of joint replacement procedures is increasing and with this, the revision burden is predicted to increase. It is therefore imperative to understand the causes of aseptic loosening, in order to reduce its occurrence. In this article the main causes of aseptic loosening are discussed, highlighting the integral part that wear particles play and the host's biological response to these particulates, resulting in osteolysis of the peri-prosthetic bone leading to aseptic loosening of the implants. Factors which result in an increase in the production of these wear particles are focused on, as it is crucial to be able to show how to prevent their production. The role of therapeutic treatments will also be discussed to show how they can be used to dampen down the host's response to these wear particles. The ultimate goal of these strategies is to ultimately reduce the catastrophic outcome of aseptic loosening and help reduce the revision burden. This will not only have both huge financial and significant service implications, it will also more importantly, significantly improve long-term patient outcomes and overall satisfaction and well-being.

Keywords arthroplasty; aseptic loosening; failure; materials; osteolysis; particles; prevention; revision; tribology; wear

Introduction

Aseptic loosening is the most common cause for failure of total joint arthroplasty. The National Joint Registry (NJR) for England, Wales, Northern Ireland and the Isle of Man reported 24.3% of all revision total hip replacements (THR) and 35.0% of all single stage revision total knee replacements (TKR) were due to aseptic loosening.[1]

Aseptic loosening is defined as the loosening of a prosthesis from bone, in the absence of infection or trauma[2] and it was initially coined the term 'cement disease'. However, it is now understood that aseptic loosening can occur because of inadequate fixation at the initial surgery, mechanical loss of fixation over time or biological loss of fixation due to any type of particulate debris leading to aseptic osteolysis and aseptic loosening of the prosthesis.[3]

The number of primary THR and TKR is increasing year on year,[1] and the revision burden is predicted to increase with subsequent consequences to both the patient and to the resources available. It is therefore imperative to understand the causes of aseptic loosening in order to reduce its occurrence. Identifying and addressing these causes can reduce the onset of aseptic loosening, and reduce the number of patients undergoing revision arthroplasty procedures.

Pathogenesis of aseptic loosening

Particulate debris can be formed from wear between articulating surfaces, non-articulating surfaces or between modular interfaces of the joint arthroplasty resulting in production of wear particles. These particles accumulate within the effective joint space. The effective joint space is the area around the joint where the implant comes into contact with bone, including around any screws, behind the cup and along the shaft of the stem.[4] Wear occurs via three main mechanisms: abrasive wear, adhesive wear and fatigue wear, all resulting in the production of wear debris and particles that play a central role in the development of aseptic loosening.[5]

Abrasive wear

Abrasive wear occurs when two materials with different mechanical properties come into contact. The harder of the two materials produces microscopic grooves in the softer of the two materials.[5] At a microscopic level, all materials have a roughened surface with peaks, termed asperities, and troughs. Asperities on the harder material abrade the softer material causing release of wear particles as a groove is created.[4] Abrasive wear is also seen when a third body material, such as cement, becomes embedded in a softer material, such as the polyethylene liner. This harder material causes abrasive wear of the femoral head, producing greater asperities and resulting in further increased abrasive wear of the polyethylene liner.[5]

Adhesive wear

Intermolecular bonds within a material differ in strength to the intermolecular bonds formed between two materials. When mechanical forces are applied to two contacting materials, this difference in strength results in the breakage of the weaker intermolecular bonds within one of the materials, causing adhesive wear.[5] For example, in a THR when the femoral head articulates with a polyethylene liner, the intermolecular bond formed between the junction of these two opposing materials is stronger than the cohesive strength of the polyethylene. As a result, the tips of the asperities are pulled off the polyethylene and adhere to the femoral head.

Fatigue wear

Fatigue wear occurs in a material due to cyclic loading at a stress that is below its ultimate tensile strength.[5] As a material is repeatedly loaded, the stress required to cause failure gradually reduces, known as the endurance limit. The process of fatigue wear can be expressed by the stress-number of cycles curve (S-n curve).[4,5] If a material is exposed to stresses below its endurance limit, then it will not fail and will survive indefinitely. Fatigue

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wear occurs more often in TKR than in THR as the stresses exposed to the polyethylene in TKR can be above the endurance limit, resulting in fatigue failure.[5]

Measurement of wear

Wear can be measured as either linear or volumetric wear over a defined time period. Linear wear describes the loss of height of the bearing surface and is measured in mm/year. Volumetric wear describes the volume of material that is removed by wear and is measured in mm^3/year. Several techniques exist for the measurement or calculation of both linear and volumetric wear. Linear wear can be measured simply by comparing the initial radiographs against the follow up radiographs, and measuring the distance of migration of the implant.[5] Approximate estimates of the volumetric year can be calculated by this method in THR, by assuming that the linear wear forms a cylinder the diameter of the femoral head and applying the equation: $V = \pi r^2 L$ where V is volumetric wear, r is the radius of the femoral head and L is linear wear.[4] Other methods include by direct examination of explanted cups[5] or by use of radiostereometric analysis using a radiopaque bead implanted in the bone at the time of surgery that can then be assessed in comparison to each other.[6] Wear is increased by the load, the sliding distance and the softer the material; it is reduced by the harder the material. These factors have a direct effect on the number of wear particles.

Wear particles

Wear particles produced have been theorized to cause an inflammatory reaction. The particles produced vary in size and shape, usually between 0.1 and 10 μm.[5] This particle size is recognized and phagocytosed by macrophages, resulting in their activation and initiation of an inflammatory cascade. The inflammatory response results in the production of numerous cytokines, including: tumour necrosis factor-α (TNF-α); interleukin (IL)-1 and IL-6; matrix metalloproteinases (MMP); prostaglandin (PG) E_2; transforming growth factor (TGF)-β and osteoclast precursors such as monocyte- and granulocyte-colony stimulating factors (M-CSF and G-CSF).[2,3,5] Plastic and metal particles are not able to be degraded by the enzymatic release from the macrophages. This results in repeated phagocytosis of the particles and a sustained release of these cytokines.[7]

Osteolysis

Bone homoeostasis is a closely regulated process, reliant on a balance between bone resorption by osteoclasts and bone formation by osteoblasts.[4] In aseptic loosening, exposure to particulate debris leads to long term release of cytokines and chronic inflammation, ultimately causing an imbalance in bone haemostasis.[2] Overall, this process leads to bone loss through increased rates of bone resorption.

Osteoclasts are derived from mononuclear osteoclast precursor cells, from a haematopoietic stem cell heritage, which fuse to form multinucleated osteoclasts. These cells differentiate and are activated in the presence of inflammatory cytokines, such as TNF-α and IL-1 and from receptor activator of nuclear factor kappa B ligand (RANKL) which is a TNF-related cytokine[7] formed by osteoblasts. Activation of osteoclasts results in resorption of bone. This resorption, if left unregulated around prostheses, leads to bone defects which in turn results in reduced bony support of the implant and micromotion. Micromotion leads to increased wear particles and further prosthesis loosening. Increasing the number of wear particles leads to further inflammatory response which increases the hydrostatic pressure within the effective joint space. This increased pressure allows circulation of the debris which further propagates osteolysis and ultimately, failure of the prosthesis, causing pain, instability and ultimately may require revision surgery.

Materials

All materials undergo wear, but the rate at which they wear depends on a number of factors. Material properties play a key role in wear resistance and therefore aseptic loosening. The main materials used in total joint arthroplasty include ultra-high-molecular-weight polyethylene (UHMWPE), polymethylmethacrylate (cement), metal alloys and ceramics. It is important to understand their manufacture, their mechanical properties, storage and their use as part of the joint arthroplasty to understand how they will wear, methods to reduce this wear rate and consequently reduce aseptic loosening and failure of the implant.

Ultra-high-molecular-weight polyethylene

UHMWPE is the most common bearing in total joint arthroplasty.[1] The final implanted product has undergone an extensive manufacturing processes which can both improve or worsen its material and wear properties. UHMWPE is made from the polymerization of the monomer ethylene. The production of high-density polyethylene was originally prepared via the Ziegler process[5] but there are now many methods to produce the UHMWPE we use today. The structure of polyethylene consists of both crystalline and amorphous regions; the crystalline component gives the polyethylene its mechanical strength, and helps to resist shear and compression forces. The amorphous component gives the polyethylene good wear characteristics. The ratio of these regions can be altered during the manufacturing process.

The solid polyethylene then undergoes further manufacturing processes to produce its final shape. This can be done by different techniques but the two most common methods are via direct compression moulding and ram-bar extrusion. Direct compression moulding directly produces the exact implant shape, whereas ram-bar extrusion needs to undergo secondary machining to form the desired shape.[5,8] The benefits of direct compression moulding are that it produces a smoother final product with better wear properties when compared to those produced with ram-bar extrusion, as the secondary machining results in increased surface roughness.[5]

Once the polyethylene implant has been manufactured, it needs to be sterilized for human use. Frequently, this is done using gamma irradiation, a process that results in formation of free radicals due to rupture of the polyethylene bonds. The free radicals produced either bond with oxygen resulting in oxidized polyethylene, or in an oxygen-free environment, the free radicals bond with adjacent polyethylene chains creating a cross-link within the amorphous regions, resulting in the formation of cross-linked polyethylene.[4] Cross-linking has a direct beneficial effect on its wear properties, producing increased resistance to both adhesive and abrasive wear, therefore producing fewer

polyethylene particles. The use of high-dose irradiation leads to highly cross-linked polyethylene (HCLPE) which has even better wear resistance. However, the increased number of crosslinks within the polyethylene adversely effects the material's mechanical properties. The polyethylene becomes more brittle, with reduced tensile and fatigue strength, pre-disposing it to fatigue and catastrophic wear.[5] HCLPE is used in THR bearing surfaces[9] rather than in TKR bearing surfaces as THR tend to fail due to adhesive wear, so increasing the cross-links reduces this, whereas TKR tend to fail due to fatigue wear which is more likely to happen in HCLPE.[5]

Secondary processing can be used to reduce the number of free radicals present within the polyethylene, formed during its production. The most common method is by use of heat annealing, a manufacturing process that heats the polyethylene to a temperature close to its melting point and then cooling. This reduces the number of free radicals, but does not completely remove the potential risk of in-vivo oxidation and polyethylene debris formation. Vitamin E can also be added to the polyethylene during the manufacturing process. Vitamin E acts as a free radical scavenger to remove the free radicals, therefore reducing the oxidization of the polyethylene.[4,5]

Maintaining an oxygen-free environment when storing polyethylene prior to its use is important to avoid any exposure to oxygen that can lead to oxidized polyethylene and greatly reduced mechanical properties. This is achieved by using vacuum packaging and oxygen-free gas packaging in argon or nitrogen.[4] Polyethylene products that are not used frequently, such as those at extreme of sizes, may remain unused on the shelf for long periods. This means they are more likely to become oxidized within their packaging and so are more vulnerable to increased risk of mechanical failure.

Polymethylmethacrylate (PMMA)

PMMA is used as cement in arthroplasty surgery. It is a polymer that is a solid in the polymer form. It is made from the polymerisation of methylmethacrylate monomers in an exothermic reaction. It interlocks with the endosteal bone and acts as a grout to anchor the prosthesis.[5] PMMA fatigues with cyclic loading and this fatigue occurs in stress points within the cement mantle.[4] Mechanical forces acting on the cement can therefore cause fracture and form particles which can then be recognized by macrophages and produce osteolysis. Fractures of the cement can lead to mechanical aseptic loosening of the prosthesis leading to micromotion and further biological loosening by particulate debris.[8] Cement debris also contributes to third body wear, with cement getting into the bearing surface resulting in abrasive third body wear, and forming wear particles from the bearing surfaces. It is therefore important to understand what factors can increase the fatigue of the cement so as to reduce it failing and resulting in aseptic loosening.

As PMMA polymerizes, it produces an exothermic reaction, which in large, thick cement mantles, can cause bone thermal necrosis. This can result in disruption of the bone-cement interface, leading to micromotion, wear and aseptic loosening. Methods to reduce this include pre-cooling the cement or pre-heating the implant, resulting in a reduction of the peak temperature at the bone-cement interface.[10]

Quality of cementation also has an effect on the initial stability of the prosthesis and can ultimately affect the chances of aseptic loosening. Decreasing the porosity of the cement, performed intraoperatively by the use of vacuum mixing, reduces air bubbles and results in less stress points in the cement. This results in a greater resistance to bending and therefore reducing fracture risk.[5] Lavage and drying of the trabecular bone prior to pressurized cementation enhances cement interdigitation and improves the bone-cement interface.[4] A field contaminated with blood produces a cement mantle with more defects and therefore increased failure risk.[5] A stem centralizer, used with stemmed arthroplasty prostheses, allows for a uniform cement mantle and prevents the prosthesis from touching the bone which would result in a high rate of stem loosening.[4,8]

PMMA is made up of many components, all of which can affect the material properties of the final product. Antibiotics are commonly added to reduce periprosthetic infection, but in large quantities can adversely affect the material properties and leave antibiotic inclusions within the cement, resulting in increased risk of loosening.[5]

Finally, the use of a stiff prosthesis such as with the use of cobalt chromium and stainless steel stems reduces the bending stresses on the cement mantle and results in less failure of the cement.[4]

Metal alloys

Cobalt chrome, stainless steel and titanium are the three main metal alloys used in orthopaedic implants.[5] Their wear properties are dependent on their composition of metallic and non-metallic elements and the method used to produce them. These metal alloys are subject to both mechanical and electrochemical wear.

Mechanical wear between metal-on-metal articulations produces small metal wear particles measuring between 10 and 500 nm.[5,8] At this size, the metal wear particles produce less local inflammatory reaction from macrophages than polyethylene, therefore macrophage driven osteolysis is very rarely seen with metal-on-metal bearings.[5] These particles can be excreted, unlike the larger particles of UHMWPE, as they can be transported away from the joint capsule and taken up systemically. These metal particles can also corrode and therefore disappear.[8] Metal-on-metal bearings also have the benefit of being able to 'self-heal'.[5] This means that when third body wear occurs on a bearing surface, the imperfections are polished smooth, leading to less abrasive wear. However, these wear particles do still produce a T-cell lymphocyte[4] mediated biological response. This can result in two responses: an initial hypersensitivity reaction and a delayed adverse local soft tissue reaction in the form of a pseudotumour formation; this has been termed aseptic lymphocyte vasculitis-associated lesions (ALVAL).[5] This is driven by the RANKL system resulting in osteolysis and aseptic loosening of the prosthesis as well as necrosis of surrounding soft tissues.[4] This explains why metal-on-metal bearings in THR, despite their many benefits, have been largely phased out of clinical practice in the last few years.[1]

Electrochemical wear occurs through corrosion. This is when a metal within a solution undergoes unwanted dissolution.[5] The three most common metal alloys are usually highly resistant to corrosion, as they form a self-passivation layer. However, it remains important to understand factors leading to corrosion, in order to reduce the amount of electrochemical wear and therefore reducing the risk of aseptic loosening. Corrosion can either be generalized, termed galvanic corrosion, or localized pitting and crevice corrosion. Galvanic corrosion occurs when two dissimilar metals come into contact. Therefore, where two metals come into contact in joint arthroplasty, for example at the neck taper junction of a modular femoral stem and head, it is important to use similar metals to reduce the electrochemical degradation with human tissue. Using cobalt chrome and stainless steel together has the highest potential for galvanic corrosion.[4] Localized corrosion occurs due to damage to the metal, particularly at the passivation layer. It is therefore important to understand the factors which increase localized damage to this passivation layer such as at the junction of the modular components, so as to reduce the localized damage to the metal alloy, and to prevent localized corrosion which can lead to premature structural failure of the implant.

Cobalt chrome is commonly used as a bearing surface in THRs along with UHMWPE.[1] Overall, metals are tough and resist abrasive wear but cobalt chrome can be manufactured to overcome adhesive wear by having a high carbide content which increases its hardness and therefore scratch resistance.[5] Improving these wear properties results in lower wear rates and reduces aseptic loosening.

Cobalt chrome has a high elastic modulus and is stiffer than cortical bone.[5] As a result, when used within a prosthesis it can lead to stress shielding due to this mismatch which results in micromotion of the implant, subsequently leading to aseptic loosening. However, cobalt chrome does produce less wear particles than titanium alloys and has a better resistance to corrosion than stainless steel.[4]

Stainless steel is another common metal alloy used in joint arthroplasty. It has a similar Young's modulus as cobalt chrome, which again means it is stiff compared to cortical bone, leading to stress shielding. It is less resistant to corrosion than cobalt chrome alloys but it can be manufactured to improve this resistance with the use of nickel, chromium, manganese and molybdenum.[4]

Titanium: unlike stainless steel and cobalt chromium alloys, the elastic modulus of titanium is lower, meaning that there is less of a mismatch between that and cortical bone. Titanium implants therefore undergo less stress shielding so lead to less aseptic loosening due to this. Titanium undergoes self-passivation which helps decrease corrosion.[4] However, it is relatively soft, which means that it is highly likely to undergo abrasive and third body wear[5] leading to reduced particulate formation and aseptic loosening.

Ceramics

Within joint arthroplasty, ceramics are commonly used as a bearing surface in THR; most commonly as a ceramic femoral head on UHMWPE cup with increasing numbers over the years,[1] but also as a ceramic-on-ceramic THR bearing[1] as well as for TKR.[5]

Ceramics are popular in bearing surfaces as they are very smooth, leading to low friction and abrasion resistance.[5] They are also known to be highly wettable, a property which aids in lubrication of the bearing surface and further reduces friction leading to reduced linear wear rates in ceramic-on-ceramic bearings when compared to standard bearings.[5] Despite these properties, osteolysis, albeit rare,[5] still occurs with ceramic bearings[8] and can lead to aseptic loosening.

Ceramics have a higher elastic modulus than metal alloys, making them stiff.[4,5,11] When compared to bone, there is a large mismatch and so stress shielding occurs, which can lead to loosening and the production of further wear particles. Ceramics are also brittle, which limits some of their uses, but production processes can improve this property to make them less likely to fracture.[5]

Techniques to reduce aseptic loosening

Understanding the biological response to wear particles and their method of production needs to be understood to establish methods to reduce aseptic loosening of total joint arthroplasty. Reducing the number of wear particles produced has largely been discussed earlier in this review, with the main focus on the use of materials within the total joint arthroplasty that have better wear characteristics to prevent their production. However pharmacological therapies can be utilized to address the biological reaction to the particles that are produced to reduce the osteolysis that occurs leading to aseptic loosening.

Preventive strategies

The best method of reducing aseptic loosening is to prevent the wear particles being produced in the first place. This can be done by addressing implant design, patient factors and intraoperative surgical factors.

Implant factors: the most important implant factors related to the development of wear and aseptic loosening are the material properties of the implant, the bearing surface, implant modularity, geometry and method of fixation.[12]

The choice of material plays a large role in governing the number of wear particles. Implants acting at a bearing surface should: have a low coefficient of friction; be hard, to improve their scratch resistance and reduce adhesive wear; have a low surface roughness; be tough to reduce abrasive wear. Choosing materials mentioned earlier in this review with these properties will reduce wear rates, for example ceramic-on-ceramic bearings in THR have the lowest linear and volume wear rates per year.[5] However, it is evident from the NJR that metal-on-polyethylene bearings are still the most commonly used,[1] possibly due to other unfavourable properties of ceramic bearings.

It is also important to understand the materials used and how they are manufactured, as this can also reduce wear rates. For example, the use of HCLPE in THR as a bearing surface has been shown to have less wear than UHMWPE,[9] and UHMWPE that is manufactured by ram-bar extrusion has a higher linear wear rate than when manufactured via compression moulding.[5] Understanding this, and accounting for it at the time of surgery will

prevent the production of wear particles and subsequently reduce aseptic loosening and failure of the implant.

Implant materials are also important when trying to reduce stress shielding. Implants with a large mismatch between their elastic modulus and the bone's elastic modulus will result in more force being transmitted through the implant rather than the bone. This will then result in stress shielding of the bone leading to aseptic loosening of the implant.[4]

The modularity of implants can affect the wear rates of total joint arthroplasty. Modularity is utilized as it allows liner exchange, fine-tuning of implants to improve stability, rotation of bearing surfaces and screw fixation of acetabular shells. However, this leads to another non-articulating surface within the construct, increasing the risk of the production of wear particles. It also allows interaction of potentially different metal alloys, which can increase the chance of electrochemical wear. It is important to weigh up the risks and benefits of a modular system. For example, the use of mobile bearings in TKRs has been used to try and eliminate the high contact stresses produced from the lack of conformity in all TKRs. However, this has not been shown clinically to reduce wear rates or lower revision rates.[5] Furthermore, the use of screws and screw holes within metal backed acetabular components also increases the effective joint space, which increases the potential area that wear particles can be distributed to and cause osteolysis and aseptic loosening.[4]

Geometry of implants should be considered to reduce the production of wear particles. Large femoral heads have an increased volumetric wear rate compared to smaller femoral heads.[4,5,12] However there is a trade-off, as the smaller the head the higher the linear wear rate is, and so the more likely it is to wear through the polyethylene.[4] Large diameter femoral stems that are solid are stiffer than stems that are hollow or have slots or flutes. This leads to an increase in femoral stress shielding of the proximal femur leading to aseptic loosening.[4] In TKR, the geometry of the articulating surfaces is extremely important. In posterior cruciate retaining TKR, the polyethylene insert is usually flat to allow for flexion rollback. This can lead to increased edge loading and contact stresses resulting in increased production of wear particles.[5] Moreover, the posterior cruciate retaining TKR has altered mechanics leading to a forward sliding movement, which causes significant sliding wear of the polyethylene insert and can also lead to aseptic loosening.[4] A more congruent articulation, such as with a posterior cruciate sacrificing TKR, despite having reduced contact stress between the femoral component and polyethylene insert, increases the constraint, which subsequently increases the shear stresses at the implant—bone interface which can lead to loosening[5] as well as having an additional tibial post on the insert which can wear and subsequently lead to wear particles and osteolysis.[4]

Lastly, the method of fixation of the implants can also affect the risk of aseptic loosening. Implants can either be fixed to bone with or without cement (cemented and uncemented implants respectively).[4,5] If an implant has a circumferential fixation to bone or cement this may prevent debris from gaining access to the bone—implant interface thereby reducing the effective joint space and area that osteolysis can occur at. The other main reason for the importance of the fixation of the implants is to reduce the wear particles produced from a non-articulating surface. Cemented implants can either have all interfaces fixed, such as the composite beam THR, or just the bone interface fixed with the implant free to move such as with the taper slip THR.[5] Cement can fatigue with cyclic loading and starts at stress points within the mantle, which have been mentioned earlier. This can lead to mantle defects which can then lead to the prosthesis moving within the cement and forming wear particles and leading to aseptic loosening.[4] Debonding at the implant—cement interface also allows for a potential non-articulating surface, with an increase in shear stresses occurring in the cemented femoral component of a THR and compressive stress forces occurring in the cemented acetabular component, leading to wear particle production.[8]

Cementless fixation relies on biological fixation either via bone ingrowth or bone ongrowth. Initial fixation is important before this biological fixation occurs and can be either using the press fit technique, relying on compression hoop stresses to secure the implant in place, or line-to-line technique which relies on frictional fit of the implant in the bone with potential for screws through the implant into bone to secure it in place.[4] It is this initial fixation that is important, as movement of the implant before biological fixation has occurred can lead to wear particle production at the bone—implant interface, as well as abnormal positioning, which can affect the biomechanics of the total joint arthroplasty, subsequently leading to increased wear rates and osteolysis.

Patient factors that can lead to aseptic loosening can either be modifiable or non-modifiable factors. One non-modifiable risk factor related to increased aseptic loosening in THR is the male sex. A recent systematic review exhibited an odds ratio (OR) of 1.39 (95% confidence interval (CI), 1.22—1.58; $p = 0.001$) for aseptic loosening in males when compared to females.[13] Other reviews of aseptic loosening[8] have also reported on studies that have shown a large variation between individuals in the response to polyethylene wear particles. Therefore, genetic factors play a role in the host response to wear particles and subsequent osteolysis and aseptic loosening. Total joint arthroplasty in the future, through further research and developments in this area may be able to identify those patients with a heightened response and target it with treatments to reduce their response and reduce aseptic loosening.

Modifiable risk factors are important in identifying as these can be targeted to reduce the risk of aseptic loosening in patients undergoing total joint arthroplasty. However, a systematic review by Cherian et al.[13] only identified one modifiable risk factor associated with aseptic loosening, and this was high activity levels in patients with a THR compared to those with moderate or low activity levels (OR 4.24; 95% CI 2.46—7.31; $p = 0.001$). Body mass index (BMI) and tobacco use in TKR and THA and activity levels in TKA were not associated with increased aseptic loosening, but the authors suggest their cohorts are too small, and so with appropriately powered studies, this may show areas for potential focus.

Surgical factors: intraoperative techniques are very important in optimizing total joint arthroplasty to reduce the production of wear particle production. This review has already discussed the importance of third body wear in the production of wear

particles. This is overcome intraoperatively by the use of irrigation which helps to ensure that debris such as small fragments of cement and bone are washed out at the time of the operation.[12]

When using PMMA in total joint arthroplasty, reducing the imperfections can help improve quality of the cementation and the bonding at the bone—cement and cement—implant interface. This results in a reduced effective joint space and reduced movement of the implant. This leads to a reduction of the amount of wear particles produced at these non-articulating surfaces. Additionally, this leads to a reduction in the failure of the cement, which can lead to fracture and failure of the total joint arthroplasty. Intraoperative techniques have been largely discussed earlier in this review, however, using third-generation cementation techniques with vacuum mixing, use of a cement restrictor, lavage and drying of the trabecular bone, pressurization of the cement and the use of stem centralizers improves the cementation technique[5] and can help reduce aseptic loosening in the long-term.

Careful handling of implants can reduce intraoperative damage to their surface. Scratches and imperfections made during surgery can result in damage to the protective passivation layer on the surface of metal alloy implants. Damage to this layer, if not reformed, can result in electrochemical wear which can accelerate the wear process of the implant, leading to aseptic loosening. Similarly, scratches and damage to bearing surfaces, particularly the femoral head, lead to increased surface roughness, ultimately accelerating abrasive wear, volumetric wear, total penetration and ultimately higher wear particle production.[5] This can then lead to premature aseptic loosening.

The positioning of implants is important to postoperative function and outcome. Malalignment of implants can increase the risk of micromotion[8] and contribute to the risk of revision.[1] Micromotion can affect implant stability, leading to an increased effective joint space, production of wear particles at a non-articulating surface and loosening of the implant. In THR, a vertically aligned acetabular component leads to pelvic osteolysis due to abnormal load distribution and load bearing through the lateral aspect of the liner.[12] Correct positioning of the components will reduce this and allow for a congruous bearing surface, with distribution of the load, and reduced wear. In TKR, an implant that has not been balanced correctly, will lead to increased varus—valgus, anteroposterior and rotational movements, which can lead to an increase in load and contact stresses at the bearing surfaces. This can lead to increase wear particle formation and accelerated osteolysis around the implant and aseptic loosening.[5] Therefore, accurate implant positioning and restoration of normal anatomy for soft tissue balancing, is very important in reducing the risk of aseptic loosening in total joint arthroplasty.

Pharmacological therapies

The biological response to wear particles is complex and involves many pro-inflammatory cytokines and cell lineages. This response ultimately results in osteoclastic mediated bone resorption around the implant, leading to the development of aseptic loosening. These complex pathways offer several potential therapeutic targets to inhibit or prevent these biological responses and therefore aseptic loosening. Three distinct pathways have been proposed as potential therapeutic targets:

1) immune cells that mediate the inflammatory response to wear particles
2) osteoclasts that mediate bone resorption
3) osteoblasts and osteoclasts whose anabolic function is inhibited by wear debris.[14]

Bisphosphonates are small organic compounds that are understood to have an anti-resorptive effect on bone. Bisphosphonates are deposited within the bone matrix, making it more resistant to resorption. In addition, nitrogen-containing bisphosphonates, such as alendronate, ibandronate and risedronate, also exhibit specific inhibitory activity towards osteoclastic bone resorption, inhibiting the formation of the cellular brush border and proper functioning of signalling proteins.[5] They have been well established for use in the treatment of diseases characterized by osteoclast-mediated bone resorption, such as osteoporosis, Paget's disease and metastatic bone disease.[15] Additionally, they may also have a beneficial effect on periprosthetic bone resorption. Multiple studies have examined the use of bisphosphonates after THR and TKR and their effect on the maintenance of peri-prosthetic bone mineral density. Meta-analyses of these studies has demonstrated that bisphosphonates reduce early peri-prosthetic bone loss following both THR and TKR.[15,16] Furthermore, analysis of data from the UK General Practice Research Database found patients concurrently taking bisphosphonates and undergoing primary THR or TKR had an almost twofold increase in implant survival time compared with those not taking bisphosphonates. It was found that 107 patients needed treatment to avoid one failure.[17] However, it should be noted that the observed improvement in implant survival time may be as a result of both the anti-resorptive effect causing a reduction in fracture risk in addition to a reduction in aseptic loosening. The potential side effects associated with bisphosphonates should also be taken into account when considering therapeutic use, including atypical femoral fractures, which have been observed in the context of hip arthroplasty.

Biologics are a group of medications used to suppress the immune system and reduce inflammation. Their efficacy has been established for the treatment of inflammatory conditions, including rheumatoid arthritis.[18] Biologic agents act upon components of the immune system that play key roles in the development of inflammatory joint pain, destruction and deformity.[14] Some of these biologics act to inhibit TNF-α (adalimumab, certolizumab, etanercept, golimumab, infliximab), IL-1 (anakinra) and IL-6 (tocilizumab). These inflammatory cytokines are also central to the process of osteoclast mediated bone resorption and therefore offer potential therapeutic options for the prevention and management of aseptic loosening. However, these drugs are associated with serious potential adverse effects, including higher rates of serious opportunistic and bacterial infections.[18] Unlike for inflammatory conditions, the potential benefits of reducing inflammation related to wear particles may not outweigh the potential harm of these drugs, therefore making their potential routine use less attractive.[14]

The RANK antagonist biologic drug denosumab offers another potential therapeutic agent in the management of periprosthetic osteolysis.[14] The RANK signalling pathway is essential for osteoclast differentiation. The inhibition of RANK signalling and the resultant inhibition of osteoclastogenesis has been shown to

prevent wear particle debris-induced inflammatory osteolysis in mouse models[19] and offers a potential future research avenue in the prevention of aseptic loosening.

Recombinant parathyroid hormone (teriparatide) is an anabolic agent used in the treatment of osteoporosis.[5] Its intermittent administration results in increased bone formation via an anabolic effect on osteoblasts in excess of the resorptive effects it produces upon osteoclasts. It is this effect upon bone homoeostasis that may allow teriparatide to be considered as a prophylactic agent for the prevention of wear particle-induced osteolysis.[14]

Conclusion

Aseptic loosening continues to be a major complication and is the leading cause of failure and subsequent revision of total joint arthroplasty. The production of wear particles, from both the intended articulating surface as well as from non-intended articulating surfaces, play a pivotal role in the process of aseptic loosening via the host's biological response to the wear particles and the osteolysis of the bone around the implant that ensues. Understanding the factors that lead to the production of wear particles and strategies to prevent their production and to reduce the biological response is paramount so as to aid in reducing this catastrophic outcome of aseptic loosening. This will have huge implications in reducing the revision burden that is predicted which will not only have both huge financial and significant service implications, it will also more importantly, significantly improve long-term patient outcomes and overall satisfaction and well-being. Further work is needed to improve these current rates of aseptic loosening, with prevention being the main target for new total joint arthroplasty but with therapeutic strategies being utilized for existing patients. ◆

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