HHS Public Access

Author manuscript

Expert Rev Med Devices. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Expert Rev Med Devices. 2020 January ; 17(1): 41–56. doi:10.1080/17434440.2020.1702024.

Diagnosis and management of implant debris-associated inflammation

Stuart B. Goodman[a,b], **Jiri Gallo**[c], **Emmanuel Gibon**[d], **Michiaki Takagi**[e]

[a]Department of Orthopaedic Surgery, Stanford University, Redwood City, CA, USA

[b]Department of Bioengineering, Stanford University, Stanford, CA, USA

[c]Department of Orthopaedics, Palacký University Olomouc, Olomouc, Czech Republic

[d]Department of Orthopaedic Surgery, University of Florida, Gainesville, FL, USA

[e]Department of Orthopaedic Surgery, Yamagata University, Yamagata, Japan

Abstract

Introduction—Total joint replacement is one of the most common, safe, and efficacious operations in all of surgery. However, one major long-standing and unresolved issue is the adverse biological reaction to byproducts of wear from the bearing surfaces and modular articulations. These inflammatory reactions are mediated by the innate and adaptive immune systems.

Areas covered—We review the etiology and pathophysiology of implant debris-associated inflammation, the clinical presentation and detailed work-up of these cases, and the principles and outcomes of non-operative and operative management. Furthermore, we suggest future strategies for prevention and novel treatments of implant-related adverse biological reactions.

Expert opinion—The generation of byproducts from joint replacements is inevitable, due to repetitive loading of the implants. A clear understanding of the relevant biological principles, clinical presentations, investigative measures and treatments for implant-associated inflammatory reactions and periprosthetic osteolysis will help identify and treat patients with this issue earlier and more effectively. Although progressive implant-associated osteolysis is currently a condition that is treated surgically, with further research, it is hoped that non-operative biological interventions could prolong the lifetime of joint replacements that are otherwise functional and still salvageable.

Keywords

Joint replacement; joint arthroplasty; hip; knee; wear; particles; osteolysis

CONTACT Stuart B. Goodman goodbone@stanford.edu Department of Orthopaedic Surgery, Stanford University Medical Center Outpatient Center, 450 Broadway St. M/C 6342, Redwood City, CA 94063, USA.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

1. Introduction

Joint replacement of the hip, knee, shoulder, and other anatomical locations is amongst the most safe and cost-effective operations in all of surgery. By 2030, it is estimated that there will be 635,000 primary total hip arthroplasties (THAs) and 1.28 million primary total knee arthroplasties (TKAs) performed in the USA alone [1]. Revision THA (72,000) and revision TKA (120,000) are expected to increase as well. By 2060, both primary and revision surgeries are predicted to increase further: to 1.23 million (primary THA), 2.60 million (primary TKA), 110,000 (revision THA), and 253,000 (revision TKA), respectively. Thus, despite improvements in patient selection, implant design, surgical technique, and peri-operative rehabilitation and pain control, revision surgeries still constitute about 10% of all arthroplasty surgeries. Revision surgeries are generally harder and longer procedures, have a higher complication rate and a poorer clinical outcome, and are more expensive than primary procedures.

Why do patients with orthopedic implants require revision surgery? Prior to the introduction of modern bearing surfaces for THAs, polyethylene wear and periprosthetic osteolysis were among the common reasons for revision surgery [2]. Recently, due t the introduction and widespread use of highly cross-linked polyethylene and ceramics, other causes have supplanted wear of the articulation as a primary cause of failure of THAs. The current reasons for failure of THAs now include deficient osseointegration of cementless implants with subsequent loosening, instability due to chronic subluxation or dislocation, and infection [3]. For TKAs, revision is now indicated most commonly due to instability, stiffness, and infection [4,5]. Minimally invasive knee or hip surgery with inadequate visualization is also a risk factor for subsequent failure of a joint replacement [6]. Specific complex medical comorbidities including parkinsonism, drug abuse, obesity, and diabetes, as well as specific prosthetic designs have been shown to increase the risk for revision [7]. Interestingly, many of the medical risk factors for revision arthroplasty are modifiable [8].

What are the long-term reasons leading to revision joint replacement? Although prosthetic infection is still a major cause of failure, byproducts from the implants are also a potential problem. Adverse effects associated with implant debris have been a major concern since the origins of THA. Sir John Charnley first noted the poor wear characteristics of the polymer polytetrafluoroethylene (PTFE), a polymer originally used as a bearing surface for the acetabular component [9]. PTFE debris leads to an exuberant foreign body and chronic inflammatory reaction. This material was abandoned for high-density polyethylene (HDP), due to the latter’s more optimal resistance to wear. Polymethylmethacrylate (PMMA) was originally used by Charnley to fix the components for THA to the surrounding bone. Despite, the general biocompatibility of PMMA bone cement in bulk form [10,11], subsequent studies reported severe periprosthetic bone loss due to the chronic inflammatory reaction to particulate PMMA [12,13]. With the implantation of joint replacements into younger more active patients, especially younger males, new problems arose. For THA, so-called cement disease stimulated the development of cementless components that were stabilized by a press fit, with/without porous coating or other surface technology, and the use of supplemental screw fixation. The most common bearing surface for THA in the 1980s and 1990s was a cobalt-chrome alloy femoral head articulating with a conventional ultra-

high molecular weight polyethylene (UHMWPE) acetabular liner. These acetabular components often were modular, and had poor locking mechanisms of the UHMWPE liner to the metallic shell, leading to interfacial micromotion; furthermore, the thin polyethylene insert was irradiated and packaged in air. The above characteristics lead to polymer abrasion, oxidation and accelerated wear. The wear particles of UHMWPE stimulated a chronic inflammatory reaction resulting in periprosthetic osteolysis [14–17]. Modern highly cross-linked UHMWPE has even better wear characteristics, compared to conventional UHMWPE and has positively impacted the long-term outcome of THA in a major way.

Alternative bearings also included metal-on-metal articulations. The idea was to generate a metallic bearing couple made of cobalt-chrome alloy, in which the components were made to exact specifications to generate surfaces separated by fluid film lubrication. The artificial femoral head could be larger in diameter than with UHMWPE bearings, thus affording added stability to the articulation. Metal-on-metal (MOM) implants were often implanted in younger, more active individuals as resurfacing arthroplasties or THAs. Unfortunately, breakdown in the lubricating layer of MOM bearings leads to the generation of nanoparticles of the metallic alloy as well as metallic ions due to tribocorrosion [18,19]. These metallic byproducts could cause severe bone and soft tissue loss due to widespread local inflammation and necrosis [20]. In vitro and retrieval studies have demonstrated that metallic byproducts can cause cytotoxicity, genotoxicity, a hypersensitivity reaction and pseudotumors [21,22]. MOM bearing couples are now rarely used.

More recently, corrosion of the femoral component trunnion and metallic femoral head has been identified as another major source of metallic byproducts [23–26]. This is a phenomenon (known as ‘trunnionosis’), that may necessitate further biochemical and imaging investigations, and surgical intervention. This mechanically assisted crevice corrosion can also occur with other junctions in modular implants.

All byproducts from implant materials in current use cause an inflammatory response, to a greater or lesser degree [27,28]. The specific response is dependent on numerous variables including patient characteristics, implant materials and anatomical location, surgical technique, and the subsequent loading patterns to which the implant is subjected. The following sections will explore the consequences of the inflammatory response to byproducts of implants for joint replacement from basic scientific investigations to the clinical translational science points of view.

2. Pathophysiology of implant debris-associated inflammation

2.1. Particle matter

The size of implant-derived byproducts influences the biologic host response. A simple size-based classification, ‘Bulk’, ‘Large’, ‘Moderate’, ‘Small’ and ‘Very small’, has been used to understand the reaction [29]. ‘Bulk’ is equivalent to the products for artificial joint surgery. Insertion of implants induces transient acute inflammation due to surgical stress. Soon after, osseointegration and/or a thin fibrous tissue layer forms between implants and bone bed. The artificial joint develops a synovial-like lining, which ultrafiltrates plasma and adds hyaluronan and more or less joint fluid specific components to the components used.

However, particulate matter threatens the longevity of artificial joints. The particles of ‘Large’ size (tens of micron) generated by microfracture and/or wear mechanisms are normally embedded in the extracellular matrix around the artificial joint. They do not usually contribute to intense inflammation and tissue-destructive granuloma formation as long as the particle number is limited (Figure 1). However, if they are trapped in the gliding surface, smaller particles are produced by a third body wear mechanism. This generates ‘Moderate’ (between submicron and several micron size)- and ‘Small’-sized (several nanometers) particles. ‘Moderate’-sized particles are embedded in the extracellular matrix without harmful reaction but are often phagocytosed to cause a foreign body reaction and chronic inflammation as the particle number increases (Figures 2 and 3). A threshold for osteolysis by wear has been described [30]. Joint fluid increases due to the particle stimulus. Although wear debris is produced at the implant–implant interface, i.e. at the joint articulation, the debris and reaction can be seen all around the implant. Increased fluid volume and cyclic physical activities generate fluid pressure waves [31], by which the particles are transported elsewhere, and induce a foreign body reaction, often called ‘small particle disease’ [32] and ‘access disease’ [33]. ‘Moderate’-sized particles can also provide surface area for corrosion and anchor spaces for adhesion of endogenous and exogenous molecules. For example, endotoxin-coated particles can enhance the inflammatory response via innate immune sensors [34,35]. ‘Small’-sized particles (several nanometers) remain in the extracellular matrix and/or interstitial fluid or are pinocytosed. These small particles may not elicit a response, but potentially provide surface areas for corrosion and anchor spaces for molecular adhesion as well [29]. Nanometer-sized particles also can induce an inflammatory reaction [36,37]. Metal ions, categorized as ‘Very small’, arise from corrosion. They have haptenic potential and have been presumed to induce a delayed-type hypersensitivity-like response. Metal ions induce local tissue necrosis, often followed by more extensive tissue destruction [38,39]. They can be a remote cause of organ toxicity.

The influence of the shape of debris and type of material on the inflammatory response has been under debate. Metal ions, categorized as ‘Very small’, arise from corrosion. They have cytotoxic as well as haptenic potential and have been presumed to induce an adverse reaction to metallic debris (ARMD) and a delayed-type hypersensitivity-like response [38,39]. However, the size of wear particles produced in vivo is not homogeneous. In addition, wear found in the granuloma is not always derived from the same material. In vitro tests have tried to compare the characteristics of different particles, but a lack of standardization of experimental conditions, for method of endotoxin-removal, sterilization and surface charge, and other characteristics makes it difficult to reach general conclusions; one exception is the cell damage by metal ions.

Systemic exposure to chromium (Cr), cobalt (Co), Nickel (Ni), and aluminum (Al) occurs as a result of metal wear byproducts released from the articulation and metal interface, resulting in a postoperative increase in metal ion levels at different organ sites. The physiologic effects of these metallic byproducts are still poorly understood and their potential toxicity, as well as carcinogenicity, remain a cause for concern [40]. However, neurologic complications, cardiac pathology, thyroid dysfunction, and allergic dermatitis have been described [41–43].

2.2. Cellular players

Excess production of ‘Moderate’- and ‘Small’-sized particles induces a foreign body type cellular response and chronic inflammation (Figure 3). This occurs both in the interfacial tissue between bone and implants and the regenerated capsular tissue around artificial joints [44]. CD68+ monocytes and macrophages are the responsible cell types for handling these wear debris by the process of phagocytosis. Macrophages have been subcategorized as naïve M0, proinflammatory M1, and anti-inflammatory M2. M1 macrophages are dominant in the foreign body granuloma [45]. Another consequence of a foreign body and chronic inflammatory reaction is the fusion of macrophages into foreign body giant cells. Fibroblasts can encapsulate the particles to the collagenous fibrous bed. Fibroblasts and vascular endothelial cells frame the granuloma. Neutrophil infiltration is scarce. If neutrophils are found to a greater degree, then indolent infection is suspected [46]. Lymphocyte infiltration is occasionally observed in the macrophage dominant foreign body granuloma, but limited [16]. Mast cells are also recognized, but the precise role is still unclear [47,48].

In the periprosthetic bone tissues adjacent to foreign body granuloma, osteoclastic bone resorption and fragile bone matrix are observed. In addition, increased osteoblastic activity is often coupled with osteoclastic activity; thus, high turnover of periprosthetic bone can be seen [49]. Osteocytes are also active participants in the periprosthetic bone remodeling coupled with the foreign body granuloma [49,50].

Another important cellular response relates to metal particles and ions produced by corrosion [20]. Electrochemical dissolution of metal ions is an important source of implant-derived debris in particular with metal-on-metal articulations, head-neck junctions, and modular implants. In hypersensitivity-like reactions and pseudotumors due to metal particles and ions, various types of inflammation can be detected [38,39,48]. A lymphocyte dominant tissue reaction can be observed [39,48] (Figures 4–6). The role of dendritic cells is still unclear.

The exact correlation between the form and severity of cellular responses to byproducts of wear and the health of patients has not been fully analyzed. However, similar foreign body cellular responses are found in patients with total hip arthroplasty who are younger or more elderly, as well as those with osteoarthritis or autoimmune disease, such as rheumatoid arthritis. The underlying primary disease may form a histological backdrop; however, the biological reaction to implant debris is similar among different medical conditions and diagnoses.

2.3. Molecular events

The most important molecular consequence of the foreign body and inflammatory reaction is local production of cytokines and chemokines [44,51–53]. In in vitro tests, usually a fixed number of cells is subjected to wear particles, and cytokine and chemokine production are assessed. It is noteworthy that in vitro tests may reflect the acute phase of wear-loading to cell; animal models simulate the acute and/or subacute phase. The in vivo situation in humans is more complex. However, various cytokines and chemokines have been identified in the periprosthetic granuloma. Marked expression of inflammatory cytokines, such as

tumor necrosis factor (TNF)-alpha, interleukin (IL)-1s, IL-6, and macrophage-colony stimulating factor (M-CSF), has been reported. Chemokine system analyses revealed increased expression of CCL2, 3, and CXCL8, 9, 10 [53–56]. Receptor activator of nuclear factor kappa-B ligand (RANKL) and M-CSF expressed on osteoblasts and neighboring stromal cells are required for osteoclastic differentiation in periprosthetic bone [57,58].

Increased expression of proteinases is another important molecular consequence of the reaction. Neutral proteinases are produced for export into the extracellular space. It is thought that under physiological conditions 'physiological' pH close to 7.4 prevails. Indeed, it has been described that mononuclear phagocytes and foreign body giant cells produce excessive amounts of neutral proteinase, collagenases and other matrix metalloproteinases (MMPs). In concert, these substances are able to degrade all components of the extracellular matrix. It is well known that MMP-1 (collagenase-1, fibroblast collagenase), MMP-14 (membrane-type MMP; MT1-MMP) and MMP-2/−9 (gelatinase) and other MMPs with collagenolytic and/or gelatinolytic potential are produced [44,59]. Inflammatory cytokines, such as IL-1, TNF-alpha, and platelet-derived growth factor (PDGF) can induce MMP production. Excessive activation of the secreted proteinases leads to weakening of the extracellular matrix components at the implant-host interface [60]. As the pH in the peri-implant tissues is quite low, acidic cysteine proteinase, cathepsin K, could become autoactivated [61]. Cathepsin K was first found to be the major proteinase of osteoclasts. Cathepsin K is generally considered to be responsible for bone collagen degradation in the acidic Howship's lacunae after HCl-mediated dissolution of the bone hydroxyapatite mineral. Later cathepsin K has been found in other cells, including macrophages, osteoblasts, and fibroblasts. Auto-activated cathepsin K in the acidic peri-implant milieu has been found in high concentrations in peri-implant fluid and tissues [61,62]. Thus, extracellular matrix-degrading enzymes could be responsible for the weakening of the implant-host interface.

The role of innate-immune sensors is presently a topic of great interest in inflammation research. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) can recognize not only exogenous pathogen-associated molecular pattern (PAMPs) but also endogenous molecules created upon tissue remodeling and inflammation. Thus, these substances can augment the local host response. Indeed, marked immunoreactivity of TLR1, TLR2, TLR5, TLR6, and TLR9 molecules was mainly detected in monocytes/macrophages and occasionally in neighboring stromal cells; the presence of these molecules paralleled their upregulation at messenger RNA levels in the aseptic foreign body granuloma around implants. NLRs and their related molecules, namely NLRP (Nacht, leucine-rich repeat and pyrin domain-containing protein) 3, caspase-1, and apoptosis-associated speckle-like protein containing caspase recruitment domain (ASC), were also found in the foreign body granuloma [35,63]. TLRs can sense not only endogenous molecule of microbial origin, but also endogenous products relating to inflammation, such as heat-shock proteins, high mobility group box (HMGB)1, fibronectin, and hyaluronic acid. NLRP3 can be activated by adenosine triphosphate (ATP), radical oxygen species (ROS), and uric acid released from damaged cells. Cellular debris and products relating to foreign body reaction can stimulate these sensors [63]. In addition, endogenous products, as well as exogenous microbial molecules, can attach to surfaces of wear debris, which can also

enhance the cellular response, after phagocytosis of the particles. Thus, the distinction between aseptic and septic conditions in particle-laden periprosthetic joint inflammation is still somewhat unclear.

3. Work-up

3.1. History

There is no single specific clinical finding that would inform orthopedic surgeons or patients early of pathological implant-associated inflammation (**PIAI**). Low-grade inflammation is typically insidious, not easily diagnosed, and the etiology is often unclear. Symptoms of pain or a lack of function may bring the patient to his/her orthopedic surgeon. However, increasing pain and diminishing function are usually associated with structural failure as implant loosening, expanding bursitis or a periprosthetic fracture (PPF) rather than with PIAI. Thus, there are many asymptomatic patients, for whom periprosthetic osteolysis (PPOL) is an unpleasant surprise. In addition, an expanding bursitis, tendinitis, or pseudocyst can be detected around normally functioning/dysfunctional TJAs at some anatomical sites.

The surgeon should enquire about the date of the surgery, type of implant, previous history of the patient and prosthesis during the examination (e.g. satisfaction, activities, level of performance, falls and other traumas, other joint surgeries).

3.2. Physical examination

The surgeon should inspect and palpate the surgical site and examine joint function (usually range of motion, stability, performance of specific tasks), and assess limb length, muscular power and gait. A relatively normal clinical picture can be found in patients without implant loosening or other major pathology. Symptomatic patients usually manifest joint deterioration due to pain (at least a limited ROM) and can demonstrate positive tests for tendinitis or muscle impairment. It is occasionally possible to palpate a hip pseudotumor in the groin [64] or a popliteal cyst in case of TKA [65]. A painful joint located at the limb usually disturbs the normal fluid nature of gait.

3.3. Laboratory tests

Blood tests are currently not useful in the case of identification of PIAI. Still, these tests are of importance for distinguishing a prosthetic joint infection (PJI) which demonstrates elevation of the C Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR), Interleukin 6 (IL-6), and D-dimers in the blood serum [66,67]. Elevation of first-line blood tests (ESR, CRP) is an indication of aspiration of the TJA in order to exclude PJI as a source of symptoms (importantly, all examined TJAs are aspirated at many institutions regardless of the outcomes of screening blood tests). Microbiological examination of the culture is essential; a diagnosis of infection is based less often on techniques not involving culture [68,69]. Joint fluid samples are also examined for biomarkers (alpha-defensin, synovial CRP, interleukin 6, calprotectin and other biomarkers of infection) [70–73], and cytological examinations (synovial white blood cell count, differential count) [74–76]. If the amount of aspirated fluid is small, aliquots are sent to microbiological and biochemical examinations

according to the clinical importance of the tests. Rules for optimal combination of the above tests have been suggested [67,77,78]. Signs of chronic low-grade inflammation can be distinguished from PJI via experienced histopathological examination [79,80].

An adverse reaction to metal debris (ARMD) can be suspected when blood levels of Co and Cr are increased especially in patients with MoM type of bearings [81]. A wide range of tissue signs of ARMD as well as chronic low-grade inflammation can be distinguished from PJI via experienced histopathological examination [39,79,82,83]. ARMD is the most frequent reason for revision surgery among the patients with large-diameter head metal-on-metal THA [84]. As a result, these and other potentially risky implant combinations/configurations (based on the literature and registry reports) should be closely monitored with clinical, radiographic, and laboratory examinations. There is no consensus on the safe upper limit for serum Co, Cr levels, several concentrations have been suggested by individual studies or regulatory agencies. These range from 2 to 8 ppb (parts per billion) [84–86]. However, these values can differ depending on the implant parameters/design and the number of joints with metallic implants [87,88]. ARMD can be suspected from blood examination of Co and Cr (Co/Cr ratio); however, it is not a perfect predictor [89]. Revision surgery is indicated if the patient suffers severe symptoms (pain, limited range of motion, swelling, clicking, etc.) in conjunction with positive imaging findings and/or increased blood levels of Co/Cr. In addition, surgery is indicated for the patient with a large pseudotumor shown on CT or MRI, regardless of symptoms or blood levels of Co/Cr [84]. Finally, some advocate that a very high level of Co (>10 ppb) is a clear reason for revision surgery regardless of symptoms [90].

Finally, an analysis of pro-inflammatory cytokines/chemokines in periprosthetic tissues and joint fluid might support the diagnosis of PIAI [55,91,92]. However, there is no one single molecule that is specific only for PIAI to date, either in tissue or joint fluid samples. The response to prosthetic byproducts is largely nonspecific and is similar to the response to any other tissue damage signal; metallic byproducts stimulating TLR pathways, however, are different [93,94]. In the future, it may be possible to identify more characteristic patterns for PIAI using multiple data points (also in terms of number of biomarkers) and machine learning or patient-similarity network [95,96].

3.4. Radiographs

The main imaging tool is a standard radiograph of the particular joint. The implant position and fixation interface are assessed [97], and the radiographs also provide basic information of wear (most reliably in the case of THA). It is not possible to diagnose PIAI on the basis of simple radiographs; only the consequences on the surrounding bone bed (PPOL, periprosthetic fracture) can be visualized. However, intraoperative observations during revision surgery confirm that simple radiographs often underestimate the entire scope of PPOL.

Thus, computed tomography (CT) or magnetic resonance imaging (MRI) examination is more useful for detection of PPOL and soft-tissue manifestations of PIAI due to wear debris (edema, bursitis, tendinitis, pseudocysts, pseudotumors, etc.). CT is excellent for evaluating bony structures but it can also contribute to the assessment of soft tissue pathology. MRI can

detect bone marrow changes, cavities, and especially soft-tissue extensions of PIAI. Metal artifact reduction sequence MRI (MARS MRI) eliminates metal artifacts and offers high-quality resolution even in the vicinity of the implant, and is presently the gold standard [98,99].

Ultrasonography can differentiate between fluid collections and solid lesions around an artificial joint. An additional clinical value is provided by ultrasound-guided aspiration or biopsy in differential diagnosis of soft-tissue mass around TJA.

3.5. Bone scintigraphy

Nuclear medicine imaging modalities can be used for assessment of the fixation interface of implants in symptomatic patients who have negative radiographs [100]. This examination can even contribute to the detection of causes of pain of unclear origin in TJAs [101,102]. White blood cell scintigraphy (with 99mTc or 111In), anti-granulocyte monoclonal antibody scintigraphy, and FDG-PET/CT scan have been widely tested in relation to diagnosing of PJI [103]. Recently, a molecularly specific detection of bacterial lipoteichoic acid has been described [104].

4. Differential diagnosis

Clinical manifestations of PIAI must be differentiated from PJI. A range of tests is available to exclude or confirm the presence of PJI (see part 3.3); combinations of these tests demonstrate an accuracy that exceeds 90% for sensitivity and specificity. For details, the reader is referred to the recent ICM 2018 guidelines [71] or guidelines by other organizations [105].

Pain around a stable implant is one of the most difficult diagnostic tasks [106–109]. All intrinsic (aseptic loosening, PPOL, PJI, periprosthetic fractures, pseudotumors, tendinitis, bursitis, instability, etc.) and extrinsic (mainly spinal etiologies neuropathies, etc.) causes of pain should be excluded (Figure 7).

It is important to exclude the occurrence of a more serious tumor in the case of pseudotumors in the pelvis. It is not possible to exclude the occurrence of a primary [110] or secondary bone tumor in the case of PPOL [111] without careful and extensive examination.

5. Principles of non-operative management with specific examples and outcomes

The main focus of this section is on the potential pharmaceutical interventions to manage periprosthetic bone loss. Particle-induced osteolysis has a complex pathophysiology and multiple strategies can be used to mitigate or reverse this phenomenon. However, non-surgical interventions should be implemented early in the process, as when there is insufficient bone to sustain physiological loads, the remaining bone is more likely to undergo continued damage, jeopardizing long-term implant stability.

Pharmacologic modulation of periprosthetic osteolysis has been previously reported [112]. Although none of these experimental strategies have achieved clinical use to date, it is worth considering that some patients with stable implants and limited osteolysis might benefit from these approaches in the future. Below are some specific examples of ongoing research topics for non-operative management of debris-associated inflammation (Figure 8).

5.1. Targeting NF-κB

Osteoprotegerin (OPG) is a natural soluble decoy protein that has the ability to inhibit the Receptor Activator of NF-κB Ligand (RANKL). In a mouse calvarial model of osteolysis, Ulrich-Vinther et al. investigated a gene therapy drug using a recombinant adeno-associated virus (rAAV) to induce production of OPG in myocytes [113]. Titanium-implanted mice treated with the rAAV showed high levels of OPG and significantly decreased numbers of osteoclasts and bone resorption. Yang et al. [114] exposed implanted bone tissue, within established pouches in BALB/c mice, with UHMWPE particles. AAV encoding the human OPG gene (rAAV-hOPG) or the β galactosidase marker gene (rAAV-LacZ) was then injected into the air pouches. This resulted in significantly less mRNA expression of osteoclast markers in OPG-transduced pouches, compared with rAAV-LacZ-transduced pouches. The transduction and expression of OPG also considerably decreased the gene copies of the biologic RANK. Similar results were obtained by Kim et al. [115].

NF-κB can also be targeted using human-made molecules such as the NF-κB decoy oligodeoxynucleotide (ODN). Using an in-vivo model of continuous infusion of UHMWPE particles [116–118], Lin et al. [119] showed significantly less osteolysis and even increased bone mineral density in the infused femur when the NF-κB decoy ODN was used. The efficiency of the NF-κB decoy ODN was confirmed elsewhere [120–123].

Another way of direct NF-κB inhibition includes modulation of the IKK (IκBα kinase). This pathway was shown to be effective in PMMA-particle-induced osteolysis using a murine calvarial model [124].

5.2. Interfering with macrophage polarization

Macrophages (MΦ) are key cells in the biological cascade leading to periprosthetic osteolysis [125]. MΦ become polarized into pro-inflammatory M1 or anti-inflammatory M2 subtypes depending on the local microenvironment [126]. In vitro and retrieval studies with tissues obtained from revision arthroplasty performed for periprosthetic osteolysis have shown high concentration of M1 MΦ [45,127]. Therefore, interfering with MΦ polarization represents another potential way to mitigate particle-associated inflammation. Lin et al. [128] showed that when genetically modified MSCs that secrete IL-4 as a response to NF-κB activation (NF-κB-IL4 MSCs) were co-cultured with UHMWPE-activated MΦ, these NF-κB-IL4 MSCs drove MΦ into the M2 subtype. Hachim et al. [129] used IL-4-coated implants to successfully increase the M2 to M1 ratio after implantation. Yang et al. [130] used titanium implants coated with IL-4. MΦ were firstly activated to the M1 phenotype by interferon-gamma (IFN-γ). The subsequent release of IL-4 increased the expression of M2 markers, such as interleukin-10 (IL-10), arginase-1 (ARG-1) and platelet-derived growth factor-BB (PDGF-BB). Antonios et al. [131] investigated different timing strategies to

challenge PMMA-activated MΦ with IL-4. Polarization into an M2 anti-inflammatory phenotype was optimized when IL-4 was delivered before or concurrent with PMMA particle challenge, to an M1 phenotype, rather than to uncommitted (M0) macrophages. Interestingly, Yan et al. [132] assessed the ability of the anti-diabetic drug metformin to promote the M2 subtype when MΦ were exposed to UHMWPE particles. Metformin is a potent AMP-activated protein kinase (AMPK) agonist that can suppress inflammatory cytokine production by promoting MΦ polarization to an M2 phenotype. Metformin inhibited M1 and promoted M2 MΦ polarization. Moreover, IL-6 and TNF-α production induced by UHMWPE particles decreased whereas the anti-inflammatory cytokine IL-10 was promoted.

Another approach to interfere with MΦ would be to block their activation, at the very beginning, when wear particles and MΦ interact with each other. To achieve this goal, toll-like receptors (TLRs) are key receptors to target. TLR2 and TLR4 have been found to be critical for polyethylene-induced osteolysis [133]. Pearl et al. using PMMA particles have shown that TLR activation induced TNF-α production after MΦ were challenged with these particles. The production of TNF-α was partially due to signaling through myeloid differentiation factor 88 (MyD88) after TLR activation.

5.3. Cytokines and chemokines

Activation of the NF-κB results in the release of a plethora of proinflammatory factors including chemokines such as macrophage inflammatory protein 1α (MIP-1α), monocyte chemoattractant molecule 1 (MCP-1), cytokines such as tumor necrosis factor α (TNF-α), interleukins (IL)-1β, 6, 8, and others, prostaglandins especially prostaglandin E2, nitric oxide (NO), and peroxide metabolic intermediates. Interference with these inflammatory factors has been shown to mitigate periprosthetic osteolysis. Selective inhibition of the MCP-1-CCR2 ligand-receptor axis resulted in a significant decrease in systemic trafficking of MΦ in the presence of UHMWPE particles [134]. Zhao et al. [135] used titanium (Ti) particles in a mouse air-pouch model of inflammation to assess the efficiency of progranulin (PGRN) – a known anti-inflammatory agent targeting TNF-α receptors. The downstream molecules of TNF-α signaling, such as IL-1β, IL-6, cyclo-oxygenase 2 (COX-2) and NO synthase-2, were largely inhibited by PGRN both in vivo and in vitro. PRGN also significantly reduced Ti-induced osteolysis. Luo et al. [136]. investigated resveratrol's protective effects against Ti-induced oxidative stress in RAW264.7 MΦ. Resveratrol pretreatment significantly attenuated the mRNA expression of oxidative enzymes (iNOS, NOX-1, and NOX-2) in a dose-dependent manner. Moreover, resveratrol inhibited gene expression and release of TNF-α and suppressed NF-κB activation.

Yao and colleagues [137] showed that the mutant MCP-1 protein (called 7ND) was able to dramatically reduce the chemotactic effect of human MΦ when exposed to a conditioned media obtained after challenging murine MΦ with PMMA particles. 7ND acts by blocking the chemokine receptor CCR2 which is MCP-1 receptor. Keeney et al. [138] coated 7ND protein onto titanium rods. 7ND decoy was effectively released but also remained bioactive by decreasing MΦ trafficking toward MCP-1. The concept was then brought to in-vivo studies [139–141], in which biologically active rods coated with 7ND were able to mitigate

UHMWPE particle-induced osteolysis and decrease systemic MΦ recruitment. Sato et al. [140] also showed that the continuous delivery of IL-4 led to increased trabecular bone volume in the presence of UHMWPE particles.

5.4. Bisphosphonates

Bisphophonates such as alendronate, risedronate, zoledronic acid, and others are anti-resorptive agents that induce osteoclast apoptosis. Bisphophonates inhibit mature osteoclasts from resorbing bone in settings of non-inflammatory bone loss. Alendronate is a nitrogen-containing drug which was the first of its kind to be FDA approved [142]. Zhang et al. [143] investigated the efficacy of alendronate (ALN) in tumor necrosis factor transgenic (TNF-Tg) mice that develop erosive arthritis. Their work focused on the response of osteoclasts to ALN and the expression of Bcl-xl (anti-apoptotic protein) and Ets-2 protein (regulator of apoptosis). They demonstrated an increased resistance to ALN-mediated apoptosis and higher Bcl-xL expression in osteoclasts in inflamed joints. This lack of efficacy in conditions of inflammatory bone loss might limit their potential to treat or mitigate wear particle-induced osteolysis. However, studies have shown otherwise. Wang et al. [144] studied the effect of ALN after cemented total knee arthroplasty (TKA) in 69 women. One group received ALN at a dose of 10 mg/day for 6 months post-operatively while the other group did not. The authors used dual-energy X-ray absorptiometry (DEXA) to assess bone mineral density (BMD) in the distal femur and proximal tibial regions at 6 and 12 months. Although both groups experienced decreased BMD at each time points, the group receiving ALN had significantly less decrease in BMD compared to the control group. Similarly, Trevisan et al. [145] investigated the effect of clodronate after uncemented total hip arthroplasty (THA). In their study, 91 patients (men and women) randomly received intramuscular clodronate at a dose of 100 mg weekly for 12 months or no treatment postoperatively. DEXA was also used to assess BMD around the stem. At 12 months, bone loss was significantly improved in Gruen zones 2 and 6 (proximal femur) for treated women compared to untreated women. No significant difference was found for men. Sköldenberg et al. [146] studied the effect of weekly risedronate on periprosthetic bone resorption following uncemented THA in a single-center, randomized, double-blind, placebo-controlled trial. Patients were randomized of post-operative day to receive either 35 mg of risedronate (n = 33) or a placebo (n = 37) once weekly for six months. All patients were also given calcium carbonate (1000 mg) and vitamin D (400 IU) oral supplements daily for six months. BMD and stem migration were assessed using DEXA and the Einzel-Bild-Roentgen-Analysis Femoral Component Analysis (EBRA-FCA) software, respectively. Patients were followed for 24 months. At the last time point, bone resorption was significantly lower in Gruen zone 1 and 7. However, risedronate had no effect on stem migration. Although promising, none of these studies addressed the actual diagnosed periprosthetic osteolysis but rather its prevention.

Non-operative management of inflammation and wear particle-induced periprosthetic osteolysis remain a topic that needs further investigation. Although our understanding of the pathophysiology of osteolysis has improved, further knowledge will facilitate the development of targeted drugs that are safe, efficacious and cost-effective.

6. Principles of operative management with specific examples and outcomes

In general, manifestations of PIAI can be solved in a conservative way (described elsewhere) or by surgery. The procedure chosen should include a clear understanding of the particular etiology and pathology at hand and use the best evidence available for pursuing a particular strategy.

PPOL around a stable implant should be treated with a removal of the worn bearing surface(s), debridement and filling the bone defect with bone grafts or synthetic substitutes. The perspective of TJA can significantly be changed by a removal of the ‘generator’ of a great amount of polyethylene particles [147].

For reconstruction of bone defects, there is considerable evidence supporting the use of different types of bone grafts [148,149]. The use of synthetic bone substitutes is less common, despite the fact that they are relatively unlimited in amount and do not have the potential infectious risks of allografts. A defect under the THA cup can be reached through holes in the original cup or through a strategic supraacetabular window (Figure 9). However, evidence supporting this particular technique is not very strong.

The choice of a new bearing material is absolutely essential for long-term success [150,151]. In general, a new bearing couple of similar or higher quality is implanted either a ceramic-on-ceramic or ceramic/highly polished metal-on-highly crosslinked polyethylene. A metallic sleeve is often placed on the trunnion when using a ceramic head on the femoral component with a worn metallic neck [152]. The new polyethylene liner can be also cemented into the original cup [153]. However, in the case of failed monobloc stems or sockets, as well as in situation of excessive periprosthetic bone loss, it is necessary to extract the original implant and follow the same procedure as in revision surgery for aseptic loosening.

PPOL around a loosened implant is treated by a removal of the implant, debridement, reconstruction of the bone bed (depending on the type and scope) and reimplantation of a new prosthesis. There are several proved ways of achieving the above-stated objectives [154]. More recently reconstruction of defects has been aided by the introduction of porous metal augments [155,156].

If revision surgery is indicated due to soft-tissue pathology, the excision of a pseudotumor or bursitis in the groin, trochanteric or other areas is done first. The original prosthesis is then addressed and its position and stability are assessed. If these are satisfactory, only the bearings are replaced. In fact, there is at least one study describing a spontaneous disappearance of an intra-pelvic pseudotumor without soft-tissue surgery following a simple replacement of the joint couple [157].

In the case of a popliteal pseudocyst, the TKA is addressed first. The procedure is managed according to the particular local findings, scope, and type of bone defects. The popliteal pseudocyst is usually emptied successfully indirectly, during a revision through access of the

posterior capsular area. This approach enables the surgeon to avoid an excision of the pseudocyst from an independent posterior surgical approach at the end of surgery.

7. Expert commentary

The generation of implant debris will always occur after joint replacement, due to the presence of an articulation under load. Therefore, the possibility of adverse tissue reactions to byproducts of wear will be present with all types of bearing couples [158]. The following sections will outline current and future strategies pertinent to minimizing this debris and the ensuing biological reaction in the future.

7.1. Patient characteristics

A number of host factors could affect the risk for PIAI. It is well established that wear and the risk for revision is exacerbated by heavier, younger (less than 60 years old), more active patients (especially males), as this increases the loads transmitted to the bearing surfaces [7,159,160], although the effects of BMI on wear and revision THA are more controversial than with TKA [161]. Excessive linear wear or fracture of the plastic in THA may occur in patients with very small proportions in which thinner more deformable polyethylene inserts are often used. MOM resurfacing arthroplasty in females with smaller proportions, especially bilateral cases, have demonstrated an increased incidence of adverse local tissue reactions (ALTR) to byproducts of wear [162]. Furthermore, there appears to be differences in the biological reaction to prosthetic byproducts in different individuals (i.e. individual susceptibility to PIAI), and thus the development of periprosthetic osteolysis [163–165].

Due to the above, registry data, information from government and insurance databases and other sources must help dissect the correlation between different patient characteristics and the wear characteristics, and clinical outcomes of joint replacements. Implant retrieval studies and bioassays for markers of wear would also prove useful.

7.2. Implant characteristics

7.2.1. Bearing couples—The optimal articulation for joint replacement continues to be a hot topic for arthroplasty surgeons. MOM articulations are rarely used now. Newer cross-linked polyethylene (XLPE) implants, with/without Vitamin E doping, have revolutionized THA, and are now being used more commonly for TKA [166–169]. For THA, there is controversy regarding whether a cobalt chrome or ceramic head (zirconia-toughened alumina-ZTA) is optimal for articulation with XLPE. For THA, a metal or ceramic femoral head articulating with XLPE appears to perform equally well. In fact, excluding MOM bearings, there is no evidence that any bearing couple (metal-on XLPE, ZTA-on-XLPE or ceramic-on-ceramic) is superior in the intermediate term, with revision as the end-point [150,170]. However, ceramic parts and bearings are more costly than the alternative ones. Longer follow-up will help determine the efficacy and cost-effectiveness of different articulations. In particular, we require data from cases with 20–30 years of follow-up, as the newer bearings are being implanted in younger and more active patients.

Polyurethane is being examined as a bearing surface for joint replacement, as the mechanical properties are similar to articular cartilage [167]. Another material is polyether ether ketone

(PEEK) with or without carbon-fiber reinforcement usually for articulation with another polymer or ceramic. These materials are less stiff than metals, and thus far, the generated particles and byproducts do not cause major inflammatory reactions leading to osteolysis. Biomechanical and biocompatibility studies are currently being performed with these materials.

7.2.2. Modularity and implant design—Modularity of implants was originally designed to give surgeons options for femoral head size, neck length, and offset, for replacing worn parts (such as polyethylene inserts) without the need for exchanging the entire implant, and for optimizing femoral implant anteversion, fit and fill during THA. However, many of the advantages of modularity have been overshadowed by new issues such as implant breakage at modular junctions, and mechanically assisted crevice corrosion [19]. Newer more robust modular junctions need to be designed that minimize the liberation of undesired wear debris. The design of implants needs to be further enhanced to facilitate for straightforward and accurate insertion of the prosthesis without impingement. With the advent of 3D printing and related technologies, future instrumentation and implants will be personalized to the individual characteristics of the patient [171,172]. However presently, there are concerns regarding necessity, biomechanical sturdiness of the implant, and cost.

7.2.3. Implant coatings—Implant coatings are being developed to further two main goals: prevention and/or treatment of deep infection and to expedite osseointegration [173–177]. Infection has been postulated to be a contributing factor to particle disease [178–180]. Furthermore, the ingress of particles from the bearing couple and joint to the deeper cancellous surfaces is impeded by a component that has undergone osseointegration. Implant surface modification and coatings are being developed to accomplish both of these goals [181].

7.3. Surgical technique

Improved methods of preoperative planning, instrumentation, preparation of bone surfaces, and more accurate placement of implants are currently evolving using computer-assisted techniques and robotics [182–185]. These methodologies should result in more accurate and reproducible prosthesis positioning, with the goal of increasing implant longevity and minimizing wear.

7.4. Sensors and pharmacological therapy

Current methods for determining implant wear and osteolysis rely primarily on simple imaging (radiographs, MRI, etc.) and blood tests (e.g. metal ions in the blood) [186]. Future implants might incorporate sensors that could be queried non-invasively to report on the important functions of implants including the degree of wear. More sophisticated biomarkers of wear and wear byproducts must also be developed, paralleling our current tests for implant infection.

No successful pharmacological treatment has yet been developed to treat implant wear and osteolysis in humans. However, the biological processes of inflammation and osteolysis have been elucidated [187,188]. Future treatments to mitigate local inflammation and bone

destruction, and enhance osteogenesis using local or systemic delivery of biologics, immunotherapeutic agents and cellular therapies are currently in the preclinical stages [189–191]. Whereas none of these methods deal with wear debris directly, these treatments potentially could limit the adverse effects of byproducts of wear, and extend the longevity of the implant.

7.5. Five-year view

As outlined above, major advances in joint replacement surgery are anticipated in the areas of optimizing patient selection and surgical technique based on best available evidence and registries, the use of machine/computer-assisted techniques for prosthesis implantation, development of improved bearing surfaces and prosthesis designs possibly incorporating 3D printing techniques, coating of implants to facilitate initial osseointegration and obviate infection, sensors in the prosthesis and/or soft tissues and the use of local or systemic biomarkers to periodically interrogate the implant and interface, and pharmacotherapies to treat osteolysis at an early stage.

Acknowledgments

Funding

This paper was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institute of Health, grant numbers [R01AR055650, R01AR063717, R01AR073145, R01AR072613] and the Ellenburg Chair in Surgery. One of the authors (J.G.) was supported in his work by the Ministry of Health of the Czech Republic, grant number (VES16-31852A).

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Projected volume of primary and revision total joint replacement in the U.S. 2030 to 2060 [Internet]. New Orleans, LA, USA: AAOS; 2018 [cited 2018 Mar 6]. Available from: https://aaos-annualmeeting-presskit.org/2018/research-news/sloan_tjr/
2. Hopper RH Jr., Ho H, Sritulanondha S, et al. Otto Aufranc Award: crosslinking reduces THA wear, osteolysis, and revision rates at 15-year followup compared with noncrosslinked polyethylene. Clin Orthop Rel Res. 2018 2;476(2):279–290.
3. Bozic KJ, Kurtz SM, Lau E, et al. The epidemiology of revision total hip arthroplasty in the United States. J Bone Joint Surg Am. 2009 1;91(1):128–133. [PubMed: 19122087]
4. Le DH, Goodman SB, Maloney WJ, et al. Current modes of failure in TKA: infection, instability, and stiffness predominate. Clin Orthop Rel Res. 2014 7;472(7):2197–2200.
5. Bozic KJ, Kurtz SM, Lau E, et al. The epidemiology of revision total knee arthroplasty in the United States. Clin Orthop Rel Res. 2010 1;468(1):45–51.
6. Mayle RE Jr., Graw BP, Huddleston HG, et al. MI TKA: a risk factor for early revision surgery. J Knee Surg. 2012 11;25(5):423–427. [PubMed: 23150354]
7. Bottle A, Parikh S, Aylin P, et al. Risk factors for early revision after total hip and knee arthroplasty: national observational study from a surgeon and population perspective. PloS One. 2019;14(4): e0214855. [PubMed: 30964880]
8. Kee JR, Mears SC, Edwards PK, et al. Modifiable risk factors are common in early revision hip and knee arthroplasty. J Arthroplasty. 2017 12;32(12):3689–3692. [PubMed: 28780223]
9. Charnley J Low friction arthroplasty of the hip. New York (NY): Springer-Verlag; 1979.
10. Charnley J The reaction of bone to self-curing acrylic cement. A long-term histological study in man. J Bone Joint Surg Br. 1970 5;52(2):340–353. [PubMed: 5445416]

11. Willert HG, Ludwig J, Semlitsch M. Reaction of bone to methacrylate after hip arthroplasty: a long-term gross, light microscopic, and scanning electron microscopic study. J Bone Joint Surg Am. 1974 10;56(7):1368–1382. [PubMed: 4433360]
12. Jones LC, Hungerford DS. Cement disease. Clin Orthop Rel Res. 1987 12;225:192–206.
13. Willert HG, Bertram H, Buchhorn GH. Osteolysis in alloarthroplasty of the hip. The role of bone cement fragmentation. Clin Orthop Rel Res. 1990 9;258:108–121.•• References 13 and 14 by Professor Willert and colleagues are some of the classic observations describing why wear particles cause chronic inflammation and periprosthetic osteolysis.
14. Willert HG, Bertram H, Buchhorn GH. Osteolysis in alloarthroplasty of the hip. The role of ultra-high molecular weight polyethylene wear particles. Clin Orthop Rel Res. 1990 9;258:95–107.•• References 13 and 14 by Professor Willert and colleagues are some of the classic observations describing why wear particles cause chronic inflammation and periprosthetic osteolysis.
15. Schmalzried TP, Kwong LM, Jasty M, et al. The mechanism of loosening of cemented acetabular components in total hip arthroplasty. Analysis of specimens retrieved at autopsy. Clin Orthop Rel Res. 1992;274:60–78.
16. Santavirta S, Hoikka V, Eskola A, et al. Aggressive granulomatous lesions in cementless total hip arthroplasty. J Bone Joint Surg Br. 1990 11;72(6):980–984. [PubMed: 2246301]
17. Rubash HE, Sinha RK, Shanbhag AS, et al. Pathogenesis of bone loss after total hip arthroplasty. Orthop Clin North Am. 1998 4;29(2):173–186. [PubMed: 9553563]
18. Meneghini RM, Hallab NJ, Jacobs JJ. The biology of alternative bearing surfaces in total joint arthroplasty. Instr Course Lect. 2005;54:481–493. [PubMed: 15948473]
19. Berry DJ, Abdel MP, Callaghan JJ, et al. What are the current clinical issues in wear and tribocorrosion? Clin Orthop Rel Res. 2014 12;472(12):3659–3664.
20. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am. 2005 1;87(1):28–36.
21. Gill HS, Grammatopoulos G, Adshead S, et al. Molecular and immune toxicity of CoCr nanoparticles in MoM hip arthroplasty. Trends Mol Med. 2012 3;18(3):145–155. [PubMed: 22245020] •• This paper summarizes the reasons for toxicity of metal particles and their byproducts from joint replacements.
22. Grammatopoulos G, Pandit H, Kamali A, et al. The correlation of wear with histological features after failed hip resurfacing arthroplasty. J Bone Joint Surg Am. 2013 6 19;95(12):e81. [PubMed: 23783212]
23. Urish KL, Giori NJ, Lemons JE, et al. Trunnion corrosion in total hip arthroplasty-basic concepts. Orthop Clin North Am. 2019 7;50 (3):281–288. [PubMed: 31084829]
24. Esposito CI, Wright TM, Goodman SB, et al. What is the trouble with trunnions? Clin Orthop Rel Res. 2014 12;472(12):3652–3658.
25. Sultan AA, Cantrell WA, Khlopas A, et al. Evidence-based management of trunnionosis in metal-on-polyethylene total hip arthroplasty: a systematic review. J Arthroplasty. 2018 10;33(10):3343–3353. [PubMed: 29929829]
26. Pourzal R, Lundberg HJ, Hall DJ, et al. What factors drive taper corrosion? J Arthroplasty. 2018 9;33(9):2707–2711. [PubMed: 29705684]
27. Gibon E, Amanatullah DF, Loi F, et al. The biological response to orthopaedic implants for joint replacement: part I: metals. J Biomed Mater Res A. 2017 10;105(7):2162–2173. [PubMed: 28371271]
28. Gibon E, Cordova LA, Lu L, et al. The biological response to orthopedic implants for joint replacement. II: polyethylene, ceramics, PMMA, and the foreign body reaction. J Biomed Mater Res A. 2017 8;105(6):1685–1691.
29. Goodman SB, Gomez Barrena E, Takagi M, et al. Biocompatibility of total joint replacements: a review. J Biomed Mater Res A. 2009 5 28;90(2):603–618. [PubMed: 18508337]
30. Dumbleton JH, Manley MT, Edidin AA. A literature review of the association between wear rate and osteolysis in total hip arthroplasty. J Arthroplasty. 2002 8;17(5):649–661. [PubMed: 12168184]
31. Paul JP. Forces transmitted by joints in the human body. Proc Inst Mech Eng. 1967;181:8–15.

32. Schmalzried TP, Callaghan JJ. Wear in total hip and knee replacements. J Bone Joint Surg Am. 1999 1;81(1):115–136. [PubMed: 9973062]
33. Manley MT, D'Antonio JA, Capello WN, et al. Osteolysis: a disease of access to fixation interfaces. Clin Orthop Rel Res. 2002;405:129–137.
34. Hirayama T, Tamaki Y, Takakubo Y, et al. Toll-like receptors and their adaptors are regulated in macrophages after phagocytosis of lipopolysaccharide-coated titanium particles. J Orthop Res. 2011 7;29(7):984–992. [PubMed: 21308757]
35. Naganuma Y, Takakubo Y, Hirayama T, et al. Lipoteichoic acid modulates inflammatory response in macrophages after phagocytosis of titanium particles through Toll-like receptor 2 cascade and inflammasomes. J Biomed Mater Res A. 2016 2;104 (2):435–444. [PubMed: 26440284]
36. Posada OM, Tate RJ, Grant MH. Toxicity of cobalt-chromium nanoparticles released from a resurfacing hip implant and cobalt ions on primary human lymphocytes in vitro. J Appl Toxicol. 2015 6;35 (6):614–622. [PubMed: 25612073]
37. Xia Z, Ricciardi BF, Liu Z, et al. Nano-analyses of wear particles from metal-on-metal and non-metal-on-metal dual modular neck hip arthroplasty. Nanomedicine. 2017 4;13(3):1205–1217. [PubMed: 27888094]
38. Mahendra G, Pandit H, Kliskey K, et al. Necrotic and inflammatory changes in metal-on-metal resurfacing hip arthroplasties. Acta Orthop. 2009 12;80(6):653–659. [PubMed: 19995315]
39. Campbell P, Ebramzadeh E, Nelson S, et al. Histological features of pseudotumor-like tissues from metal-on-metal hips. Clin Orthop Rel Res. 2010 9;468(9):2321–2327.•• This paper outlines the criteria for assessing pseudotumors around joint replacements.
40. Polyzois I, Nikolopoulos D, Michos I, et al. Local and systemic toxicity of nanoscale debris particles in total hip arthroplasty. J Appl Toxicol. 2012 4;32(4):255–269. [PubMed: 22328167]
41. Bradberry SM, Wilkinson JM, Ferner RE. Systemic toxicity related to metal hip prostheses. Clin Toxicol (Phila). 2014 Sep-Oct;52 (8):837–847. [PubMed: 25132471]
42. Wong CC, Nixon RL. Systemic allergic dermatitis caused by cobalt and cobalt toxicity from a metal on a metal hip replacement. Contact Dermatitis. 2014 8;71(2):113–114. [PubMed: 25040712]
43. Zywiel MG, Cherian JJ, Banerjee S, et al. Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition part 2. measurement, risk factors, and step-wise approach to treatment. Bone Joint J. 2016 1;98(B(1)):14–20.
44. Takagi M Neutral proteinases and their inhibitors in the loosening of total hip prostheses. Acta Orthop Scand. 1996 10;271:3–29.
45. Rao AJ, Gibon E, Ma T, et al. Revision joint replacement, wear particles, and macrophage polarization. Acta Biomater. 2012;8 (7):2815–2823. [PubMed: 22484696]
46. Bori G, Soriano A, Garcia S, et al. Usefulness of histological analysis for predicting the presence of microorganisms at the time of reimplantation after hip resection arthroplasty for the treatment of infection. J Bone Joint Surg Am. 2007 6;89(6):1232–1237. [PubMed: 17545426]
47. Solovieva SA, Ceponis A, Konttinen YT, et al. Mast cells in loosening of totally replaced hips. Clin Orthop Rel Res. 1996;322:158–165.
48. Ricciardi BF, Nocon AA, Jerabek SA, et al. Histopathological characterization of corrosion product associated adverse local tissue reaction in hip implants: a study of 285 cases. BMC Clin Pathol. 2016;16:3. [PubMed: 26924942]
49. Takagi M, Santavirta S, Ida H, et al. High-turnover periprosthetic bone remodeling and immature bone formation around loose cemented total hip joints. J Bone Miner Res. 2001 1;16(1):79–88. [PubMed: 11149493]
50. Ormsby RT, Solomon LB, Yang D, et al. Osteocytes respond to particles of clinically-relevant conventional and cross-linked polyethylene and metal alloys by up-regulation of resorptive and inflammatory pathways. Acta Biomater. 2019 3;15(87):296–306.
51. Jiranek WA, Machado M, Jasty M, et al. Production of cytokines around loosened cemented acetabular components. Analysis with immunohistochemical techniques and in situ hybridization. J Bone Joint Surg Am. 1993 6;75(6):863–879. [PubMed: 8314826]

52. Nakashima Y, Sun DH, Trindade MC, et al. Signaling pathways for tumor necrosis factor-alpha and interleukin-6 expression in human macrophages exposed to titanium-alloy particulate debris in vitro. J Bone Joint Surg Am. 1999 5;81(5):603–615. [PubMed: 10360689]

53. Dyskova T, Gallo J, Kriegova E. The role of the chemokine system in tissue response to prosthetic by-products leading to periprosthetic osteolysis and aseptic loosening. Front Immunol. 2017;8:1026. [PubMed: 28883822]

54. Koulouvaris P, Ly K, Ivashkiv LB, et al. Expression profiling reveals alternative macrophage activation and impaired osteogenesis in periprosthetic osteolysis. J Orthop Res. 2008 1;26(1):106–116. [PubMed: 17729302]

55. Tomankova T, Kriegova E, Fillerova R, et al. Comparison of periprosthetic tissues in knee and hip joints: differential expression of CCL3 and DC-STAMP in total knee and hip arthroplasty and similar cytokine profiles in primary knee and hip osteoarthritis. Osteoarthritis Cartilage. 2014 11;22(11):1851–1860. [PubMed: 25151085]

56. Dasa V, Kramer JM, Gaffen SL, et al. Is monocyte chemotactic protein 1 elevated in aseptic loosening of TKA? A pilot study. Clin Orthop Rel Res. 2012 7;470(7):1879–1884.

57. Takei I, Takagi M, Ida H, et al. High macrophage-colony stimulating factor levels in synovial fluid of loose artificial hip joints. J Rheumatol. 2000 4;27(4):894–899. [PubMed: 10782812]

58. Wang CT, Lin YT, Chiang BL, et al. Over-expression of receptor activator of nuclear factor-kappaB ligand (RANKL), inflammatory cytokines, and chemokines in periprosthetic osteolysis of loosened total hip arthroplasty. Biomaterials. 2010 1;31(1):77–82. [PubMed: 19781765]

59. Takei I, Takagi M, Santavirta S, et al. Messenger ribonucleic acid expression of 16 matrix metalloproteinases in bone-implant interface tissues of loose artificial hip joints. J Biomed Mater Res A. 2000 12 15;52(4):613–620.

60. Takagi M, Santavirta S, Ida H, et al. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in loose artificial hip joints. Clin Orthop Rel Res. 1998;352:35–45.

61. Konttinen YT, Takagi M, Mandelin J, et al. Acid attack and cathepsin K in bone resorption around total hip replacement prosthesis. J Bone Miner Res. 2001 10;16(10):1780–1786. [PubMed: 11585341]

62. Ma GF, Ali A, Verzijl N, et al. Increased collagen degradation around loosened total hip replacement implants. Arthritis Rheum. 2006 9;54(9):2928–2933. [PubMed: 16948130]

63. Takagi M, Takakubo Y, Pajarinen J, et al. Danger of frustrated sensors: role of Toll-like receptors and NOD-like receptors in aseptic and septic inflammations around total hip replacements. J Orthop Translat. 2017;10:68–85. [PubMed: 29130033]

64. Persson A, Eisler T, Boden H, et al. Revision for symptomatic pseudotumor after primary metal-on-polyethylene total hip arthroplasty with a standard femoral stem. J Bone Joint Surg Am. 2018 6 6;100(11):942–949. [PubMed: 29870445]

65. Niki Y, Matsumoto H, Otani T, et al. Gigantic popliteal synovial cyst caused by wear particles after total knee arthroplasty. J Arthroplasty. 2003 12;18(8):1071–1075. [PubMed: 14658115]

66. Ahmad SS, Shaker A, Saffarini M, et al. Accuracy of diagnostic tests for prosthetic joint infection: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2016 10;24(10):3064–3074. [PubMed: 27377905]

67. Parvizi J, Tan TL, Goswami K, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty 2018 5;33(5):1309–1314 e2. [PubMed: 29551303] •• This paper describes the criteria to be used for the accurate diagnosis of infection of joint replacements.

68. Ahmed SS, Begum F, Kayani B, et al. Risk factors, diagnosis and management of prosthetic joint infection after total hip arthroplasty. Expert Rev Med Devices. 2019;25:1–8.

69. Li M, Zeng Y, Wu Y, et al. Performance of sequencing assays in diagnosis of prosthetic joint infection: a systematic review and meta-analysis. J Arthroplasty. 2019 7;34(7):1514–1522 e4. [PubMed: 31005434]

70. Gallo J, Svoboda M, Zapletalova J, et al. Serum IL-6 in combination with synovial IL-6/CRP shows excellent diagnostic power to detect hip and knee prosthetic joint infection. PloS One. 2018;13(6):e0199226. [PubMed: 29927991]

71. Abdel Karim M, Andrawis J, Bengoa F, et al. Hip and knee section, diagnosis, algorithm: proceedings of international consensus on orthopedic infections. J Arthroplasty. 2019 2;34(2S):S339–S350. [PubMed: 30348566]

72. Bonanzinga T, Zahar A, Dutsch M, et al. How reliable Is the alpha-defensin immunoassay test for diagnosing periprosthetic joint infection? A prospective study. Clin Orthop Rel Res. 2017 2;475(2):408–415.

73. Wouthuyzen-Bakker M, JJW P, Ottink K, et al. Synovial calprotectin: an inexpensive biomarker to exclude a chronic prosthetic joint infection. J Arthroplasty. 2018 4;33(4):1149–1153. [PubMed: 29224989]

74. Gallo J, Juranova J, Svoboda M, et al. Excellent AUC for joint fluid cytology in the detection/exclusion of hip and knee prosthetic joint infection. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2017 9;161(3):310–319. [PubMed: 28529343]

75. Higuera CA, Zmistowski B, Malcom T, et al. Synovial fluid cell count for diagnosis of chronic periprosthetic hip infection. J Bone Joint Surg Am. 2017 5 3;99(9):753–759. [PubMed: 28463919]

76. Zahar A, Lausmann C, Cavalheiro C, et al. How reliable Is the cell count analysis in the diagnosis of prosthetic joint infection? J Arthroplasty. 2018 10;33(10):3257–3262. [PubMed: 29887359]

77. Bingham JS, Salib CG, McQuivey K, et al. An evidence-based clinical prediction algorithm for the musculoskeletal infection society minor criteria. J Arthroplasty. 2018 9;33(9):2993–2996. [PubMed: 29807787]

78. Gallazzi E, Drago L, Baldini A, et al. “Combined diagnostic tool” application to a retrospective series of patients undergoing total joint revision surgery. J Bone Jt Infect. 2017;2(2):107–113. [PubMed: 28540146]

79. Krenn V, Morawietz L, Perino G, et al. Revised histopathological consensus classification of joint implant related pathology. Pathol Res Pract. 2014 12;210(12):779–786. [PubMed: 25454771]

80. Bemer P, Leger J, Milin S, et al. Histopathological diagnosis of prosthetic joint infection: does a threshold of 23 neutrophils do better than classification of the periprosthetic membrane in a prospective multicenter study? J Clin Microbiol. 2018;56:9.

81. Reiner T, Do TD, Klotz MC, et al. MRI Findings in patients after small-head metal-on-metal total hip arthroplasty with a minimum follow-up of 10 years. J Bone Joint Surg Am. 2017 9 20;99(18):1540–1546. [PubMed: 28926383]

82. Park SH, Lu Z, Hastings RS, et al. Five hundred fifty-five retrieved metal-on-metal hip replacements of a single design show a wide range of wear, surface features, and histopathologic reactions. Clin Orthop Rel Res. 2018 2;476(2):261–278.

83. Inagaki Y, Uchihara Y, Munemoto M, et al. Correlation of histological and microbiological findings in septic and aseptic knee implant failure. Arch Orthop Trauma Surg. 2019 5;139(5):717–722. [PubMed: 30859303]

84. Mantymaki H, Lankinen P, Vahlberg T, et al. Repeated cobalt andchromium ion measurements in patients with large-diameter head metal-on-metal ReCap-M2A-magnum total hip replacement. Acta Orthop. 2019 6;90(3):243–248. [PubMed: 30945585]

85. Hart AJ, Sabah SA, Bandi AS, et al. Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br. 2011 10;93(10):1308–1313. [PubMed: 21969427] •• This study elucidates the role for metal ions as a surrogate for failed metal-on-metal hip arthroplasty.

86. Lardanchet JF, Taviaux J, Arnalsteen D, et al. One-year prospective comparative study of three large-diameter metal-on-metal total hip prostheses: serum metal ion levels and clinical outcomes. Orthop Traumatol Surg Res. 2012 5;98(3):265–274. [PubMed: 22480865]

87. Van Der Straeten C, Grammatopoulos G, Gill HS, et al. The 2012 Otto Aufranc Award: the interpretation of metal ion levels in unilateral and bilateral hip resurfacing. Clin Orthop Rel Res. 2013 2;471(2):377–385.

88. Matharu GS, Berryman F, Judge A, et al. Blood metal ion thresholds to identify patients with metal-on-metal hip implants at risk of adverse reactions to metal debris: an external multicenter validation study of birmingham hip resurfacing and corail-pinnacle implants. J Bone Joint Surg Am. 2017 9 20;99(18):1532–1539. [PubMed: 28926382]

89. Laaksonen I, Galea VP, Donahue GS, et al. The cobalt/chromium ratio provides similar diagnostic value to a low cobalt threshold in predicting adverse local tissue reactions in patients with metal-on-metal hip arthroplasty. J Arthroplasty. 2018 9;33(9):3020–3024. [PubMed: 29716769]

90. Rizzetti MC, Liberini P, Zarattini G, et al. Loss of sight and sound. Could it be the hip? Lancet. 2009 3 21;373(9668):1052. [PubMed: 19304018]

91. Paish HL, Baldock TE, Gillespie CS, et al. Chronic, active inflammation in patients with failed total knee replacements undergoing revision surgery. J Orthop Res. 2019 11;37(11):2316–2324. [PubMed: 31231835]

92. Dyskova T, Kriegova E, Slobodova Z, et al. Inflammation time-axis in aseptic loosening of total knee arthroplasty: a preliminary study. PloS One. 2019;14(8):e0221056. [PubMed: 31469844]

93. Samelko L, Landgraeber S, McAllister K, et al. TLR4 (not TLR2) dominate cognate TLR activity associated with CoCrMo implant particles. J Orthop Res. 2017 5;35(5):1007–1017. [PubMed: 27416075]

94. Manzano GW, Fort BP, Dubyak GR, et al. wear particle-induced priming of the NLRP3 inflammasome depends on adherent pathogen-associated molecular patterns and their cognate Toll-like receptors: an in vitro study. Clin Orthop Rel Res. 2018 12;476(12):2442–2453.

95. Pai S, Hui S, Isserlin R, et al. netDx: interpretable patient classification using integrated patient similarity networks. Mol Syst Biol. 2019 3 14;15(3):e8497. [PubMed: 30872331]

96. Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med. 2019 4 4;380(14):1347–1358. [PubMed: 30943338]

97. Narkbunnam R, Amanatullah DF, Electricwala AJ, et al. Radiographic scoring system for the evaluation of stability of cementless acetabular components in the presence of osteolysis. Bone Joint J. 2017 5;99(B(5):):601–606. [PubMed: 28455468]

98. Deshmukh S, Omar IM. Imaging of hip arthroplasties: normal findings and hardware complications. Semin Musculoskelet Radiol. 2019 4;23(2):162–176. [PubMed: 30925629]

99. Bhave S, Koff MF, Sivaram Kaushik S, et al. 3D-multi-spectral T2 mapping near metal implants. Magn Reson Med. 2019 8;82 (2):614–621. [PubMed: 30883910]

100. Signore A, Sconfienza LM, Borens O, et al. Consensus document for the diagnosis of prosthetic joint infections: a joint paper by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur J Nucl Med Mol Imaging. 2019 4;46(4):971–988. [PubMed: 30683987]

101. Vaz S, Ferreira TC, Salgado L, et al. Bone scan usefulness in patients with painful hip or knee prosthesis: 10 situations that can cause pain, other than loosening and infection. Eur J Orthop Surg Traumatol. 2017 2;27(2):147–156. [PubMed: 27900474]

102. Murer AM, Hirschmann MT, Amsler F, et al. Bone SPECT/CT has excellent sensitivity and specificity for diagnosis of loosening and patellofemoral problems after total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2019 7;1. doi: 10.1007/s00167-019-05609-w. Epub ahead of print.

103. Verberne SJ, Sonnega RJ, Temmerman OP, et al. What is the accuracy of nuclear imaging in the assessment of periprosthetic knee infection? A meta-analysis. Clin Orthop Rel Res. 2017 5;475 (5):1395–1410.

104. Pickett JE, Thompson JM, Sadowska A, et al. Molecularly specific detection of bacterial lipoteichoic acid for diagnosis of prosthetic joint infection of the bone. Bone Res. 2018;6:13. [PubMed: 29707402]

105. Sconfienza LM, Signore A, Cassar-Pullicino V, et al. Diagnosis of peripheral bone and prosthetic joint infections: overview on the consensus documents by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur Radiol. 2019 6 27;29:6425–6438. [PubMed: 31250170]

106. Henderson RA, Lachiewicz PF. Groin pain after replacement of the hip: aetiology, evaluation and treatment. J Bone Joint Surg Br. 2012 2;94(2):145–151. [PubMed: 22323676]

107. Flierl MA, Sobh AN, Culp BM, et al. Evaluation of the painful total knee arthroplasty. J Am Acad Orthop Surg. 2019 4 16;27:743–751. [PubMed: 31008874]

108. Ekelund AL. Management of painful reverse shoulder arthroplasty. Shoulder Elbow. 2017 7;9(3):212–222. [PubMed: 28588662]

109. Vulcano E, Myerson MS. The painful total ankle arthroplasty: a diagnostic and treatment algorithm. Bone Joint J. 2017 1;99(B(1)):5–11. [PubMed: 28053250]

110. Terrando S, Sambri A, Bianchi G, et al. Angiosarcoma around total hip arthroplasty: case series and review of the literature. Musculoskelet Surg. 2018 4;102(1):21–27.
111. Zhan H, Gao T, Yu X, et al. Periprosthetic metastasis following total hip arthroplasty in a patient with lung carcinoma: a case report and review of literature. Medicine (Baltimore). 2019 1;98(3):e14071. [PubMed: 30653122]
112. Goodman SB, Trindade M, Ma T, et al. Pharmacologic modulation of periprosthetic osteolysis. Clin Orthop Rel Res. 2005;430:39–45.
113. Ulrich-Vinther M, Carmody EE, Goater JJ, et al. Recombinant adeno-associated virus-mediated osteoprotegerin gene therapy inhibits wear debris-induced osteolysis. J Bone Joint Surg Am. 2002;84(8):1405–1412. [PubMed: 12177271]
114. Yang S-Y, Mayton L, Wu B, et al. Adeno-associated virus-mediated osteoprotegerin gene transfer protects against particulate polyethylene-induced osteolysis in a murine model. Arthritis Rheum. 2002;46(9):2514–2523. [PubMed: 12355500]
115. Kim KJ, Kotake S, Udagawa N, et al. Osteoprotegerin inhibits in vitro mouse osteoclast formation induced by joint fluid from failed total hip arthroplasty. J Biomed Mater Res A. 2001;58(4):393–400.
116. Ma T, Huang Z, Ren PG, et al. An in vivo murine model of continuous intramedullary infusion of polyethylene particles. Biomaterials. 2008 9;29(27):3738–3742. [PubMed: 18561997]
117. Ma T, Ortiz SG, Huang Z, et al. In vivo murine model of continuous intramedullary infusion of particles–a preliminary study. J Biomed Mater Res A. 2009 1;88(1):250–253.
118. Ortiz SG, Ma T, Epstein NJ, et al. Validation and quantification of an in vitro model of continuous infusion of submicron-sized particles. J Biomed Mater Res A. 2008 2;84(2):328–333.
119. Lin T-H, Pajarinen J, Sato T, et al. NF-κB Decoy Oligodeoxynucleotide mitigates wear particle-associated bone loss in the murine continuous infusion model. Acta Biomater. 2016;41:273–281. [PubMed: 27260104]
120. Khosla S Minireview: the OPG/RANKL/RANK system. Endocrinology. 2001;142(12):5050–5055. [PubMed: 11713196]
121. Lin T-H, Sato T, Barcay KR, et al. NF-κB decoy oligodeoxynucleotide enhanced osteogenesis in mesenchymal stem cells exposed to polyethylene particle. Tissue Eng Part A. 2015;21(5–6):875–883. [PubMed: 25518013]
122. Lin T-H, Yao Z, Sato T, et al. Suppression of wear-particle-induced pro-inflammatory cytokine and chemokine production in macrophages via NF-κB decoy oligodeoxynucleotide: a preliminary report. Acta Biomater. 2014;10(8):3747–3755. [PubMed: 24814879]
123. Sato T, Pajarinen J, Lin T-h, et al. NF-κB decoy oligodeoxynucleotide inhibits wear particle-induced inflammation in a murine calvarial model. J Biomed Mater Res A. 2015;103(12):3872–3878. [PubMed: 26123702]
124. Clohisy JC, Yamanaka Y, Faccio R, et al. Inhibition of IKK activation, through sequestering NEMO, blocks PMMA-induced osteoclastogenesis and calvarial inflammatory osteolysis. J Orthop Res. 2006;24(7):1358–1365. [PubMed: 16705717]
125. Nich C, Goodman SB. Role of macrophages in the biological reaction to wear debris from joint replacements. J Long-Term Eff Med Impl. 2014;24(4):259–265.
126. Mantovani A, Biswas SK, Galdiero MR, et al. Macrophage plasticity and polarization in tissue repair and remodelling. J Pathol. 2013;229(2):176–185. [PubMed: 23096265]
127. Mahon OR, O'Hanlon S, Cunningham CC, et al. Orthopaedic implant materials drive M1 macrophage polarization in a spleen tyrosine kinase- and mitogen-activated protein kinase-dependent manner. Acta Biomater. 2018;65:426–435. [PubMed: 29104084]
128. Lin T, Kohno Y, Huang J-F, et al. NFκB sensing IL-4 secreting mesenchymal stem cells mitigate the proinflammatory response of macrophages exposed to polyethylene wear particles. J Biomed Mater Res A. 2018;106(10):2744–2752. [PubMed: 30084534]
129. Hachim D, LoPresti ST, Yates CC, et al. Shifts in macrophage phenotype at the biomaterial interface via IL-4 eluting coatings are associated with improved implant integration. Biomaterials. 2017;112:95–107. [PubMed: 27760399]

130. Yang CL, Sun YH, Yu WH, et al. Modulation of macrophage phenotype through controlled release of interleukin-4 from gelatine coatings on titanium surfaces. Eur Cell Mater. 2018;36:15–29. [PubMed: 30047980]

131. Antonios JK, Yao Z, Li C, et al. Macrophage polarization in response to wear particles in vitro. Cell Mol Immunol. 2013;10(6):471–482. [PubMed: 24013843]

132. Yan Z, Tian X, Zhu J, et al. Metformin suppresses UHMWPE particle-induced osteolysis in the mouse calvaria by promoting polarization of macrophages to an anti-inflammatory phenotype. Mol Med. 2018;24(1):20. [PubMed: 30134793]

133. Valladares RD, Nich C, Zwingenberger S, et al. Toll-like receptors-2 and 4 are overexpressed in an experimental model of particle-induced osteolysis. J Biomed Mater Res A. 2014;102 (9):3004–3011. [PubMed: 24115330]

134. Gibon E, Ma T, Ren P-G, et al. Selective inhibition of the MCP-1-CCR2 ligand-receptor axis decreases systemic trafficking of macrophages in the presence of UHMWPE particles. J Orthop Res. 2012;30(4):547–553. [PubMed: 21913218]

135. Zhao YP, Wei JL, Tian QY. et al. Progranulin suppresses titanium particle induced inflammatory osteolysis by targeting TNFα signaling. Sci Rep. 2016;6:20909. [PubMed: 26864916]

136. Luo G, Li Z, Wang Y, et al. Resveratrol protects against titanium particle-induced aseptic loosening through reduction of oxidative stress and inactivation of NF-κB. Inflammation. 2016;39(2):775–785. [PubMed: 26878849]

137. Yao Z, Keeney M, Lin T-H, et al. Mutant monocyte chemoattractant protein 1 protein attenuates migration of and inflammatory cytokine release by macrophages exposed to orthopedic implant wear particles. J Biomed Mater Res A. 2014;102(9):3291–3297. [PubMed: 24123855]

138. Keeney M, Waters H, Barcay K, et al. Mutant MCP-1 protein delivery from layer-by-layer coatings on orthopedic implants to modulate inflammatory response. Biomaterials. 2013;34(38):10287–10295. [PubMed: 24075408]

139. Nabeshima A, Pajarinen J, Lin T-H, et al. Mutant CCL2 protein coating mitigates wear particle-induced bone loss in a murine continuous polyethylene infusion model. Biomaterials. 2017;117:1–9. [PubMed: 27918885]

140. Sato T, Pajarinen J, Behn A, et al. The effect of local IL-4 delivery or CCL2 blockade on implant fixation and bone structural properties in a mouse model of wear particle induced osteolysis. J Biomed Mater Res A. 2016;104(9):2255–2262. [PubMed: 27114284]

141. Jiang X, Sato T, Yao Z, et al. Local delivery of mutant CCL2 protein-reduced orthopaedic implant wear particle-induced osteolysis and inflammation in vivo. J Orthop Res. 2016;34(1):58–64. [PubMed: 26174978]

142. Wilkinson JM, Little DG. Bisphosphonates in orthopedic applications. Bone. 2011;49(1):95–102. [PubMed: 21256254] •• This paper summarizes the use of bisphosphonates in bone loss in different musculoskeletal disease.

143. Zhang Q, Badell IR, Schwarz EM, et al. Tumor necrosis factor prevents alendronate-induced osteoclast apoptosis in vivo by stimulating Bcl-xL expression through Ets-2. Arthritis Rheum. 2005;52 (9):2708–2718. [PubMed: 16142752]

144. Wang C-J, Wang J-W, Weng L-H, et al. The effect of alendronate on bone mineral density in the distal part of the femur and proximal part of the tibia after total knee arthroplasty. J Bone Joint Surg Am. 2003;85(11):2121–2126. [PubMed: 14630840]

145. Trevisan C, Ortolani S, Romano P, et al. Decreased periprosthetic bone loss in patients treated with clodronate: a 1-year randomized controlled study. Calcif Tissue Int. 2010;86(6):436–446. [PubMed: 20390409]

146. Sköldenberg OG, Salemyr MO, Bodén HS, et al. The effect of weekly risedronate on periprosthetic bone resorption following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. J Bone Joint Surg Am. 2011;93(20):1857–1864. [PubMed: 22012522]

147. Greenwell PH, Shield WP, Chapman DM, et al. Isolated revision of the polyethylene component at revision total knee arthroplasty has excellent survivorship at ten years. Bone Joint J. 2019 7;101-B (7_Supple_C):104–107.

148. Gibon E, Kerboull L, Courpied JP, et al. Acetabular reinforcement rings associated with allograft for severe acetabular defects. Int Orthop. 2019 3;43(3):561–571. [PubMed: 30218182]

149. Kohonen I, Koivu H, Tiusanen H, et al. Are periprosthetic osteolytic lesions in ankle worth bone grafting? Foot Ankle Surg. 2017 6;23(2):128–133. [PubMed: 28578796]

150. Lopez-Lopez JA, Humphriss RL, Beswick AD, et al. Choice of implant combinations in total hip replacement: systematic review and network meta-analysis. BMJ. 2017 11;2(359):j4651.

151. Castagnini F, Bordini B, Tassinari E, et al. Delta-on-delta ceramic bearing surfaces in revision hip arthroplasty. J Arthroplasty. 2019 9;34(9):2065–2071. [PubMed: 31160152]

152. Koch CN, Figgie M Jr., Figgie MP, et al. Ceramic bearings with titanium adapter sleeves implanted during revision hip arthroplasty show minimal fretting or corrosion: a retrieval analysis. Hss J. 2017 10;13(3):241–247. [PubMed: 28983216]

153. Brown TS, Tibbo ME, Arsoy D, et al. Long-term outcomes of constrained liners cemented into retained, well-fixed acetabular components. J Bone Joint Surg Am. 2019 4 3;101(7):620–627. [PubMed: 30946196]

154. Green CM, Buckley SC, Hamer AJ, et al. Long-term results of acetabular reconstruction using irradiated allograft bone. Bone Joint J. 2018 11;100(B(11):):1449–1454. [PubMed: 30418060]

155. Migaud H, Common H, Girard J, et al. Acetabular reconstruction using porous metallic material in complex revision total hip arthroplasty: a systematic review. Orthop Traumatol Surg Res. 2019 2;105(1S):S53–S61. [PubMed: 30138711]

156. Girerd D, Parratte S, Lunebourg A, et al. Total knee arthroplasty revision with trabecular tantalum cones: preliminary retrospective study of 51 patients from two centres with a minimal 2-year follow-up. Orthop Traumatol Surg Res. 2016 6;102(4):429–433. [PubMed: 27052939]

157. Sassoon AA, Barrack RL. Pseudotumour formation and subsequent resolution in metal-on-metal total hip arthroplasty following revision: instructional review and an illustrative case report with revision using a dual mobility design. Bone Joint J. 2016 6;98(B(6):):736–740. [PubMed: 27235513]

158. Matharu GS, Pandit HG, Murray DW, et al. Adverse reactions to metal debris occur with all types of hip replacement not just metal-on-metal hips: a retrospective observational study of 3340 revisions for adverse reactions to metal debris from the national joint registry for England, wales, Northern Ireland and the isle of man. BMC Musculoskelet Disord. 2016 12 13;17(1):495. [PubMed: 27955657]

159. Wagner ER, Kamath AF, Fruth K, et al. Effect of body mass index on reoperation and complications after total knee arthroplasty. J Bone Joint Surg Am. 2016 12 21;98(24):2052–2060. [PubMed: 28002368]

160. Christensen TC, Wagner ER, Harmsen WS, et al. Effect of physical parameters on outcomes of total knee arthroplasty. J Bone Joint Surg Am. 2018 11 7;100(21):1829–1837. [PubMed: 30399077]

161. Wagner ER, Kamath AF, Fruth KM, et al. Effect of body mass index on complications and reoperations after total hip arthroplasty. J Bone Joint Surg Am. 2016 2 3;98(3):169–179. [PubMed: 26842406]

162. Haughom BD, Erickson BJ, Hellman MD, et al. Do complication rates differ by gender after metal-on-metal hip resurfacing arthroplasty? A systematic review. Clin Orthop Rel Res. 2015 8;473 (8):2521–2529.

163. Gallo J, Mrazek F, Petrek M. Variation in cytokine genes can contribute to severity of acetabular osteolysis and risk for revision in patients with ABG 1 total hip arthroplasty: a genetic association study. BMC Med Genet. 2009 10 27;10:109. [PubMed: 19860911] •• This is a classic study on how deficiencies in the patient's genome may be associated with periprosthetic osteolysis.

164. MacInnes SJ, Hatzikotoulas K, Fenstad AM, et al. The 2018 Otto Aufranc Award: how does genome-wide variation affect osteolysis risk after THA? Clin Orthop Rel Res. 2019 2;477(2):297–309.

165. Del Buono A, Denaro V, Maffulli N. Genetic susceptibility to aseptic loosening following total hip arthroplasty: a systematic review. Br Med Bull. 2012;101:39–55. [PubMed: 21652593]

166. Garvin KL, White TC, Dusad A, et al. Low wear rates seen in THAs with highly crosslinked polyethylene at 9 to 14 years in patients younger than age 50 years. Clin Orthop Rel Res. 2015 12;473(12):3829–3835.

167. Rajpura A, Kendoff D, Board TN. The current state of bearing surfaces in total hip replacement. Bone Joint J. 2014 2;96(B(2):):147–156. [PubMed: 24493177]
168. Lachiewicz PF, Kleeman LT, Seyler T. Bearing surfaces for total hip arthroplasty. J Am Acad Orthop Surg. 2018 1 15;26(2):45–57. [PubMed: 29303922] •• This is an excellent article summarizing bearing couples for total hip replacement.
169. Brown TS, Van Citters DW, Berry DJ, et al. The use of highly crosslinked polyethylene in total knee arthroplasty. Bone Joint J. 2017 8;99(B(8)):996–1002. [PubMed: 28768774] •• This is an excellent article summarizing the use of newer polyethylene for total knee replacement.
170. Wyles CC, Jimenez-Almonte JH, Murad MH, et al. There are no differences in short- to mid-term survivorship among total hip-bearing surface options: a network meta-analysis. Clin Orthop Rel Res. 2015 6;473(6):2031–2041.
171. Henckel J, Holme TJ, Radford W, et al. 3D-printed patient-specificguides for hip arthroplasty. J Am Acad Orthop Surg. 2018 8 15;26(16):e342–e348. [PubMed: 30052547]
172. Wyatt MC. Custom 3D-printed acetabular implants in hip surgery– innovative breakthrough or expensive bespoke upgrade? Hip Int. 2015 Jul-Aug;25(4):375–379. [PubMed: 26351112]
173. Goodman SB, Yao Z, Keeney M, et al. The future of biologic coatings for orthopaedic implants. Biomaterials. 2013 4;34 (13):3174–3183. [PubMed: 23391496] •• The article summarizes biologic coatings for implants to improve integration and resist/treat infection.
174. Kargupta R, Bok S, Darr CM, et al. Coatings and surface modifications imparting antimicrobial activity to orthopedic implants. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014 Sep-Oct;6 (5):475–495. [PubMed: 24867883]
175. Raphel J, Holodniy M, Goodman SB, et al. Multifunctional coatings to simultaneously promote osseointegration and prevent infection of orthopaedic implants. Biomaterials. 2016;84:301–314. [PubMed: 26851394]
176. Zhang BG, Myers DE, Wallace GG, et al. Bioactive coatings for orthopaedic implants-recent trends in development of implant coatings. Int J Mol Sci. 2014 7 4;15(7):11878–11921. [PubMed: 25000263]
177. Tobin EJ. Recent coating developments for combination devices in orthopedic and dental applications: a literature review. Adv Drug Deliv Rev. 2017 3;112:88–100. [PubMed: 28159606]
178. Greenfield EM, Beidelschies MA, Tatro JM, et al. Bacterial pathogen-associated molecular patterns stimulate biological activity of orthopaedic wear particles by activating cognate Toll-like receptors. J Biol Chem. 2010 10 15;285(42):32378–32384. [PubMed: 20729214]
179. Greenfield EM, Bi Y, Ragab AA, et al. Does endotoxin contribute to aseptic loosening of orthopedic implants? J Biomed Mater Res. 2005 1 15;72(1):179–185.•• This paper discusses the potential role of endotoxin in loosening and osteolysis of implants for joint replacement.
180. Wasko M, Goodman SB. The Emperor's new clothes: is particle disease really infected-particle disease? J Orthop Res. 2016 9;34(9):1497–1504. [PubMed: 27175824]
181. Damiati L, Eales MG, Nobbs AH, et al. Impact of surface topography and coating on osteogenesis and bacterial attachment on titanium implants. J Tissue Eng. 2018;9:2041731418790694. [PubMed: 30116518]
182. Jacofsky DJ, Allen M. Robotics in arthroplasty: a comprehensive review. J Arthroplasty. 2016 10;31(10):2353–2363. [PubMed: 27325369]
183. Bautista M, Manrique J, Hozack WJ. Robotics in total knee arthroplasty. J Knee Surg. 2019 7;32(7):600–606. [PubMed: 30822790]
184. Buza JA 3rd, Wasterlain AS, Thakkar SC, et al. Navigation and robotics in knee arthroplasty. JBJS Rev. 2017 28;5(2):2.
185. Wasterlain AS, Buza JA 3rd, Thakkar SC, et al. Navigation and robotics in total hip arthroplasty. JBJS Rev. 2017 14;5(3):3.
186. Sumner DR, Ross R, Purdue E. Are there biological markers for wear or corrosion? A systematic review. Clin Orthop Rel Res. 2014 12;472(12):3728–3739.
187. Gallo J, Goodman SB, Konttinen YT, et al. Particle disease: biologic mechanisms of periprosthetic osteolysis in total hip arthroplasty. Innate Immun. 2013;19(2):213–224. [PubMed: 22751380]

188. Goodman SB, Gibon E, Yao Z. The basic science of periprosthetic osteolysis. Instr Course Lect. 2013;62:201–206. [PubMed: 23395025]

189. Goodman SB, Gibon E, Pajarinen J, et al. Novel biological strategies for treatment of wear particle-induced periprosthetic osteolysis of orthopaedic implants for joint replacement. J R Soc Interface. 2014 4 6;11(93):20130962. [PubMed: 24478281] •• This article summarizes some of the novel biologic strategies to prevent or treat periprosthetic osteolysis.

190. Schwarz EM. What potential biologic treatments are available for osteolysis? J Am Acad Orthop Surg. 2008;16(Suppl 1):S72–5. [PubMed: 18612019]

191. Smith RL, Schwarz EM. Are biologic treatments a potential approach to wear- and corrosion-related problems? Clin Orthop Rel Res. 2014 12;472(12):3740–3746.•• This article summarizes some of the current non-surgical treatments for inflammatory bone loss due to wear particles and other byproducts from implants

Article highlights

- The generation of byproducts from joint replacements will always occur, due to repetitive cyclic loading of the bearing surfaces and modular junctions during use.
- byproducts of wear activate the innate immune system, and in some cases (especially with metallic debris and ions), the adaptive immune system.
- progressive inflammation and osteolysis are generally addressed by surgical revision.
- non-operative biological interventions might be possible in the future, and could prolong the lifetime of joint replacements that are otherwise functional and still salvageable.

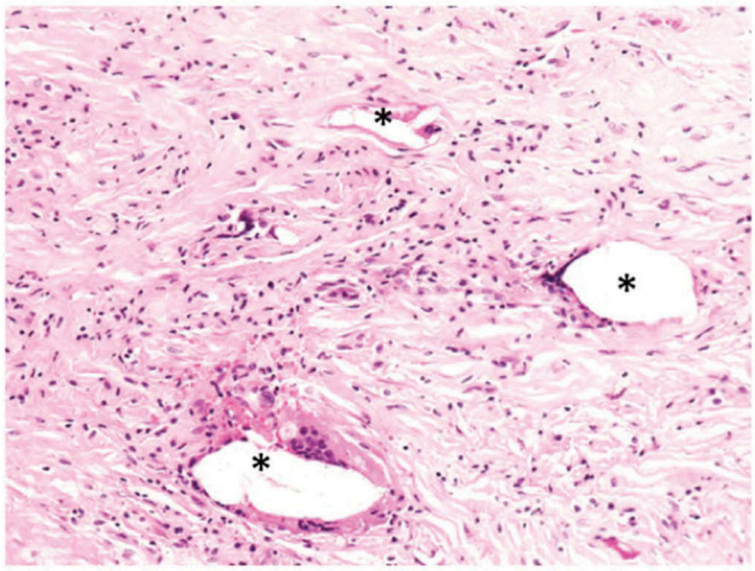

Figure 1.

The foreign body reaction to ‘Large’-sized debris. Giant cells and collagenous fibers surround the debris, which is probably composed of ultra-high molecular weight polyethylene or methyl methacrylate (*).

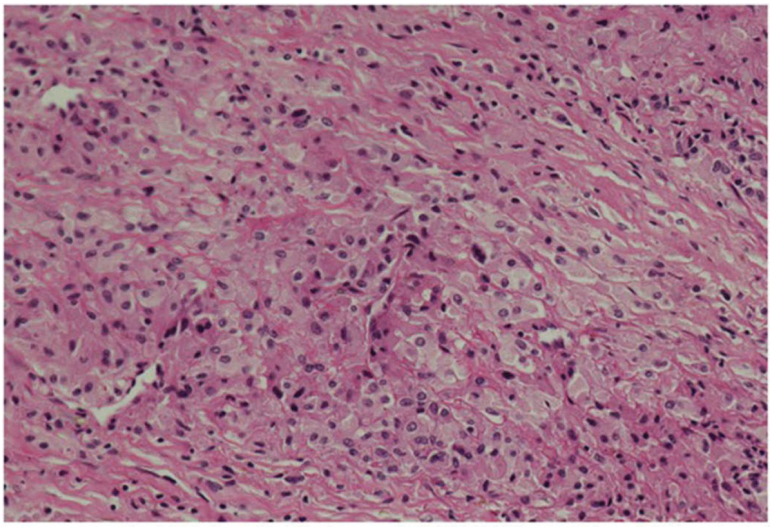

Figure 2.
Foamy macrophage sheets were observed with collagenous frame.

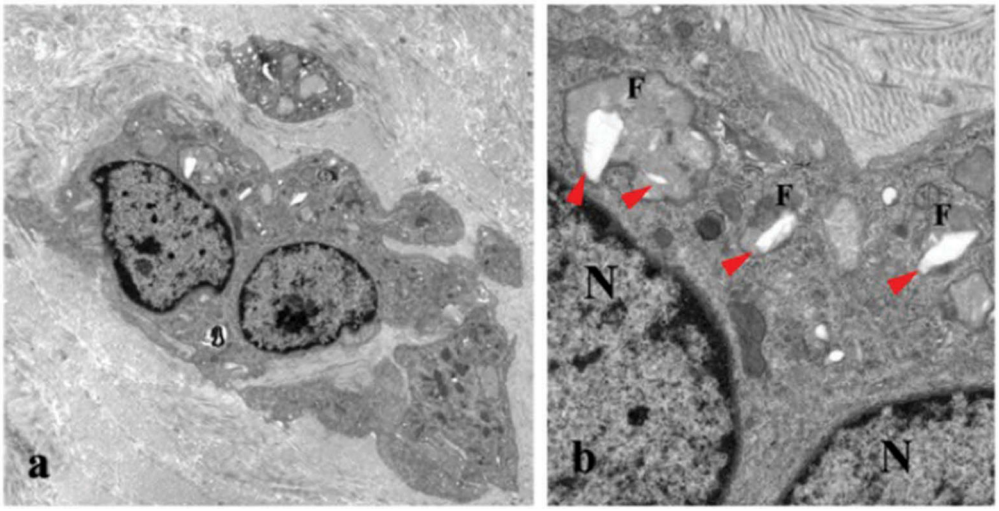

Figure 3.

Phagocytosis of ‘Moderate’-sized ultra-high molecular weight polyethylene particles by foreign body type giant cell, after cellular fusion of macrophages (Figure 2(a)). The particles are located in the phagosomes (F: phagosome, N: nucleus, arrowhead: particle) (Figure 2(b)).

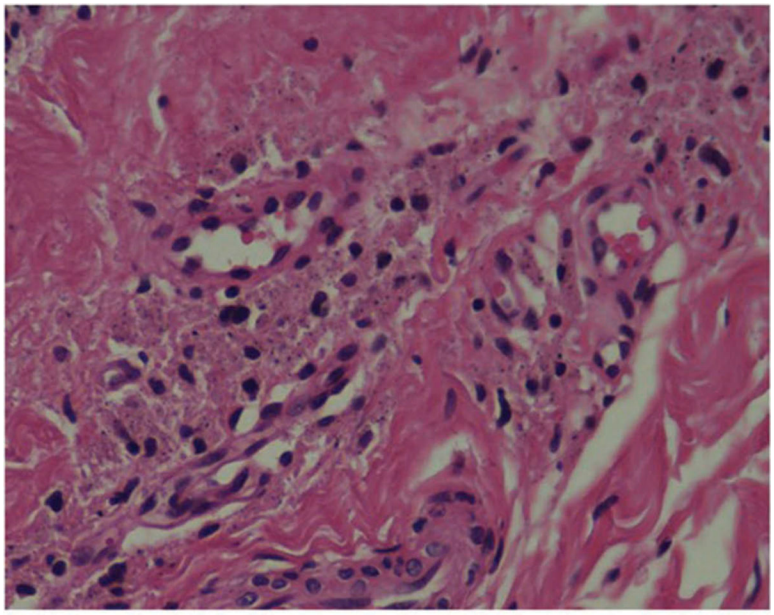

Figure 4.
Submicron-sized metal particles are found in the cytoplasm of macrophages. The cellular borders are unclear, and the nuclei are pyknotic, indicating cellular damage and/or progression of cell death.

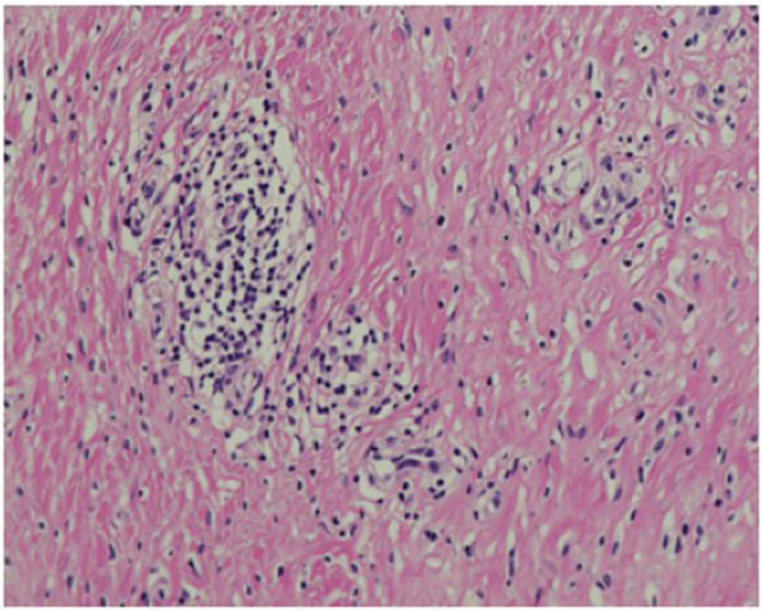

Figure 5.
Lymphocyte aggregation (arrowhead) in the stroma of pseudotumor, found in metal on metal articulation.

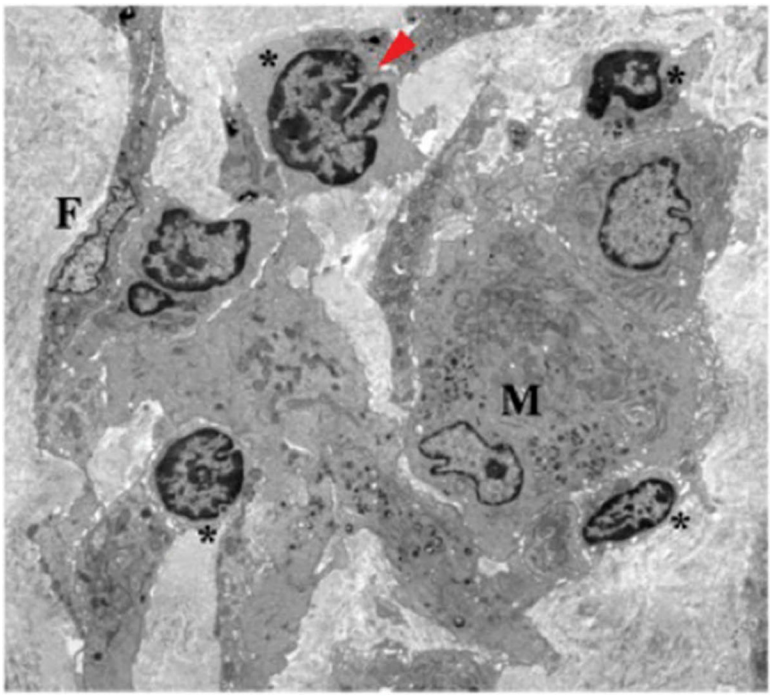

Figure 6.

Lymphocytes – macrophage/stromal cell interactions in the capsular tissue of a pseudotumor. Lymphocytes are of round shape and have less cytoplasm (*) are in contact with a macrophage (M) and a fibroblast-like stromal cell (F). Convoluted nuclei specific to T lymphocytes are also observed (arrowhead).

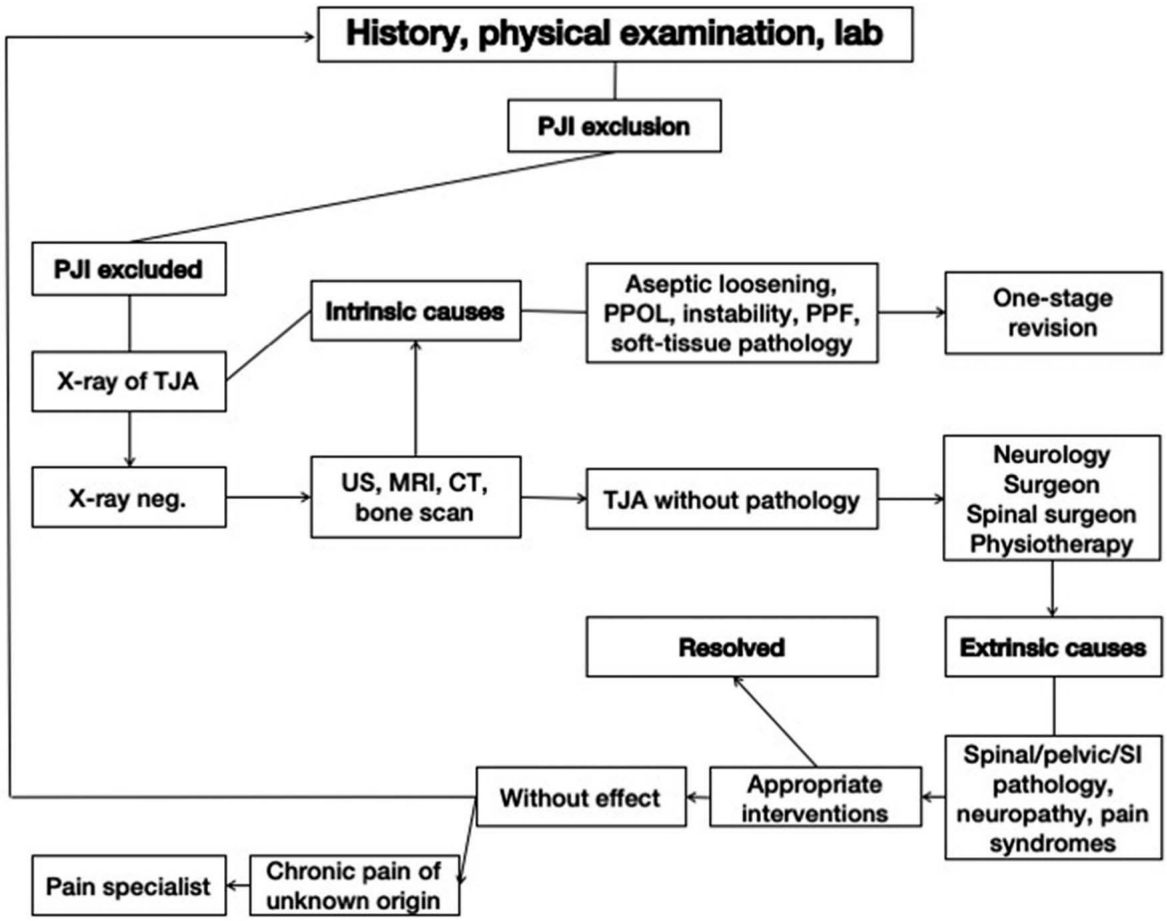

Figure 7.

Uncovering the causative mechanism underlying pain associated with mechanically stable THA represents one of the most difficult diagnostic challenges in modern orthopedics; here, an algorithm is presented addressing a wide range of pathologies in a logical, step-wise fashion; CT = computer tomography; MRI = magnetic resonance imaging; PJI = prosthetic joint infection; PPF = periprosthetic fracture; PPOL = periprosthetic osteolysis; SI = sacroiliac; TJA = total joint arthroplasty; US = ultrasound.

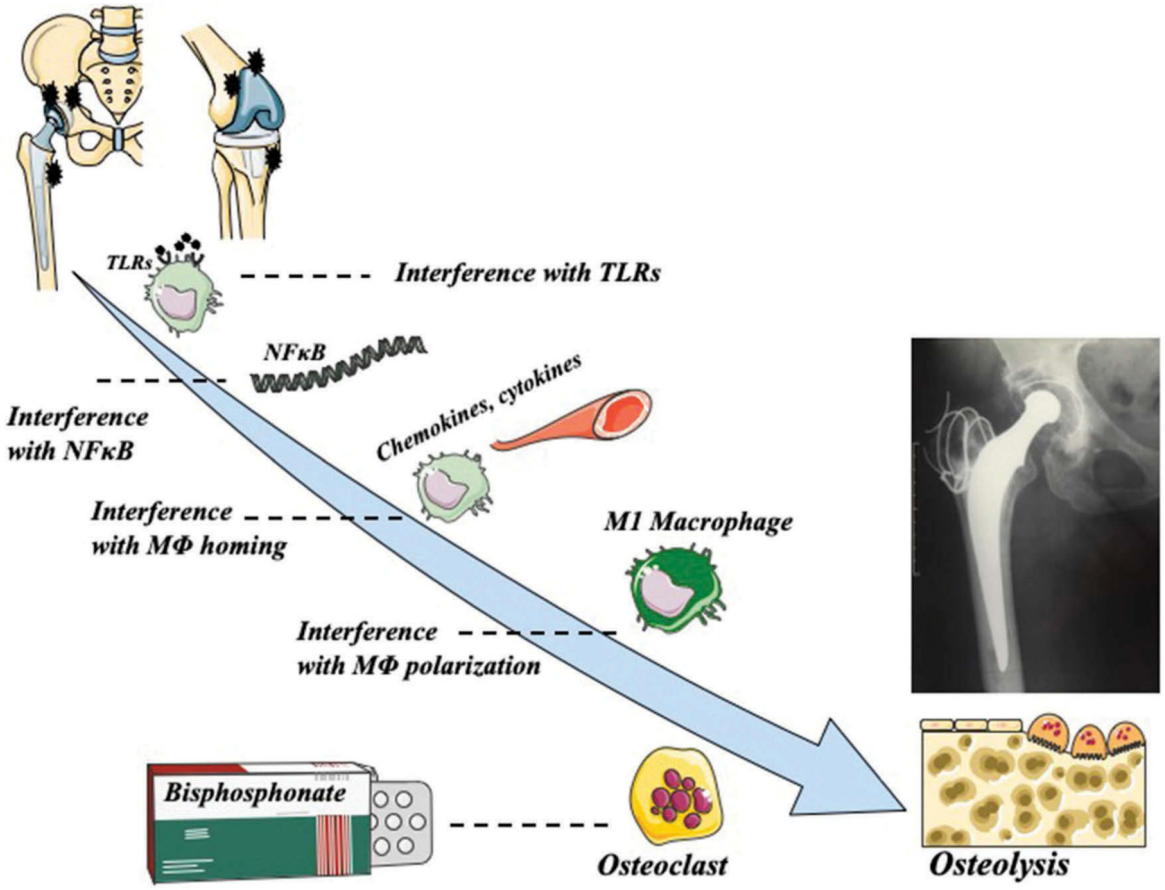

Figure 8.

Potential pharmaceutical interventions to manage periprosthetic bone loss. TLRs = toll-like receptors; NF-κB = nuclear factor-kappa B; MΦ = macrophage.

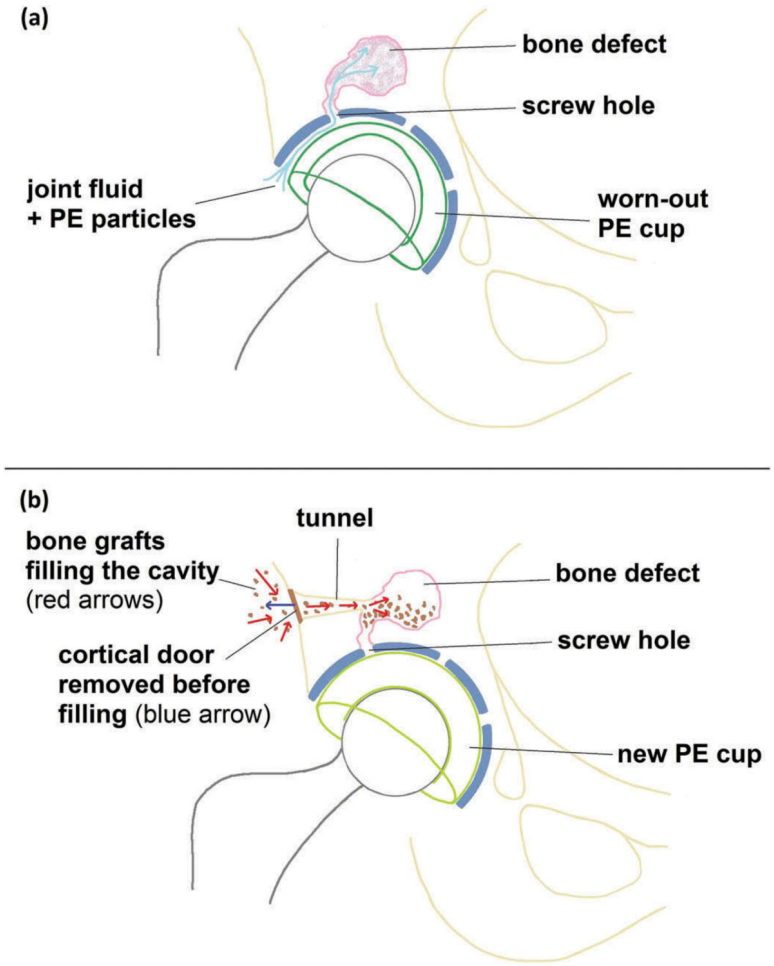

Figure 9.

A schematic presentation of the key pathogenic mechanisms behind the development of retro-acetabular osteolysis (a); a bone defect under the THA cup can be reached through holes in the original cup or through a strategic supraacetabular window (b); PE = polyethylene.