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# Aseptic Loosening in Total Hip Arthroplasty: Pathophysiology, Biomarkers, and Preventive Treatment Strategies

**Gabriele Ricciardi [1,2,†], Lorenza Siracusano [3,†], Edoardo Micale [3,*], Vito Addorisio [3], Mariagiovanna Ballato [1], Domenico Donadio [1,2,4,5], Pietro Tralongo [1], Giuseppe Giuffrè [6], Danilo Leonetti [3], Maurizio Martini [6,‡] and Biagio Zampogna [3,4,5,‡]**

1 BIOMORF Department of Biomedical, Dental, Morphological and Functional Imaging Sciences, A.O.U. Policlinico "G.Martino"-Via Consolare Valeria 1, 98124 Messina, Italy; gricciardi1998@gmail.com (G.R.); mariagiovannaballato96@gmail.com (M.B.); domenico.donadio@studenti.unime.it (D.D.); pietrotralongo@gmail.com (P.T.)
2 Istituto Clinico Polispecialistico C.O.T. Cure Ortopediche Traumatologiche s.p.a., 98124 Messina, Italy
3 BIOMORF Department of Biomedical, Dental, Morphological and Functional Imaging Sciences, Section of Orthopaedic and Trauma Surgery, A.O.U. Policlinico "G.Martino", University of Messina, Via Consolare Valeria 1, 98125 Messina, Italy; lorenza.siracusano@studenti.unime.it (L.S.); vito.addorisio@studenti.unime.it (V.A.); dleonetti@unime.it (D.L.); biagio.zampogna@unime.it (B.Z.)
4 Operative Research Unit of Orthopaedic and Trauma Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, 00128 Rome, Italy
5 Research Unit of Orthopaedic and Trauma Surgery, Department of Medicine and Surgery, Università Campus Bio-Medico Di Roma, Via Alvaro del Portillo 21, 00128 Rome, Italy
6 Department of Human Pathology of Adults and Developmental Age "Gaetano Barresi", Division of Pathology, University of Messina, 98125 Messina, Italy; giuseppe.giuffre@unime.it (G.G.); maurizio.martini@unime.it (M.M.)
* Correspondence: emicale@unime.it
† These authors contributed equally to this work.
‡ These authors share last authorship and contributed equally to this work.

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## Abstract

Aseptic loosening (AL) represents the leading cause of long-term failure in total joint arthroplasty, often necessitating revision surgery. This review explores the complex mechanisms underlying AL, which involve a multifaceted interaction between the implanted biomaterials and the host immune response. We outline the key inflammatory mechanisms triggered by wear debris from polyethylene, polymethylmethacrylate, metal, and ceramic materials. We also examine emerging biomarkers for early detection and differentiation between stable and loosened implants, including proinflammatory cytokines, bone metabolism markers, extracellular matrix degradation products, microRNAs, and genetic polymorphisms. Lastly, we discuss current and future strategies for prevention and treatment, ranging from surgical optimization and biomaterial selection to pharmacological interventions. A comprehensive understanding of these mechanisms may help reduce the incidence of AL and improve long-term outcomes in arthroplasty patients.

**Keywords:** aseptic loosening; biomarker; osteolysis; total hip arthroplasty

## 1. Introduction

Total hip arthroplasty (THA) is one of the most successful and frequently performed surgical procedures worldwide, providing substantial pain relief and functional improvement for millions of patients with degenerative or traumatic hip diseases [1]. Despite continuous advances in surgical techniques and biomaterials, its long-term success is often

compromised by aseptic loosening (AL), which remains the leading cause of non-infectious implant failure [1]. AL refers to the detachment of an implant from the surrounding bone without any evidence of infection or injury [2]. Clinically, it results in pain, functional impairment, and the need for revision surgery, a procedure technically more demanding than primary THA, associated with a higher risk of complications (e.g., infection, blood loss, periprosthetic fractures) and longer, often less favorable, recovery [3]. From an economic perspective, AL represents a substantial burden, as revision surgeries are considerably more expensive than primary procedures due to higher hospital costs, prosthetic component expenses, prolonged rehabilitation, and loss of productivity [4]. With the increasing life expectancy of the population and the expanding indications for joint arthroplasty, the incidence of AL and the demand for revision surgeries are expected to rise markedly, placing growing pressure on healthcare systems worldwide [4,5]. Understanding the multifactorial biological mechanisms underlying AL, identifying patients at risk through early biomarkers, and developing innovative preventive and therapeutic strategies are therefore essential to improve long-term outcomes and reduce healthcare costs. This review will examine the complex pathophysiology of AL, explore emerging biomarkers for early detection, and discuss current and future strategies for prevention and management.

## 2. Methodology

This narrative review was conducted to synthesize the existing scientific literature on pathophysiological mechanisms, biomarkers, and preventive and therapeutic strategies related to AL in THA. A comprehensive literature search was performed using the electronic databases PubMed, Scopus, and Web of Science. Various combinations of keywords were employed, including “aseptic loosening,” “total hip arthroplasty,” “periprosthetic osteolysis,” “wear debris,” “biomarkers,” “inflammation,” “foreign body reaction,” “preventive strategies,” “treatment,” “pharmacological intervention,” “biomaterials,” and “coatings.” The search was limited to articles published in English.

Inclusion criteria encompassed original studies (in vitro, animal studies, clinical and translational research) and review articles addressing the pathophysiology, biological mechanisms, biomarker identification, or prevention and treatment strategies of AL. Conference abstracts, letters to the editor, and non-peer-reviewed articles were excluded. Two independent reviewers (GR and LS) screened titles and abstracts for relevance. Potentially eligible articles underwent full-text review. Discrepancies were resolved through discussion and consensus or consultation with a third reviewer (EM). Relevant data were extracted and narratively synthesized, organized around key themes such as inflammatory mechanisms, biomarkers, and intervention strategies.

Due to the narrative nature of the review, a formal quality assessment of included studies using specific tools was not performed. However, priority was given to high-quality studies with robust designs and reproducible results. The potential for publication bias was acknowledged, with efforts made to include a broad range of studies and to highlight areas of controversy where present. The literature search covered the period from the earliest identification of aseptic loosening mechanisms up to July 2025, ensuring inclusion of the most recent discoveries and emerging trends.

## 3. Immune Response to Biomaterial

AL is a complex process driven by biological mechanisms that gradually destabilize the implant. This multifactorial process involves intricate interactions between the implant, immune system cells, and bone cells [6–8]. In fact, orthopedic implant placement triggers an innate immune response, beginning with acute inflammation followed by chronic inflammation driven by wear particle phagocytosis [9]. This process promotes granulation

tissue formation, periprosthetic fibrosis, and increased osteoclast activity, disrupting bone homeostasis and leading to osteolysis [9]. Concurrently, a distinct and persistent foreign body reaction (FBR) occurs in response to non-degradable particulate debris. The FBR is characterized by sustained macrophage activation, multinucleated foreign body giant cells (FBGCs) formation, and fibrotic encapsulation of debris [7]. Importantly, the FBR depends on and is influenced by the chronic inflammatory environment, demonstrating that these pathways are interconnected and mutually reinforcing [7,9]. Together, they amplify extracellular matrix remodeling and bone resorption, ultimately leading to AL. Figure 1 illustrates the process flowchart.

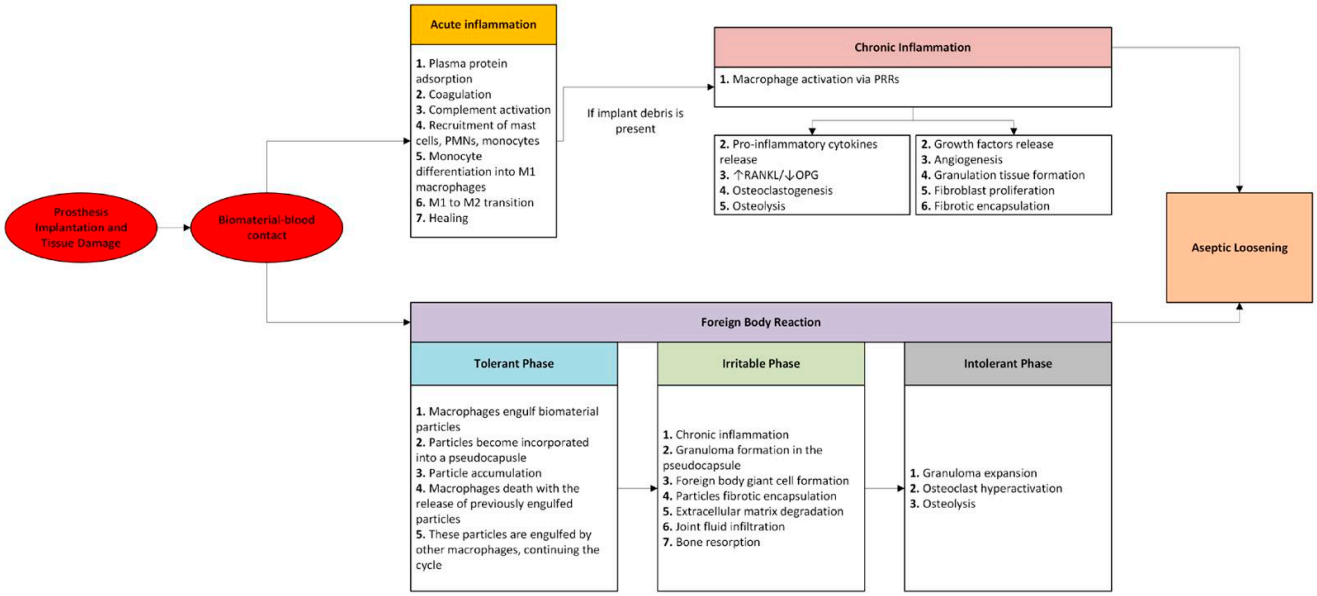


**Figure 1.** Inflammatory and Foreign Body Reactions Leading to Aseptic Loosening.

### *3.1. Acute Inflammation*

The surgical introduction of biomaterials leads to inevitable tissue damage, triggering an acute inflammatory response, which occurs alongside the body's specific reaction to the biomaterial [6,10]. Upon implantation, biomaterials rapidly adsorb proteins from blood and interstitial fluid proteins, forming a layer that influences immune cell recruitment, inflammation, and matrix formation [10,11]. Among these adsorbed proteins, albumin, fibrinogen, fibronectin, and complement factors regulate cell adhesion and immune activation, shaping the host response [6]. Biomaterials can also trigger the coagulation pathway through Factor XII (FXII) and tissue factor (TF). Surface contact activates FXII, leading to thrombin generation, while platelet adhesion amplifies coagulation and inflammation [12,13]. Fibrinogen adsorption on biomaterials promotes phagocyte activation, contributing to clot formation and immune responses [14]. Concurrently, complement system activation results in the formation of C3 convertase. This, in turn, generates the anaphylatoxins C3a and C5a, which trigger inflammation by activating immune cells, increasing vascular permeability, and promoting mast cell degranulation [6]. The complement and coagulation cascades interact and modulate each other's activities [15]. Leukocytes exit blood vessels and migrate into perivascular tissues in response to the implant [6,16–20]. Their interaction with biomaterial surfaces is mediated by adsorbed proteins acting as ligands for integrins that are the key adhesion receptors on leukocytes [6,14,21]. Among these ligands are fibrinogen, factor X, iC3b, fibronectin, and vitronectin [19,20]. Initial phagocyte attachment and spreading are facilitated by β2 integrins, which later promote the expression of additional integrins [6,19]. Mast cell degranulation, with histamine release, directs polymorphonuclear leukocytes

(PMNs) and monocytes to implants and modulates the immune response through IL-4 and IL-13 secretion [6,22,23]. PMNs secrete IL-8, which recruits additional neutrophils and enhances the immune response; with certain biomaterials like chitosan, this migration may persist due to ongoing IL-8 signaling [6,24–27]. Activated PMNs release monocyte chemotactic protein-1 (MCP-1/CCL2) and macrophage inflammatory protein-1 (MIP-1), which serve as strong chemoattractants and activation signals for monocytes, macrophages, immature dendritic cells, and lymphocytes [6,28,29]. This chemokine release shifts the immune response by limiting further neutrophil infiltration while promoting the recruitment of monocytes. Once at the implantation site, monocytes differentiate into macrophages, initially adopting a proinflammatory M1 phenotype [7,30–33]. These macrophages amplify inflammation by releasing cytokines and recruiting mesenchymal stem cells (MSCs) [7]. Additionally, these factors enhance the osteogenic differentiation of mesenchymal stem cells (MSCs) into osteoblasts and stimulate angiogenesis, both essential processes for bone repair [7,34–36]. Tissue injury causes damage to the bone microvasculature, resulting in hematoma formation around the lesion [37,38]. The early inflammatory response promotes new blood vessel development, while macrophages and osteoclasts remove damaged bone tissue [38,39]. Newly formed blood vessels ensure oxygen and nutrient supply, essential for MSC differentiation and bone regeneration [38]. The transition from M1 to the anti-inflammatory M2 macrophage phenotype plays a crucial role in resolving the inflammation and supporting tissue remodeling [7]. As the inflammation subsides, PMNs undergo apoptosis due to the absence of further activation signals. Their clearance by macrophages via phagocytosis facilitates the M1-to-M2 transition, stabilizing new vascular networks and promoting long-term tissue healing [6]. Typically, PMNs are no longer present at the surgical site within the first 48 h of biomaterial implantation [6,9].

### 3.2. Chronic Inflammation

Inflammation around the implant site represents the tissue's defense against multiple stressors, such as surgical intervention, trauma, infections, the implant, and its wear debris. To prevent tissue damage and persistent immune reactions, anti-inflammatory mechanisms are simultaneously activated to restore tissue homeostasis [40,41]. However, not all patients with joint prostheses achieve a stable state, and some stressors persist [7,42,43]. Ongoing inflammation at the bone–implant interface, driven by wear particles, results in periprosthetic osteolysis (PPOL) [44]. Excessive wear particle production can induce chronic inflammation, driven by cytokine release from macrophages and foreign body giant cells (FBGCs), resulting in a continuous cycle of inflammatory stress in the affected tissues [6]. The immune response to wear particles is influenced by multiple factors [6]. Size plays a crucial role, as particles between 0.1 and 1 μm are the most biologically active [45–49]. Smaller particles (<1 μm) are engulfed by macrophages through phagocytosis, while larger particles (>10 μm) are typically encased by multiple macrophages and FBGCs [50]. Material composition also plays a key role, as substances like polyethylene, PMMA, and metals tend to provoke a stronger inflammatory reaction. Shape and surface texture contribute as well, with irregular, rough particles triggering a more intense immune reaction [47,50]. The quantity of particles is another key factor, as exceeding a certain threshold can lead to periprosthetic osteolysis [46,47,51]. The inflammatory response is further influenced by factors such as surface charge and the capacity of periprosthetic tissues to clear debris [47]. The body's ability to balance pro- and anti-inflammatory mechanisms further determines the severity of the response. Furthermore, surface charge and the efficiency of periprosthetic tissue clearance also affect the inflammatory process. The body's capacity to modulate pro- and anti-inflammatory mechanisms is a pivotal factor in determining the severity of the response [47]. Finally, genetic susceptibility, including

particular single-nucleotide polymorphism (SNP) variations, may have the potential to render certain individuals more prone to an aggressive inflammatory response [47]. Although various cells respond to implant debris by initiating inflammation, the central role belongs to resident macrophages, whose particle-clearing activity drives the inflammatory processes around the implant [52,53]. Macrophage activation by wear particles is mediated through pattern recognition receptors (PRRs). PRRs differ by location, with Toll-like receptors (TLRs)—particularly TLR2 and TLR4—playing a central role in how macrophages detect implant particles [44,54]. Wear debris functions as alarmins, engaging PRRs either at the cell surface or after phagocytosis. This interaction leads to the secretion of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6, and prostaglandin E-2 (PGE-2) [44,55]. Moreover, macrophages release growth factors like macrophage colony-stimulating factor 1 (M-CSF), osteoclast-activating signals including receptor activator of nuclear factor kappa B ligand (RANKL), and chemokines such as IL-8, macrophage inflammatory protein-1α (MIP-1α), and MCP-1 [44,55]. This process draws in more macrophages and osteoclast precursors, worsening inflammation and bone loss [55]. Wear particles activate the NLRP3 inflammasome, which, through a two-step process involving NF-κB and ASC, leads to the release of IL-1β and IL-18 [56]. Macrophage phagocytosis of wear debris activates this inflammasome pathway, leading to the release of IL-1β, which plays a key role in osteolysis [57]. Macrophage release of TNF-α and IL-1β in response to wear particles induces osteoblasts and fibroblasts to increase RANKL expression and decrease osteoprotegerin (OPG) production [58,59] A decreased OPG/RANKL ratio has been associated with enhanced osteolysis [60]. When RANKL binds to RANK on osteoclast precursors, it activates signaling cascades including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK), leading to osteoclast formation and enhanced bone resorption that contributes to implant loosening [61]. This process is summarized in Figure 2.

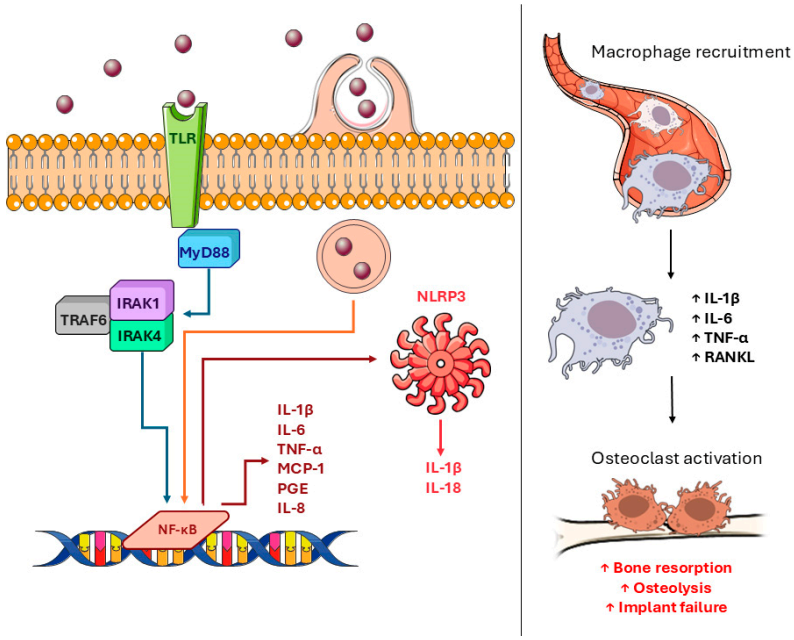


**Figure 2.** Macrophages react to implant wear particles by engaging Toll-like receptors (TLRs) or internalizing debris via phagocytosis. This activates nuclear factor kappa B (NF-κB), triggering the release of proinflammatory cytokines (TNF-α, IL-1, IL-6, PGE-2), growth factors (M-CSF), osteoclast-promoting factors (RANKL), and chemokines (IL-8, MIP-1α, MCP-1). These signals recruit more macrophages and osteoclast precursors, driving inflammation, bone resorption, osteolysis, and implant failure. This figure was created with Servier Medical Art (https://smart.servier.com, accessed on 25 March 2025) and NIH Bioart (https://bioart.niaid.nih.gov/, accessed on 25 March 2025).

### 3.3. Granulation Tissue and Fibrosis

It has been observed that, during the chronic inflammation phase, the release of growth factors such as Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), Transforming Growth Factor-β (TGF-β), and Epidermal Growth Factor (EGF) from macrophages stimulates the formation of new blood vessels and connective tissue [62]. At the site of implantation, fibroblasts and vascular endothelial cells proliferate, forming granulation tissue, a key feature of the healing inflammatory response. This tissue, distinguished by its pink, granular appearance in healing wounds, is characterized by the growth of new blood vessels and fibroblast proliferation [9,62].

New blood vessels form by sprouting from existing ones, a process called neovascularization or angiogenesis, involving endothelial cell growth, maturation, and assembly into capillaries [62]. As granulation tissue develops, fibroblasts proliferate and synthesize collagen and proteoglycans, leading to fibrotic encapsulation. The consequence of this persistent immune response is the continuous production of an extracellular matrix around the implant. This, in turn, results in implant loosening and potential failure. [62].

### 3.4. Foreign Body Reaction

Foreign body reaction (FBR) refers to the body's response to small particles and debris from implanted medical devices, such as prostheses [7]. This response involves various immune cells, including monocytes, macrophages, fibroblasts, FBGCs, and osteoclasts [7]. However, FBR around implants differs from acute and chronic inflammation, progressing through three phases: tolerant, irritable, and intolerant [7]. Importantly, FBR to prosthetic implants is a dynamic and evolving process characterized by sequential phases, each distinguished by specific clinical features, radiological findings, and underlying biological mechanisms related to the host response to wear particle accumulation [63,64]. The duration of each phase is highly variable and depends on patient factors, implant design, biomaterial characteristics, and the extent of particulate generation [7,47].

#### 3.4.1. Tolerant Phase

Biocompatibility is defined as the ability of these materials not to induce a significant adverse reaction in the body but instead activate a protective response that helps maintain the body's homeostasis [7]. When introduced into the body, wear particles are phagocytosed by macrophages and become embedded in the fibrous matrix of the forming pseudo-capsule. During this phase, no obvious granulomas are formed [7,65–67]. This phase typically lasts from months to several years post-implantation. Patients are usually asymptomatic or report mild, occasional pain, with preserved joint function. Standard radiographs often show no osteolysis, while advanced imaging (MRI or CT) may reveal minimal capsular thickening or periprosthetic effusion without bone loss or implant loosening. Here, the inflammatory response remains controlled and non-destructive [68].

As particles accumulate, macrophages become overwhelmed and undergo apoptosis, resulting in the engulfment of debris by other macrophages or its embedding in the extracellular matrix [67]. When this immune response is insufficient, granulomas form around the pseudo-capsule, amplifying inflammation and triggering the shift from the tolerant to the irritable phase [7].

#### 3.4.2. Irritable Phase

As wear particle accumulation exceeds the body's clearance capacity, chronic inflammation intensifies, leading to granuloma formation within the regenerating capsule [7]. This phase is characterized by an imbalance between the host's defense mechanisms (phagocytosis and fibrotic tissue formation) and the persistent influx of wear debris [7]. When

macrophages cannot engulf large particles (>10 μm), they fuse to form multinucleated FBGCs. These cells then attempt to degrade and isolate the debris but inadvertently prolong inflammation, exacerbating tissue damage [7,9,69–71]. Granulomas recruit additional macrophages, monocytes, lymphocytes, and mast cells, amplifying the inflammatory response. Excessive fibroblast activation results in the formation of a dense fibrous capsule around the particles, encapsulating them within a collagen-rich matrix [7,69]. While this process initially helps contain the debris, prolonged inflammation leads to tissue remodeling and extracellular matrix degradation, ultimately compromising implant stability [7,32,72]. The inflammatory microenvironment also promotes the release of cytokines (TNF-α, IL-1, IFN-γ), ROS, and growth factors, which further stimulate the innate immune response [7,32,47]. Radiologically, early periprosthetic osteolysis becomes evident as radiolucent lines adjacent to the implant, reflecting the interface between the fibrous pseudocapsule and bone undergoing resorption. CT and MRI provide detailed visualization of granuloma formation and the extent of bone loss [73,74]. Clinically, symptoms become more pronounced and persistent, with patients experiencing moderate, recurrent pain. The duration of this critical transition phase ranges from months to several years and represents a pivotal stage toward implant failure [7,75]. Furthermore, the dissemination of wear particles throughout the body can trigger a systemic immune response, known as particle disease [7,76,77].

#### 3.4.3. Intolerant Phase

As the immune response escalates beyond the host's ability to control it, the foreign body reaction becomes increasingly destructive. Granulomas, primarily composed of activated macrophages, fibroblasts, endothelial cells, lymphocytes, and inflammatory mediators, expand, triggering osteoclast activation and excessive bone resorption at the bone–implant interface [7,76]. Mast cells have been shown to amplify the inflammatory response by releasing histamine, IL-3, and IL-4, thereby exacerbating tissue degradation [7,66,70,71]. The infiltration of inflammatory joint fluid, rich in cytokines and wear particles, has been demonstrated to accelerate extracellular matrix breakdown and disrupt bone homeostasis [7]. The resulting imbalance is known to favor osteoclast-mediated bone resorption, leading to progressive weakening of the peri-implant bone tissue [7,47]. Within an acidic microenvironment, the excessive release of proteolytic enzymes, particularly cathepsin K, drives aggressive extracellular matrix degradation [9]. As osteolysis progresses, a synovial-like lining forms around the implant, further compromising structural integrity. The persistent immune activation and bone loss ultimately lead to implant loosening and failure [7,9]. This phase represents the most advanced and destructive stage, characterized by uncontrolled chronic inflammation and massive bone loss due to a profound imbalance favoring osteoclast-mediated resorption [7]. The duration varies from rapid progression over a few months to gradual evolution over one to two years, often necessitating revision surgery [7]. Clinically, patients present with severe, persistent pain, implant instability, marked limp, and significant functional impairment. Audible joint noises, clicks, or sensations of giving way may also occur [1]. Radiographically, extensive periprosthetic osteolysis appears as pronounced radiolucent lines along the entire implant interface. CT and MRI confirm the extent of bone damage, widespread periprosthetic membranes, and frequently detect implant migration or macroscopic instability [73,74].

#### 3.4.4. Clinical Progression and Illustrative Scenarios

Although specific case studies illustrating the clinical progression through the tolerant, irritable, and intolerant phases of FBR are limited, typical patient presentations can exemplify this evolution. During the tolerant phase, patients are often asymptomatic

or report only mild discomfort, with imaging showing minimal capsular changes and no bone loss [68]. As the response progresses to the irritable phase, patients experience moderate, recurrent pain, and radiological evidence of early periprosthetic osteolysis becomes apparent [73,74]. Finally, in the intolerant phase, severe pain, implant instability, and significant functional impairment dominate the clinical picture, frequently requiring revision surgery [73,74]. This clinical progression reflects the escalating imbalance between host defense mechanisms and wear particle burden, emphasizing the dynamic nature of FBR [7].

### *3.5. Inflammatory Response to Different Implant Materials*

#### 3.5.1. Polyethylene Wear Particles

Polyethylene (PE) is a material frequently utilized in joint implants, wherein a PE liner is affixed to a metallic acetabular shell and a metallic femoral head [60,78]. Wear particles are continuously generated over time due to joint movement, with volumetric wear being the primary factor influencing particle production. It has been demonstrated that larger femoral heads (for example, with a diameter of 36 mm) produce a greater number of particles than smaller ones (for example, with a diameter of 22 mm) [60,79]. Particles of PE, particularly those measuring between 0.1 and 1 μm, have been observed to trigger inflammatory responses, with those between 0.3 and 1 μm being the most potent in stimulating FBGCs. In contrast, particles smaller than 0.3 μm are generally eliminated via pinocytosis [7,60,80]. They can trigger the release of proinflammatory cytokines and promote bone resorption [7]. In vitro studies have investigated how cells respond to particles of different sizes and compositions. Smaller PE particles (0.24 μm) have been found to be highly effective in stimulating proinflammatory cytokine release and bone resorbing activity in murine peritoneal macrophages [46]. Ultra-high molecular weight polyethylene (UHMWPE) is the polymer most frequently used in joint implants, valued for its excellent performance when paired with metal or ceramic bearing surfaces. It exhibits exceptional biocompatibility and high resistance to corrosion. Because UHMWPE produces many wear particles, it has been modified into cross-linked polyethylene (XLPE), which releases significantly fewer particles [44,81]. This cross-linking involves irradiating UHMWPE, creating free radicals [82]. If these radicals stay trapped, they may react with oxygen over time, causing oxidative degradation, embrittlement, and eventual mechanical failure [82–84].

In order to overcome this problem, new XLPE products have been produced with the addition of Vitamin E, a powerful antioxidant, to neutralize these free radicals and prevent oxidation without compromising the material's mechanical properties [85,86]. Both UHMWPE and XLPE particles have the potential to trigger an inflammatory response by inducing the overexpression of TLR2 and TLR4, pathways previously described. In addition, there is a possibility that they may also activate the NLRP3 inflammasome [44,87,88]. These particles are recognized not only through TLRs but also via phagocytosis. Once internalized, they accumulate in phagosomes, where they are resistant to enzymatic degradation [60,89,90]. Both pathways ultimately activate NF-κB, triggering the release of proinflammatory cytokines and mediators that drive bone resorption [44,60,91–93]. Transcriptomic analyses of human macrophages reveal increased expression of inflammatory and bone resorption markers such as CCL2, CCL3, CCL4, CCL20, IL-8, IL-1β, IL-6, TNF-α, M-CSF, and MMPs [94].

#### 3.5.2. Polymethylmethacrylate Wear Particles

Polymethylmethacrylate (PMMA) particles, resulting from bone cement, promote osteoclastogenesis and osteolysis, primarily through TLR activation, leading to IL-1β and TNF-α secretion and monocyte recruitment via MCP-1 signaling [44,95–99].

The MyD88-dependent pathways are the main signaling mechanism for most TLRs except TLR3. MyD88 activation leads to NF-κB and AP-1 signaling, which stimulates the production of inflammatory cytokines like TNF-α, IL-1, and IL-12 [100]. Studies in patient samples and animal models confirm that TLRs mediate the immune response to implant debris. Experiments show that blocking MyD88 in macrophages lowers inflammation caused by PMMA particles, while mice lacking MyD88 exhibit a reduced inflammatory reaction [97]. PMMA also activates the NALP3 inflammasome, driving caspase-1-mediated IL-1β release and exacerbating inflammation [44,101]. Additionally, PMMA particles upregulate the vascular endothelial growth factor (VEGF), promoting angiogenesis, which has been linked to osteolysis progression. Murine studies show that VEGF inhibition reduces TNF-α production, inflammation, and osteoclast formation, highlighting its role in PMMA-induced bone resorption [44,102].

#### 3.5.3. Metallic Wear Debris

Metallic wear debris drives chronic periprosthetic inflammation. Mediated mainly by macrophages and FBGCs, this process triggers proinflammatory cytokine and growth factor release, stimulating osteoclasts and leading to osteolysis [44]. The exact molecular mechanisms remain a subject of considerable debate, with both experimental and clinical evidence showing substantial heterogeneity [44]. Metallic particles, especially cobalt (Co) and titanium (Ti), have been shown to elicit strong immune responses [44,60]. Several studies indicate that Co alloy debris can activate both TLR4 and the NLRP3 inflammasome, resulting in increased production of IL-1β and IL-18 [44,103,104]. Nevertheless, other investigations suggest that Co primarily activates the inflammasome pathway, with minimal TLR4 involvement [104]. This discrepancy likely reflects differences in particle size, surface chemistry, ion release kinetics, and experimental models (human vs. murine macrophages) [104]. While some studies using purified cobalt or nickel ions demonstrate TLR4 activation [105], others using cobalt alloy particles in vitro have reported that blocking TLR4 does not reduce the inflammatory response, pointing instead to a predominant role of NLRP3-dependent mechanisms [104]. In addition to these innate immune pathways, Co ions can induce hypoxia-like responses by up-regulating HIF-1α, VEGF, TNF-α, and ROS production, further exacerbating osteolysis [104]. Titanium (Ti) particles similarly activate IL-1β, IL-6, and TNF-α via NLRP3 inflammasome, a process dependent on TNF-α priming [44]. Furthermore, metal ions can act as haptens, triggering a Type IV hypersensitivity reaction with recruitment of T-lymphocytes, contributing to adverse reactions to metal debris (ARMD) and perivascular lymphocytic infiltrates [7,32,44]. Taken together, these findings highlight that the immunological effects of metallic debris, particularly Co, remain an area of controversy [44]. While TLR4 activation by Co may occur under specific physicochemical and biological conditions, it is not universally required for Co-induced inflammation [104]. Moreover, recent studies have identified heterogeneous infiltration of adaptive immune cells, including T and B lymphocytes, within periprosthetic tissues, suggesting a more complex interplay between innate and adaptive immunity in AL [106]. Clarifying these mechanisms through standardized experimental approaches and well-designed clinical studies will be essential to fully understand the immunological impact of metal wear debris and to develop targeted preventive or therapeutic strategies.

#### 3.5.4. Ceramic Wear Debris

Over the past decades, ceramic-on-ceramic (CoC) implants have become the most commonly used bearing surfaces. CoC implants generate minimal wear particles, have a reduced risk of osteolysis, and offer strong durability over time. These properties make it a favorable option for young and active patients [107]. Compared to polymeric particles, ceramic materials like alumina ($Al_2O_3$) and zirconia ($ZrO_2$) produce very little wear debris, show minimal immune system toxicity, and provoke only a mild release of TNF-α and IL-1β [44,60,108]. Ceramic debris causes minimal macrophage death and has a limited effect on RANKL, OPG, and TNF-α expression, which, of course, increases in a concentration-dependent manner. [44,109]. However, zirconia has been found to activate TLR3, TLR7, and TLR10, though its influence on cytokine release is minimal [44,110]. Overall, ceramic-on-ceramic prostheses have been demonstrated to exhibit a reduced propensity for debris formation, osteolysis, loosening, and prosthetic failure, provided that they are implanted in a satisfactory manner. However, cases of squeaking and ceramic fracture have been reported [111,112].

## 4. Biomarkers

Implant loosening is a multifactorial process influenced by biomechanical forces and the balance between osteoblast and osteoclast activity [113]. This balance can be assessed through objective biomarkers, including serum and urinary markers, which offer a minimally invasive and easily accessible means of monitoring biological processes [114]. Several studies have explored the potential of these biomarkers in distinguishing between aseptically loosened and stable implants.

Among the most studied biomarkers are those related to inflammation, as this process plays a central role in AL. Elevated levels of TNF-α, IL-1β, IL-6, and IL-8 have been found in patients with AL, indicating an active immune response contributing to bone resorption [115–120]. A study by Wu et al. (2009) demonstrated that elevated TNF-α expression was associated with higher levels of CD14+CD16+ monocytes in the blood, suggesting that these monocytes could also serve as potential biomarkers for AL [117]. Several chemokines, such as MCP-1 and CCL18, are also increased, supporting their role in recruiting immune cells to the loosening site [121,122]. Bone metabolism markers play a crucial role in assessing AL, as the condition disrupts the balance between bone formation and resorption. In particular, RANKL levels are elevated in patients with AL, contributing to enhanced osteoclastogenesis and subsequent bone resorption. This increase in RANKL promotes osteoclast activation, leading to excessive bone resorption and ultimately, the loosening of the implant [118,121]. Specifically, markers of bone resorption, such as CTX, NTX, TRAP5b, and ICTP (C-telopeptide of type I collagen), are elevated, indicating heightened osteoclastic activity [118,123–127]. In contrast, markers of bone formation, including osteocalcin and PiCP, show significant alterations, with PiCP levels notably reduced, suggesting a disruption in the bone formation process [123,127]. These changes reflect the abnormal bone remodeling characteristic of AL and underscore the potential of these markers in assessing the condition.

In addition to these markers, extracellular matrix degradation also plays a key role in AL. Hyaluronic acid, an important component of the joint matrix, was found to be upregulated in AL patients, suggesting damage to the joint environment [119]. Similarly, CHIT1, a marker involved in the degradation of bone and cartilage, is elevated both in blood and synovial fluid, further pointing to ongoing matrix breakdown [122]. Cell adhesion molecules, such as CD18, CD11b, and CD11c, are also found at increased levels, which may reflect enhanced cellular activation and migration to areas of bone resorption [128]. Emerging research into microRNAs has revealed their potential as biomarkers for AL [129]. Several

miRNAs, including miR-21, miR-92a, miR-106b, miR-130, miR-135, and miR-155, are up-regulated in AL patients, while miR-29 appears reduced, suggesting their involvement in regulating both inflammatory responses and bone remodeling [130]. Several studies have explored genetic factors that may predispose individuals to AL, focusing on SNPs in key inflammatory and bone remodeling genes. López-Anglada et al. (2021) demonstrated that polymorphisms in exon 2 of *NOS2* and the +3954C/T polymorphism (exon 5, rs11436434) of *IL-1β* are associated with an increased frequency of AL [120]. Specifically, the AA genotype of *NOS2* and the TT genotype of *IL-1β* appear to be linked to a higher risk of developing the condition [120]. Additionally, Malik et al. (2007) assessed SNPs in *MMP1*, revealing an association between these genetic variations and an elevated risk of AL [131]. These findings suggest that genetic predisposition plays a significant role in the development of AL, highlighting the potential for using genetic markers to better identify individuals at higher risk [131].

Monitoring systemic biomarkers can be further enhanced by assessing metal ion concentrations, particularly in patients with metal-on-metal implants. Whole-blood Co and chromium (Cr) levels exceeding 5 µg/L are generally considered abnormal and may indicate implant wear, ARMD, or imminent mechanical failure. Such elevations can precede clinical or radiological signs and warrant further investigation [132]. In addition, simple inflammatory markers like C-reactive protein (CRP) can assist in clinical evaluation. Although CRP is non-specific and cannot differentiate AL from infection, persistently elevated CRP levels in the absence of infection may indicate ongoing periprosthetic inflammation or tissue damage [133,134]. Combining metal ion monitoring with inflammatory markers can therefore improve early detection and management of prosthetic complications.

Table 1 summarizes key biomarkers and genetic factors involved in AL, indicating their typical levels in patients, their biological roles, and the sample type for their detection.

**Table 1.** Biomarkers in Aseptic Loosening (AL).

| Category | Biomarkers | Levels in AL Patients | Role | Sample | References |
|---|---|---|---|---|---|
| **Inflammatory Biomarkers** | TNF-α, IL-1β, IL-6, IL-8, CD14+CD16+ monocytes, MCP-1, CCL18 | High | Indicative of an active inflammatory response that promotes the recruitment and activation of immune cells, contributing to bone destruction. | Blood, synovial fluid | [115–122,133,134] |
| | C-reactive protein (CRP) | High | Can assist in clinical evaluation. Persistently elevated in the absence of infection may indicate ongoing periprosthetic inflammation or tissue damage. | | |
| **Bone Metabolism** | RANKL, CTX, NTX, TRAP5b, ICTP | High | Represent the altered balance between bone formation and resorption; increased resorption and reduced bone formation, typical of AL. | Blood, urine | [118,121,123–127] |
| | Osteocalcin, PiCP | Low | | | |
| **Matrix Degradation** | Hyaluronic acid, CHIT1, CD18, CD11b, CD11c | High | Signals of extracellular matrix degradation and cellular activation, indicative of tissue damage and local immune response. | Blood, synovial fluid | [119,122,128] |
| **MicroRNA** | miR-21, miR-92a, miR-106b, miR-130, miR-135, miR-155 | High | Involved in the regulation of inflammatory processes and bone remodeling, contributing to the altered balance between osteoresorption and formation. | Blood | [129,130] |
| | miR-29 | Low | | | |
| **Genetic Factors** | SNPs in *NOS2* (AA genotype), *IL-1β* (TT genotype), and *MMP1* | Associated with increased risk | Genetically predisposed to the establishment of an accentuated inflammatory response and aberrant bone remodeling, favoring the development of AL | Blood | [120,131] |
| **Systemic Biomarkers** | Whole-blood Cobalt (Co) and Chromium (Cr) levels | >5 µg/L | May indicate implant wear, ARMD, or imminent mechanical failure. Elevations can precede clinical or radiological signs and warrant further investigation. | Blood | [132] |

*Diagnostic Accuracy and Critical Evaluation of Biomarkers in Aseptic Loosening*

Among the biomarkers previously discussed, some have been specifically investigated for their diagnostic value in identifying AL or distinguishing it from periprosthetic joint infection (PJI). For example, bone metabolism markers such as ICTP demonstrate a high sensitivity of 91% but moderate specificity (69%), indicating that while ICTP is effective at detecting AL, it may lead to false positives [127]. TRAP 5b stands out with perfect sensitivity (100%), making it excellent for ruling out AL when negative; however, its low specificity (31%) and likely low positive predictive value limit its use as a definitive diagnostic tool due to a high false-positive rate [127]. Osteocalcin shows moderate sensitivity and specificity (69% and 65%, respectively), with no clear advantage in diagnostic reliability [127]. NTX offers a better balance, with 82% sensitivity and 87% specificity, suggesting stronger potential for detecting osteoclastic activity associated with AL and a more reliable predictive performance [127]. Similarly, cobalt and chromium ions from metal implants show moderate sensitivity (63%) but relatively high specificity (86%), making them useful especially in metal-on-metal implant monitoring, though insufficient as standalone diagnostic markers [135].

In the context of differentiating AL from PJI, inflammatory cytokines provide more targeted diagnostic information. IL-6 demonstrates solid diagnostic performance with 80% sensitivity, 87.7% specificity, and a positive predictive value (PPV) of 69,6% and a high negative predictive value (NPV) of 92.6%, making it particularly useful to rule out infection when levels are low [136]. IL-1β shows even higher sensitivity (94.6%) and specificity (86.2%), reinforcing its role in differentiating PJI from AL [137]. IL-8 stands out with excellent specificity (100%) and good sensitivity (86.1%), indicating that elevated IL-8 strongly supports PJI presence, with minimal risk of false positives [137]. Conversely, TNF-α has low sensitivity (35%) despite moderate specificity (86%), with a modest NPV of 79% and PPV of 46.7%, which considerably limits its usefulness as a diagnostic marker [136]. CRP, widely used in clinical practice, has good sensitivity (80%) but limited specificity (64%), a high NPV of 92.3% NPV but a low PPV of 37.2%, implying that while CRP effectively signals inflammation, it cannot reliably differentiate between AL and PJI on its own [136].

These data highlight that no single biomarker achieves the combination of high sensitivity, specificity, and predictive values necessary for a standalone diagnostic test. Many markers excel in either sensitivity or specificity but fail to provide consistent reliability across all parameters, leading to possible false positives or negatives. Therefore, integrating multiple biomarkers alongside clinical assessment and imaging remains the most effective strategy for accurate diagnosis. It is also important to note that for many other promising biomarkers, comprehensive data on diagnostic performance, including sensitivity, specificity, PPV, and NPV, are still lacking. Most current research focuses primarily on whether these markers are elevated in affected tissues or serum, without thorough validation of their diagnostic utility.

In conclusion, biomarker analysis offers valuable insights into AL pathophysiology and its differentiation from PJI. However, current evidence supports their use as part of a multimodal diagnostic approach rather than standalone tests. Ongoing research is essential to refine and validate effective biomarker panels that could improve early detection, guide clinical decision-making, and ultimately enhance patient outcomes. Table 2 summarizes the sensitivity, specificity, and predictive values of the key biomarkers discussed.

**Table 2.** Sensitivity, specificity, and predictive values of key biomarkers for aseptic loosening (AL) and differentiation from periprosthetic joint infection (PJI).

| Biomarker | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Reference |
|---|---|---|---|---|---|
| **ICTP** | 91 | 69 | NA | NA | [127] |
| **TRAP 5b** | 100 | 31 | NA | NA | [127] |
| **Osteocalcin** | 69 | 65 | NA | NA | [127] |
| **NTX** | 82 | 87 | NA | NA | [127] |
| **Cobalt (Co) and Chromium (Cr) ions** | 63 | 86 | NA | NA | [135] |
| **IL-6** | 80 | 87.7 | 69.6 | 92.6 | [136] |
| **IL-1β** | 94.6 | 86.2 | NA | NA | [137] |
| **IL-8** | 86.1 | 100 | NA | NA | [137] |
| **TNF-α** | 35 | 86 | 46.7 | 79 | [136] |
| **CRP** | 80 | 64 | 37.2 | 92.3 | [136] |

## 5. Prevention and Treatment of Aseptic Loosening

At present, the only effective treatment for AL is implant revision arthroplasty. AL accounts for approximately 40% of all revision procedures, both for hip and knee arthroplasties [138]. Consequently, efforts must focus on prevention, which involves reducing patient-related risk factors and selecting an appropriate prosthetic implant. Additionally, ongoing research is being conducted to develop therapeutic protocols that prevent AL. In the context of prevention, we can adopt preoperative, intraoperative, and postoperative measures. About patient-related risk factors, a Body Mass Index (BMI) greater than 35 kg/m$^2$ has been demonstrated to be associated with a twofold increase in the incidence of aseptic loosening. Conversely, an excessively low BMI has been demonstrated to heighten the risk of implant component migration and delays in osseointegration. Consequently, preoperative planning should encompass the attainment of optimal body weight, in conjunction with appropriate nutritional therapy and physical activity [139]. Osteoporosis has been shown to impair implant osseointegration. This phenomenon can be attributed to the presence of estrogen deficiency, which has been shown to result in diminished osteoblast longevity, increased osteoclast activity, and impaired differentiation of mesenchymal stromal cells into osteoblasts. Therefore, osteoporosis diagnosis and careful management are advised to facilitate osseointegration [140]. Smoking raises the risk of AL in both cemented and cementless joint replacements [141]. This is mainly due to nicotine's narrowing of blood vessels and the reduced oxygen supply caused by higher levels of carboxyhemoglobin. These factors reduce blood flow to the local tissue, causing hypoxia that likely hinders osseointegration [142]. Kapadia et al. found no significant difference in AL rates between former smokers (those who quit at least 30 days before surgery) and current smokers over an average follow-up of four years. Consequently, smoking cessation 30 days before surgery does not appear to be associated with reduced implant loosening rates. Further studies are required to determine the optimal time for patients to cease smoking before and after surgery to achieve the best possible results [143].

The role of cardiovascular disease, cancer, and psychotic disorders regarding the risk of AL is still controversial. On the other hand, in the case of other comorbidities, including neurodegenerative diseases, diabetes mellitus, and pulmonary diseases, the survival rate of hip titanium implants seems to remain unaffected [144]. To summarize, preoperative optimization should include BMI adjustment, osteoporosis treatment, smoking cessation, and control of cardiovascular and psychiatric conditions [145].

To determine the optimal course of action before hip replacement surgery, selecting the implant is crucial to minimize the risk of AL. Material stiffness, measured by the Young's modulus, needs to be low enough (but not excessively) to avoid bone stress shielding. This occurs when a stiffness mismatch between the implant and bone causes improper load transfer, leading to increased bone resorption and impaired remodeling, which can ultimately result in AL [146]. Stress shielding increases bone resorption and inhibits remodeling, ultimately leading to AL. An ideal implant should have a Young's modulus similar to bone (10–30 GPa). For instance, Ti6Al4V titanium alloy has a modulus of 110 GPa, compared to stainless steel's 180 GPa. Additionally, the implant's structure and elasticity influence its long-term survival. Elasticity, given by a low Young's modulus, results in an increased micromotion, which can lead to fibrous tissue formation at the bone–implant interface instead of bone ingrowth [145]. Extensive research has focused on treating titanium surfaces using methods such as plasma spraying, hydroxyapatite coating, acid etching, sandblasting, alkali heat treatment, ion implantation, and nanotechnology. The most commonly used coatings are hydroxyapatite and porous coatings. Observations have revealed better outcomes and reduced incidence of AL in hydroxyapatite-coated implants [147,148]. Future developments may involve coatings with silicatitanate or growth factors like bone morphogenetic protein (BMP). Porous surfaces on uncemented titanium implants help stimulate and secure bone growth. Specific pore shapes and sizes promote optimal osseointegration. It has been established that a porosity level exceeding 40% is conducive to optimal bone growth [149]. In conclusion, regarding the choice of materials, the goal is to use advanced alloys that prioritize resistance to corrosion and wear in order to ensure the best longevity of the prosthetic construct in total hip replacement (THR). In THR, the most commonly used metallic biomaterials are Co-Cr alloys and Titanium Alloys (Ti), particularly Ti-6Al-4V. The main advantage of Co-Cr alloys is their superior wear resistance compared to Titanium, making them particularly suited for withstanding high stresses. On the other hand, the biocompatibility of this material appears to be lower than that of Titanium [150]. The main advantage of using titanium-based alloys is their light weight, increased mechanical strength, and high biocompatibility, such as promoting osteoblast adhesion, thereby stimulating bone production around the implant. Regarding osseointegration, Tantalium appears advantageous as it offers better corrosion resistance compared to the other two metals. However, its use is limited due to its very high cost [151]. Advanced metallic materials are Ti-25Nb-2Mo-4Sn, Ti-15Zr-4Nb-4Ta, and Ti-35Nb-7Zr-5Ta that improve longevity of the implant, preventing wear on the metal surfaces underneath, and are very good at reducing stress on the surrounding bone [152].

A further pivotal element in selecting the implant to prevent AL is its size, which is essential for ensuring a proper press fit and stability. Isaacson et al. observed that micromovements of up to 30 µm are beneficial, but those exceeding 150 µm compromise osseointegration. Furthermore, it is imperative to ensure that the acetabular cup is properly oriented; it should not be excessively horizontal (45°). It has been established that femoral head sizes greater than 32 mm are associated with an elevated rate of revision surgery due to AL, despite a concomitantly lower incidence of dislocation [153].

The selection of surgical approach may also impact the risk of AL, although this remains uncertain. McCormick et al. found no statistically significant difference in revision rate between patients treated with a posterolateral approach or an anterior approach (either direct anterior or anterior-based muscle sparing approach) [154]. Conversely, data from the Swedish Hip Arthroplasty Register show higher AL revision rates with the anterolateral approach, likely due to component malpositioning. Surgeon experience may influence this risk, making optimal joint exposure crucial when using the anterior approach. Moreover,

it has been demonstrated that excessive drilling or rasping can lead to mechanical and thermal bone damage, thereby impairing osseointegration [155].

One promising approach to reduce arthroplasty failures from AL is using anti-inflammatory drug-releasing devices postoperatively, aiming to improve the 10-year revision rate of 10%, as reported by the NICE guideline [138]. Anti-inflammatory agents reduce periprosthetic inflammation that leads to bone loss and subsequent AL. Among the most extensively studied is dexamethasone (DEX), a molecule rendered water-soluble via phosphate group binding. DEX release has been shown not to affect osteoblast and fibroblast proliferation while retaining anti-inflammatory activity. These drug-eluting systems appear promising in reducing prosthetic revision rates. In uncemented prostheses, DEX coatings are applied to the porous surface of the implant to prevent exposure to friction forces [138]. DEX has recently been used mostly for opioid-sparing analgesic protocols, in combination with other drugs. The RECIPE trial compared different non-opioid analgesic combinations after total hip arthroplasty in over 1000 patients. The three-drug regimen (paracetamol, ibuprofen, and dexamethasone) led to the lowest morphine consumption and the most favorable safety profile, especially in reducing nausea, vomiting, and dizziness. Pain scores at rest were similar to those of other drug combinations, but during mobilization, the three-drug group reported slightly less pain. Overall, adding dexamethasone to paracetamol and ibuprofen appears beneficial in multimodal pain management for hip replacement [156]. On the other hand, new studies are needed to research the relationship between DEX and the possible risk of AL development. Studies on the effects of NSAIDs on osteoblast activity and osseointegration show conflicting results, particularly when comparing selective COX-2 inhibitors with non-selective NSAIDs. In vitro, both non-selective (e.g., indomethacin) and selective COX-2 inhibitors (e.g., celecoxib) reduce prostaglandin E2 (PGE2) production in osteoblasts attached to rough titanium surfaces, potentially impairing proliferation and differentiation processes associated with osseointegration [157]. Some findings, such as those from celecoxib-treated cultures, indicate a dose-dependent inhibitory effect on osteoblast growth. Animal studies suggest COX-2 plays an important physiological role in new bone formation and implant integration, as COX-2 knockout mice show markedly reduced bone-to-implant contact. However, the functional impact of COX-2 inhibition remains inconsistent across experimental models: certain studies report that non-selective NSAIDs like diclofenac delay peri-implant healing, while COX-2 inhibitors such as meloxicam or parecoxib show no detrimental effects; long-term use of either drug type has also been reported to cause no significant impairment in bone growth or osseointegration [158]. Overall, current evidence suggests that COX-2 activity supports osseointegration, non-selective NSAIDs are more frequently associated with negative effects, and the influence of selective COX-2 inhibitors may depend on dosage, treatment duration, and experimental conditions [159].

Another promising pharmacological class includes bisphosphonates. Zoledronic acid has been demonstrated to reduce cortical osteopenia in the calcar region of the proximal femur, thus proving efficacious in the management of stress-shielding-induced osteopenia. The administration of bisphosphonate treatment has been demonstrated to mitigate the effects of stress shielding, thereby reducing the risk of wear-related AL by enhancing periprosthetic bone retention. It is conceivable that these pharmaceuticals could also play a role in the treatment of patients who are not candidates for revision surgery due to elevated surgical and anesthesiologic risks [160].

Finally, evidence-based strategies for reducing AL can be categorized into preoperative, intraoperative, and postoperative measures.

Preoperative: act on modifiable factors such as BMI and osteoporotic bone; selection of porous coatings such as tantalum or hydroxyapatite, pore size around 600 μm, porosity >70%, and the use of the right size of femoral stems.

Intraoperative: Minimize excessive drilling or rasping, ensure stable fixation, adequate bone coverage, and proper containment for long-term success.

Postoperative: Pharmacological management with risedronate or zoledronic acid to modulate bone metabolism; avoidance of NSAIDs.

## 6. Conclusions

In conclusion, biomarkers related to inflammation, bone metabolism, extracellular matrix degradation, microRNAs, and genetic factors show promise in improving the diagnosis and monitoring of AL. While these markers provide valuable insights into the mechanisms underlying AL, there are still inconsistent results across studies regarding the identification of the most reliable indicators for differentiating between stable and loosened implants, despite the broad range of biomarkers analyzed in both total hip and knee arthroplasties. In order to validate these biomarkers and to better understand their role in the early detection of AL, further larger, well-designed studies are required. These studies should also attempt to identify patterns that can be used to prevent and manage patients affected by AL without the need for revision surgery.

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## Abbreviations

| | |
|---|---|
| AL | aseptic loosening; |
| FXII | factor XII |
| TF | TF |
| IL | interleukin |
| MCP-1/CCL2 | monocyte chemotactic protein-1/chemokine CC motif ligand 2 |
| MIP-1 | macrophage inflammatory protein-1 |
| PMN | polymorphonuclear leukocyte |
| FBR | foreign body reaction |
| MSC | mesenchymal stem cell |
| PPOL | periprosthetic osteolysis |
| FBGC | foreign body giant cell |
| PRR | pattern recognition receptor |
| TNF | tumor necrosis factor |
| PGE | prostaglandin E |
| RANKL | receptor activator of nuclear factor kappa B ligand |
| MIP-1α | macrophage inflammatory protein-1α |
| TLR | Toll-like receptors |
| OPG | osteoprotegerin |

| | |
|---|---|
| NF-κB | nuclear factor kappa-light-chain-enhancer of activated B cells |
| MAPK | mitogen-activated protein kinase |
| PDGF | platelet-derived growth factor |
| FGF | fibroblast growth factor |
| TGF | transforming growth factor |
| EGF | epidermal growth factor |
| ROS | reactive oxygen species |
| PE | polyethylene |
| UHMWPE | ultra-high molecular weight polyethylene |
| XLPE | cross-linked polyethylene |
| PMMA | polymethylmethacrylate |
| ARMD | adverse reactions to metal debris |

## References


1. Varacallo, M.A.; Luo, T.D.; Johanson, N.A. Total Hip Arthroplasty Techniques. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. Available online: http://www.ncbi.nlm.nih.gov/books/NBK507864/ (accessed on 9 August 2025).
2. Li, C.; Schmid, S.; Mason, J. Effects of pre-cooling and pre-heating procedures on cement polymerization and thermal osteonecrosis in cemented hip replacements. *Med. Eng. Phys.* **2003**, *25*, 559–564. [CrossRef]
3. Nugent, M.; Young, S.W.; Frampton, C.M.; Hooper, G.J. The lifetime risk of revision following total hip arthroplasty. *Bone Jt. J.* **2021**, *103-B*, 479–485. [CrossRef]
4. Sadoghi, P.; Koutp, A.; Prieto, D.P.; Clauss, M.; Kayaalp, M.E.; Hirschmann, M.T. The projected economic burden and complications of revision hip and knee arthroplasties: Insights from national registry studies. *Knee Surg. Sports Traumatol. Arthrosc.* 2025; *early view*. [CrossRef]
5. van Otten, T.J.; van Loon, C.J. Early aseptic loosening of the tibial component at the cement-implant interface in total knee arthroplasty: A narrative overview of potentially associated factors. *Acta Orthop. Belg.* **2022**, *88*, 103–111. [CrossRef]
6. Yao, Z.; Lin, T.-H.; Pajarinen, J.; Sato, T.; Goodman, S. Chapter 12—Host Response to Orthopedic Implants (Metals and Plas-tics). In *Host Response to Biomaterials*; Badylak, S.F., Ed.; Academic Press: Oxford, UK, 2015; pp. 315–373. [CrossRef]
7. Gibon, E.; Takakubo, Y.; Zwingenberger, S.; Gallo, J.; Takagi, M.; Goodman, S.B. Friend or foe? Inflammation and the foreign body response to orthopedic biomaterials. *J. Biomed. Mater. Res. Part A* **2024**, *112*, 1172–1187. [CrossRef]
8. Cong, Y.; Wang, Y.; Yuan, T.; Zhang, Z.; Ge, J.; Meng, Q.; Li, Z.; Sun, S. Macrophages in aseptic loosening: Characteristics, functions, and mechanisms. *Front. Immunol.* **2023**, *14*, 1122057. [CrossRef] [PubMed]
9. Anderson, J.M.; Rodriguez, A.; Chang, D.T. Foreign body reaction to biomaterials. *Semin. Immunol.* **2008**, *20*, 86–100. [CrossRef]
10. Wilson, C.J.; Clegg, R.E.; Leavesley, D.I.; Pearcy, M.J. Mediation of biomaterial–cell interactions by adsorbed proteins: A review. *Tissue Eng.* **2005**, *11*, 1. [CrossRef]
11. Andersson, J.; Ekdahl, K.N.; Larsson, R.; Nilsson, U.R.; Nilsson, B. C3 Adsorbed to a polymer surface can form an initiating alternative pathway convertase. *J. Immunol.* **2002**, *168*, 5786–5791. [CrossRef] [PubMed]
12. Sperling, C.; Fischer, M.; Maitz, M.F.; Werner, C. Blood coagulation on biomaterials requires the combination of distinct activation processes. *Biomaterials* **2009**, *30*, 4447–4456. [CrossRef] [PubMed]
13. Fischer, M.; Sperling, C.; Werner, C. Synergistic effect of hydrophobic and anionic surface groups triggers blood coagulation in vitro. *J. Mater. Sci. Mater. Med.* **2010**, *21*, 931–937. [CrossRef]
14. Hu, W.J.; Eaton, J.W.; Ugarova, T.P.; Tang, L. Molecular basis of biomaterial-mediated foreign body reactions. *Blood* **2001**, *98*, 1231–1238. [CrossRef] [PubMed]
15. Fischer, M.; Sperling, C.; Tengvall, P.; Werner, C. The ability of surface characteristics of materials to trigger leukocyte tissue factor expression. *Biomaterials* **2010**, *31*, 2498–2507. [CrossRef]
16. Henson, P.M.; Johnston, R.B. Tissue injury in inflammation. Oxidants, proteinases, and cationic proteins. *J. Clin. Investig.* **1987**, *79*, 669–674. [CrossRef]
17. Lehrer, R.I.; Ganz, T.; Selsted, M.E.; Babior, B.M.; Curnutte, J.T. Neutrophils and host defense. *Ann. Intern. Med.* **1988**, *109*, 127–142. [CrossRef] [PubMed]
18. Malech, H.L.; Gallin, J.I. Current concepts: Immunology. Neutrophils in human diseases. *N. Engl. J. Med.* **1987**, *317*, 687–694. [CrossRef]
19. Hynes, R.O. Integrins: Bidirectional, allosteric signaling machines. *Cell* **2002**, *110*, 673–687. [CrossRef]
20. Lowell, C.A.; Berton, G. Integrin signal transduction in myeloid leukocytes. *J. Leukoc. Biol.* **1999**, *65*, 313–320. [CrossRef]
21. McNally, A.K.; Anderson, J.M. Complement C3 participation in monocyte adhesion to different surfaces. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 10119–10123. [CrossRef]

22. Tang, L. Mechanisms of fibrinogen domains: Biomaterial interactions. *J. Biomater. Sci. Polym. Ed.* **1998**, *9*, 1257–1266. [CrossRef]
23. Zdolsek, J.; Eaton, J.W.; Tang, L. Histamine release and fibrinogen adsorption mediate acute inflammatory responses to biomaterial implants in humans. *J. Transl. Med.* **2007**, *5*, 31. [CrossRef] [PubMed]
24. Scapini, P.; Lapinet-Vera, J.A.; Gasperini, S.; Calzetti, F.; Bazzoni, F.; Cassatella, M.A. The neutrophil as a cellular source of chemokines. *Immunol. Rev.* **2000**, *177*, 195–203. [CrossRef]
25. Hidaka, Y.; Ito, M.; Mori, K.; Yagasaki, H.; Kafrawy, A.H. Histopathological and immunohistochemical studies of membranes of deacetylated chitin derivatives implanted over rat calvaria. *J. Biomed. Mater. Res.* **1999**, *46*, 418–423. [CrossRef]
26. VandeVord, P.J.; Matthew, H.W.T.; DeSilva, S.P.; Mayton, L.; Wu, B.; Wooley, P.H. Evaluation of the biocompatibility of a chitosan scaffold in mice. *J. Biomed. Mater. Res.* **2002**, *59*, 585–590. [CrossRef]
27. Park, C.J.; Gabrielson, N.P.; Pack, D.W.; Jamison, R.D.; Johnson, A.J.W. The effect of chitosan on the migration of neutrophil-like HL60 cells, mediated by IL-8. *Biomaterials* **2009**, *30*, 436–444. [CrossRef]
28. Kobayashi, S.D.; Voyich, J.M.; Burlak, C.; DeLeo, F.R. Neutrophils in the innate immune response. *Arch. Immunol. Ther. Exp.* **2005**, *53*, 505–517.
29. Yamashiro, S.; Kamohara, H.; Wang, J.-M.; Yang, D.; Gong, W.-H.; Yoshimura, T. Phenotypic and functional change of cytokine-activated neutrophils: Inflammatory neutrophils are heterogeneous and enhance adaptive immune responses. *J. Leukoc. Biol.* **2001**, *69*, 698–704. [CrossRef] [PubMed]
30. Gilroy, D.W.; Lawrence, T.; Perretti, M.; Rossi, A.G. Inflammatory resolution: New opportunities for drug discovery. *Nat. Rev. Drug Discov.* **2004**, *3*, 401–416. [CrossRef] [PubMed]
31. Schlundt, C.; El Khassawna, T.; Serra, A.; Dienelt, A.; Wendler, S.; Schell, H.; van Rooijen, N.; Radbruch, A.; Lucius, R.; Hartmann, S.; et al. Macrophages in bone fracture healing: Their essential role in endochondral ossification. *Bone* **2018**, *106*, 78–89. [CrossRef]
32. Goodman, S.B.; Gibon, E.; Gallo, J.; Takagi, M. Macrophage Polarization and the Osteoimmunology of Periprosthetic Osteolysis. *Curr. Osteoporos. Rep.* **2022**, *20*, 43–52. [CrossRef]
33. Murray, P.J. Macrophage Polarization. *Annu. Rev. Physiol.* **2017**, *79*, 541–566. [CrossRef]
34. Kon, T.; Cho, T.-J.; Aizawa, T.; Yamazaki, M.; Nooh, N.; Graves, D.; Gerstenfeld, L.C.; Einhorn, T.A. Expression of osteoprotegerin, receptor activator of NF-kappaB Ligand (osteoprotegerin ligand) and related proinflammatory cytokines during fracture healing. *J. Bone Miner. Res.* **2001**, *16*, 1004–1014. [CrossRef]
35. Xing, Z.; Lu, C.; Hu, D.; Yu, Y.; Wang, X.; Colnot, C.; Nakamura, M.; Wu, Y.; Miclau, T.; Marcucio, R.S. Multiple roles for CCR2 during fracture healing. *Dis. Model. Mech.* **2010**, *3*, 451–458. [CrossRef]
36. Gerstenfeld, L.C.; Cullinane, D.M.; Barnes, G.L.; Graves, D.T.; Einhorn, T.A. Fracture healing as a post-natal developmental process: Molecular, spatial, and temporal aspects of its regulation. *J. Cell. Biochem.* **2003**, *88*, 873–884. [CrossRef]
37. Kolar, P.; Schmidt-Bleek, K.; Schell, H.; Gaber, T.; Toben, D.; Schmidmaier, G.; Perka, C.; Buttgereit, F.; Duda, G.N. The early fracture hematoma and its potential role in fracture healing. *Tissue Eng. Part B Rev.* **2010**, *16*, 427–434. [CrossRef] [PubMed]
38. Lee, E.-J.; Jain, M.; Alimperti, S. Bone Microvasculature: Stimulus for Tissue Function and Regeneration. *Tissue Eng. Part B Rev.* **2021**, *27*, 313–329. [CrossRef] [PubMed]
39. Loi, F.; Córdova, L.A.; Pajarinen, J.; Lin, T.; Yao, Z.; Goodman, S.B. Inflammation, fracture and bone repair. *Bone* **2016**, *86*, 119–130. [CrossRef]
40. Kotas, M.E.; Medzhitov, R. Homeostasis, Inflammation, and Disease Susceptibility. *Cell* **2015**, *160*, 816–827. [CrossRef]
41. Kasikara, C.; Doran, A.C.; Cai, B.; Tabas, I. The role of non-resolving inflammation in atherosclerosis. *J. Clin. Investig.* **2018**, *128*, 2713–2723. [CrossRef]
42. Nathan, C.; Ding, A. Nonresolving Inflammation. *Cell* **2010**, *140*, 871–882. [CrossRef] [PubMed]
43. Pezone, A.; Olivieri, F.; Napoli, M.V.; Procopio, A.; Avvedimento, E.V.; Gabrielli, A. Inflammation and DNA damage: Cause, effect or both. *Nat. Rev. Rheumatol.* **2023**, *19*, 200–211. [CrossRef]
44. Couto, M.; Vasconcelos, D.P.; Sousa, D.M.; Sousa, B.; Conceição, F.; Neto, E.; Lamghari, M.; Alves, C.J. The Mechanisms Underlying the Biological Response to Wear Debris in Periprosthetic Inflammation. *Front. Mater.* **2020**, *7*, 274. [CrossRef]
45. Green, T.R.; Fisher, J.; Stone, M.; Wroblewski, B.M.; Ingham, E. Polyethylene particles of a 'critical size' are necessary for the induction of cytokines by macrophages in vitro. *Biomaterials* **1998**, *19*, 2297–2302. [CrossRef]
46. Green, T.R.; Fisher, J.; Matthews, J.B.; Stone, M.H.; Ingham, E. Effect of size and dose on bone resorption activity of macrophages byin vitro clinically relevant ultra high molecular weight polyethylene particles. *J. Biomed. Mater. Res.* **2000**, *53*, 490–497. [CrossRef]
47. Goodman, S.B.; Gallo, J. Periprosthetic Osteolysis: Mechanisms, Prevention and Treatment. *J. Clin. Med.* **2019**, *8*, 2091. [CrossRef] [PubMed]
48. Wang, A.; Essner, A.; Stark, C.; Dumbleton, J. Comparison of the size and morphology of UHMWPE wear debris produced by a hip joint simulator under serum and water lubricated conditions. *Biomaterials* **1996**, *17*, 865–871. [CrossRef]

49. Hallab, N.J.; McAllister, K.; Brady, M.; Jarman-Smith, M. Macrophage reactivity to different polymers demonstrates particle size- and material-specific reactivity: PEEK-OPTIMA®particles versus UHMWPE particles in the submicron, micron, and 10 micron size ranges. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2012**, *100*, 480–492. [CrossRef]
50. Ingham, E.; Fisher, J. The role of macrophages in osteolysis of total joint replacement. *Biomaterials* **2005**, *26*, 1271–1286. [CrossRef]
51. Chiu, R.; Ma, T.; Smith, R.L.; Goodman, S.B. Ultrahigh molecular weight polyethylene wear debris inhibits osteoprogenitor proliferation and differentiation in vitro. *J. Biomed. Mater. Res. Part A* **2009**, *89*, 242–247. [CrossRef] [PubMed]
52. Nich, C.; Takakubo, Y.; Pajarinen, J.; Ainola, M.; Salem, A.; Sillat, T.; Rao, A.J.; Raska, M.; Tamaki, Y.; Takagi, M.; et al. Macrophages—Key cells in the response to wear debris from joint replacements. *J. Biomed. Mater. Res. Part A* **2013**, *101*, 3033–3045. [CrossRef] [PubMed]
53. Athanasou, N.A. The pathobiology and pathology of aseptic implant failure. *Bone Jt. Res.* **2016**, *5*, 162–168. [CrossRef]
54. Gu, Q.; Shi, Q.; Yang, H. The role of TLR and chemokine in wear particle-induced aseptic loosening. *J. Biomed. Biotechnol.* **2012**, *2012*, 596870. [CrossRef]
55. Landgraeber, S.; Jäger, M.; Jacobs, J.J.; Hallab, N.J. The pathology of orthopedic implant failure is mediated by innate immune system cytokines. *Mediat. Inflamm.* **2014**, *2014*, 185150. [CrossRef] [PubMed]
56. Schroder, K.; Tschopp, J. The inflammasomes. *Cell* **2010**, *140*, 821–832. [CrossRef]
57. Shiratori, T.; Kyumoto-Nakamura, Y.; Kukita, A.; Uehara, N.; Zhang, J.; Koda, K.; Kamiya, M.; Badawy, T.; Tomoda, E.; Xu, X.; et al. IL-1β Induces Pathologically Activated Osteoclasts Bearing Extremely High Levels of Resorbing Activity: A Possible Pathological Subpopulation of Osteoclasts, Accompanied by Suppressed Expression of Kindlin-3 and Talin-1. *J. Immunol.* **2018**, *200*, 218–228. [CrossRef] [PubMed]
58. Lin, T.-H.; Tamaki, Y.; Pajarinen, J.; Waters, H.A.; Woo, D.K.; Yao, Z.; Goodman, S.B. Chronic inflammation in biomaterial-induced periprosthetic osteolysis: NF-κB as a therapeutic target. *Acta Biomater.* **2014**, *10*, 1–10. [CrossRef]
59. Kandahari, A.M.; Yang, X.; Laroche, K.A.; Dighe, A.S.; Pan, D.; Cui, Q. A review of UHMWPE wear-induced osteolysis: The role for early detection of the immune response. *Bone Res.* **2016**, *4*, 16014. [CrossRef] [PubMed]
60. Sukur, E.; Akman, Y.E.; Ozturkmen, Y.; Kucukdurmaz, F. Particle Disease: A Current Review of the Biological Mechanisms in Periprosthetic Osteolysis After Hip Arthroplasty. *Open Orthop. J.* **2016**, *10*, 241–251. [CrossRef]
61. Purdue, P.E.; Koulouvaris, P.; Potter, H.G.; Nestor, B.J.; Sculco, T.P. The cellular and molecular biology of periprosthetic osteolysis. *Clin. Orthop. Relat. Res.* **2007**, *454*, 251–261. [CrossRef]
62. Anderson, J.M. Inflammation, Wound Healing, and the Foreign-Body Response. In *Biomaterials Science*, 3rd ed.; Ratner, B.D., Hoffman, A.S., Schoen, F.J., Lemons, J.E., Eds.; Academic Press: Oxford, UK, 2013.
63. Beck, R.T.; Illingworth, K.D.; Saleh, K.J. Review of periprosthetic osteolysis in total joint arthroplasty: An emphasis on host factors and future directions. *J. Orthop. Res.* **2012**, *30*, 541–546. [CrossRef]
64. Choi, M.G.; Koh, H.S.; Kluess, D.; O'Connor, D.; Mathur, A.; Truskey, G.A.; Rubin, J.; Zhou, D.X.F.; Sung, K.-L.P. Effects of titanium particle size on osteoblast functions in vitro and in vivo. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 4578–4583. [CrossRef]
65. Takagi, M. Neutral proteinases and their inhibitors in the loosening of total hip prostheses. *Acta Orthop. Scand.* **1996**, *67* (Suppl. S271), 3–29. [CrossRef]
66. Yang, F.; Wu, W.; Cao, L.; Huang, Y.; Zhu, Z.; Tang, T.; Dai, K. Pathways of macrophage apoptosis within the interface membrane in aseptic loosening of prostheses. *Biomaterials* **2011**, *32*, 9159–9167. [CrossRef] [PubMed]
67. Renò, F.; Sabbatini, M.; Massè, A.; Bosetti, M.; Cannas, M. Fibroblast apoptosis and caspase-8 activation in aseptic loosening. *Biomaterials* **2003**, *24*, 3941–3946. [CrossRef] [PubMed]
68. Anil, U.; Singh, V.; Schwarzkopf, R. Diagnosis and Detection of Subtle Aseptic Loosening in Total Hip Arthroplasty. *J. Arthroplast.* **2022**, *37*, 1494–1500. [CrossRef]
69. Santavirta, S.; Konttinen, Y.T.; Bergroth, V.; Eskola, A.; Tallroth, K.; Lindholm, T.S. Aggressive granulomatous lesions associ-ated with hip arthroplasty. Immunopathological studies. *J. Bone Joint Surg. Am.* **1990**, *72*, 252–258. [CrossRef]
70. Solovieva, S.A.; Čeponis, A.; Konttinen, Y.T.; Takagi, M.; Suda, A.; Eklund, K.K.; Sorsa, T.D.; Santavirta, S. Mast cells in loosening of totally replaced hips. *Clin. Orthop. Relat. Res.* **1996**, *322*, 158–165. [CrossRef]
71. Sheikh, Z.; Brooks, P.J.; Barzilay, O.; Fine, N.; Glogauer, M. Macrophages, Foreign Body Giant Cells and Their Response to Implantable Biomaterials. *Materials* **2015**, *8*, 5671–5701. [CrossRef]
72. Lu, Y.-C.; Chang, T.-K.; Lin, T.-C.; Yeh, S.-T.; Fang, H.-W.; Huang, C.-H.; Huang, C.-H. The potential role of herbal extract Wedelolactone for treating particle-induced osteolysis: An in vivo study. *J. Orthop. Surg. Res.* **2022**, *17*, 335. [CrossRef]
73. Shet, S.S.; Kakish, E.; Murphy, S.C.; Roopnarinesingh, R.; Power, S.P.; Maher, M.M.; Ryan, D.J. Imaging evaluation of periprosthetic loosening: A primer for the general radiologist. *World J. Radiol.* **2025**, *17*, 102373. [CrossRef]
74. Wang, Y.; Wang, R.; Geng, L.; Li, Q.; Qi, E.; Shi, Y.; Wang, Y.; Zheng, Q.; Zhang, G.; Chen, J.; et al. Different uptake patterns of 68Ga-FAPI in aseptic loosening and periprosthetic joint infection of hip arthroplasty: A case series and literature review. *Front. Med.* **2022**, *9*, 1014463. [CrossRef] [PubMed]

75. Aspenberg, P.; Anttila, A.; Konttinen, Y.T.; Lappalainen, R.; Goodman, S.B.; Nordsletten, L.; Santavirta, S. Benign response to particles of diamond and SiC: Bone chamber studies of new joint replacement coating materials in rabbits. *Biomaterials* **1996**, *17*, 807–812. [CrossRef]
76. Schmalzried, T.P.; Jasty, M.; Harris, W.H. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. *J. Bone Joint Surg. Am.* **1992**, *74*, 849–863. [CrossRef]
77. Manley, M.T.; D'antonio, J.; Capello, W.N.; Edidin, A.A. Osteolysis: A Disease of access to fixation interfaces. *Clin. Orthop. Relat. Res.* **2002**, *405*, 129–137. [CrossRef]
78. Pap, G.; Machner, A.; Rinnert, T.; Hörler, D.; Gay, R.E.; Schwarzberg, H.; Neumann, W.; Michel, B.A.; Gay, S.; Pap, T. De-velopment and characteristics of a synovial-like interface membrane around cemented tibial hemiarthroplasties in a novel rat model of aseptic prosthesis loosening. *Arthritis Rheum.* **2001**, *44*, 956–963. [CrossRef]
79. Banerjee, S.; Pivec, R.; Issa, K.; Kapadia, B.H.; Khanuja, H.S.; Mont, M.A. Large-diameter femoral heads in total hip arthroplasty: An evidence-based review. *Am. J. Orthop.* **2014**, *43*, 506–512. [PubMed]
80. Oparaugo, P.C.; Clarke, I.C.; Malchau, H.; Herberts, P. Correlation of wear debris-induced osteolysis and revision with volumetric wear-rates of polyethylene: A survey of 8 reports in the literature. *Acta Orthop. Scand.* **2001**, *72*, 22–28. [CrossRef] [PubMed]
81. Shi, J.; Zhu, W.; Liang, S.; Li, H.; Li, S. Cross-Linked Versus Conventional Polyethylene for Long-Term Clinical Outcomes After Total Hip Arthroplasty: A Systematic Review and Meta-Analysis. *J. Investig. Surg.* **2021**, *34*, 307–317. [CrossRef] [PubMed]
82. Lambert, B.; Neut, D.; van der Veen, H.C.; Bulstra, S.K. Effects of vitamin E incorporation in polyethylene on oxidative degradation, wear rates, immune response, and infections in total joint arthroplasty: A review of the current literature. *Int. Orthop.* **2019**, *43*, 1549–1557. [CrossRef]
83. McKellop, H.; Shen, F.-W.; Lu, B.; Campbell, P.; Salovey, R. Effect of sterilization method and other modifications on the wear resistance of acetabular cups made of ultra-high molecular weight polyethylene. A hip-simulator study. *J. Bone Joint Surg. Am.* **2000**, *82*, 1708–1725. [CrossRef]
84. Gomez-Barrena, E.; Puertolas, J.-A.; Munuera, L.; Konttinen, Y.T. Update on UHMWPE research from the bench to the bedside. *Acta Orthop.* **2008**, *79*, 832–840. [CrossRef]
85. Oral, E.; Muratoglu, O.K. Vitamin E diffused, highly crosslinked UHMWPE: A review. *Int. Orthop.* **2011**, *35*, 215–223. [CrossRef]
86. Oral, E.; Rowell, S.L.; Muratoglu, O.K. The effect of α-tocopherol on the oxidation and free radical decay in irradiated UHMWPE. *Biomaterials* **2006**, *27*, 5580–5587. [CrossRef]
87. Valladares, R.D.; Nich, C.; Zwingenberger, S.; Li, C.; Swank, K.R.; Gibon, E.; Rao, A.J.; Yao, Z.; Goodman, S.B. Toll-like receptors-2 and 4 are overexpressed in an experimental model of particle-induced osteolysis. *J. Biomed. Mater. Res. Part A* **2014**, *102*, 3004–3011. [CrossRef]
88. Maitra, R.; Clement, C.C.; Scharf, B.; Crisi, G.M.; Chitta, S.; Paget, D.; Purdue, P.E.; Cobelli, N.; Santambrogio, L. Endosomal damage and TLR2 mediated inflammasome activation by alkane particles in the generation of aseptic osteolysis. *Mol. Immunol.* **2009**, *47*, 175–184. [CrossRef]
89. Vermes, C.; Chandrasekaran, R.; Jacobs, J.J.; Galante, J.O.; Roebuck, K.A.; Glant, T.T. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. *J. Bone Joint Surg. Am.* **2001**, *83*, 201–211. [CrossRef]
90. Hodrick, J.T.; Severson, E.P.; McAlister, D.S.; Dahl, B.; Hofmann, A.A. Highly crosslinked polyethylene is safe for use in total knee arthroplasty. *Clin. Orthop. Relat. Res.* **2008**, *466*, 2806–2812. [CrossRef]
91. Bichara, D.A.; Malchau, E.; Sillesen, N.H.; Cakmak, S.; Nielsen, G.P.; Muratoglu, O.K. Vitamin E-diffused highly cross-linked UHMWPE particles induce less osteolysis compared to highly cross-linked virgin UHMWPE particles in vivo. *J. Arthroplast.* **2014**, *29*, 232–237. [CrossRef]
92. Chen, W.; Bichara, D.A.; Suhardi, J.; Sheng, P.; Muratoglu, O.K. Effects of vitamin E-diffused highly cross-linked UHMWPE particles on inflammation, apoptosis and immune response against S. aureus. *Biomaterials* **2017**, *143*, 46–56. [CrossRef] [PubMed]
93. Renò, F.; Bracco, P.; Lombardi, F.; Boccafoschi, F.; Costa, L.; Cannas, M. The induction of MMP-9 release from granulocytes by Vitamin E in UHMWPE. *Biomaterials* **2004**, *25*, 995–1001. [CrossRef] [PubMed]
94. Terkawi, M.A.; Hamasaki, M.; Takahashi, D.; Ota, M.; Kadoya, K.; Yutani, T.; Uetsuki, K.; Asano, T.; Irie, T.; Arai, R.; et al. Transcriptional profile of human macrophages stimulated by ultra-high molecular weight polyethylene particulate debris of orthopedic implants uncovers a common gene expression signature of rheumatoid arthritis. *Acta Biomater.* **2018**, *65*, 417–425. [CrossRef] [PubMed]
95. Quinn, J.; Joyner, C.; Triffitt, J.; Athanasou, N. Polymethylmethacrylate-induced inflammatory macrophages resorb bone. *J. Bone Joint Surg. Brit. Vol.* **1992**, *74-B*, 652–658. [CrossRef]
96. Sabokbar, A.; Pandey, R.; Quinn, J.M.; Athanasou, N.A. Osteoclastic differentiation by mononuclear phagocytes containing biomaterial particles. *Arch. Orthop. Trauma Surg.* **1998**, *117*, 136–140. [CrossRef]
97. Pearl, J.I.; Ma, T.; Irani, A.R.; Huang, Z.; Robinson, W.H.; Smith, R.L.; Goodman, S.B. Role of the Toll-like receptor pathway in the recognition of orthopedic implant wear-debris particles. *Biomaterials* **2011**, *32*, 5535–5542. [CrossRef] [PubMed]

98. Antonios, J.K.; Yao, Z.; Li, C.; Rao, A.J.; Goodman, S.B. Macrophage polarization in response to wear particles in vitro. *Cell. Mol. Immunol.* **2013**, *10*, 471–482. [CrossRef]
99. Huang, Z.; Ma, T.; Ren, P.; Smith, R.L.; Goodman, S.B. Effects of orthopedic polymer particles on chemotaxis of macrophages and mesenchymal stem cells. *J. Biomed. Mater. Res. Part A* **2010**, *94*, 1264–1269. [CrossRef]
100. O'Neill, L.A.J.; Golenbock, D.; Bowie, A.G. The history of Toll-like receptors—Redefining innate immunity. *Nat. Rev. Immunol.* **2013**, *13*, 453–460. [CrossRef]
101. Burton, L.; Paget, D.; Binder, N.B.; Bohnert, K.; Nestor, B.J.; Sculco, T.P.; Santambrogio, L.; Ross, F.P.; Goldring, S.R.; Purdue, P.E. Orthopedic wear debris mediated inflammatory osteolysis is mediated in part by NALP3 inflammasome activation. *J. Orthop. Res.* **2013**, *31*, 73–80. [CrossRef]
102. Abu-Amer, Y.; Darwech, I.; Clohisy, J.C. Aseptic loosening of total joint replacements: Mechanisms underlying osteolysis and potential therapies. *Arthritis Res. Ther.* **2007**, *9* (Suppl. S1), S6. [CrossRef]
103. Caicedo, M.S.; Samelko, L.; McAllister, K.; Jacobs, J.J.; Hallab, N.J. Increasing both CoCrMo-alloy Particle Size and Surface Irregularity Induces Increased Macrophage Inflammasome Activation In vitro Potentially through Lysosomal Destabilization Mechanisms. *J. Orthop. Res.* **2013**, *31*, 1633–1642. [CrossRef]
104. Samelko, L.; Landgraeber, S.; McAllister, K.; Jacobs, J.; Hallab, N.J.; Ryffel, B. Cobalt Alloy Implant Debris Induces Inflammation and Bone Loss Primarily through Danger Signaling, Not TLR4 Activation: Implications for DAMP-ening Implant Related Inflammation. *PLoS ONE* **2016**, *11*, e0160141. [CrossRef]
105. Oblak, A.; Pohar, J.; Jerala, R.; Haziot, A. MD-2 Determinants of Nickel and Cobalt-Mediated Activation of Human TLR. *PLoS ONE* **2015**, *10*, e0120583. [CrossRef] [PubMed]
106. Panez-Toro, I.; Heymann, D.; Gouin, F.; Amiaud, J.; Heymann, M.-F.; Córdova, L.A. Roles of inflammatory cell infiltrate in periprosthetic osteolysis. *Front. Immunol.* **2023**, *14*, 1310262. [CrossRef]
107. Kurtz, S.M.; Holyoak, D.T.; Trebše, R.; Randau, T.M.; Porporati, A.A.; Siskey, R.L. Ceramic Wear Particles: Can They Be Retrieved In Vivo and Duplicated In Vitro? *J. Arthroplast.* **2023**, *38*, 1869–1876. [CrossRef]
108. Catelas, I.; Petit, A.; Zukor, D.J.; Marchand, R.; Yahia, L.; Huk, O.L. Induction of macrophage apoptosis by ceramic and polyethylene particles in vitro. *Biomaterials* **1999**, *20*, 625–630. [CrossRef]
109. Bylski, D.; Wedemeyer, C.; Xu, J.; Sterner, T.; Löer, F.; von Knoch, M. Alumina ceramic particles, in comparison with titanium particles, hardly affect the expression of RANK-, TNF-α-, and OPG-mRNA in the THP-1 human monocytic cell line. *J. Biomed. Mater. Res. Part A* **2009**, *89A*, 707–716. [CrossRef]
110. Lucarelli, M.; Gatti, A.M.; Savarino, G.; Quattroni, P.; Martinelli, L.; Monari, E.; Boraschi, D. Innate defence functions of macrophages can be biased by nano-sized ceramic and metallic particles. *Eur. Cytokine Netw.* **2004**, *15*, 339–346.
111. Ha, Y.-C.; Kim, S.-Y.; Kim, H.J.; Yoo, J.J.; Koo, K.-H. Ceramic liner fracture after cementless alumina-on-alumina total hip arthroplasty. *Clin. Orthop. Relat. Res.* **2007**, *458*, 106–110. [CrossRef]
112. Zywiel, M.G.; Sayeed, S.A.; Johnson, A.J.; Schmalzried, T.P.; Mont, M.A. Survival of hard-on-hard bearings in total hip arthroplasty: A systematic review. *Clin. Orthop. Relat. Res.* **2011**, *469*, 1536–1546. [CrossRef]
113. Hasan, S.; van Schie, P.; Kaptein, B.L.; Schoones, J.W.; de Mheen, P.J.M.-V.; Nelissen, R.G.H.H. Biomarkers to discriminate between aseptic loosened and stable total hip or knee arthroplasties: A systematic review. *EFORT Open Rev.* **2024**, *9*, 25–39. [CrossRef] [PubMed]
114. Biomarkers Definitions Working Group; Atkinson, A.J., Jr.; Colburn, W.A.; DeGruttola, V.G.; DeMets, D.L.; Downing, G.J.; Hoth, D.F.; Oates, J.A.; Peck, C.C.; Spilker, B.A.; et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* **2001**, *69*, 89–95. [CrossRef] [PubMed]
115. Chaganti, R.K.; Purdue, E.; Sculco, T.P.; Mandl, L.A. Elevation of serum tumor necrosis factor α in patients with periprosthetic osteolysis: A case-control study. *Clin. Orthop. Relat. Res.* **2014**, *472*, 584–589. [CrossRef] [PubMed]
116. Hundrić-Hašpl, Ž.; Pecina, M.; Haspl, M.; Tomicic, M.; Jukic, I. Plasma cytokines as markers of aseptic prosthesis loosening. *Clin. Orthop. Relat. Res.* **2006**, *453*, 299–304. [CrossRef]
117. Wu, W.; Zhang, X.; Zhang, C.; Tang, T.; Ren, W.; Dai, K. Expansion of CD14+CD16+ peripheral monocytes among patients with aseptic loosening. *Inflamm. Res.* **2009**, *58*, 561–570. [CrossRef]
118. He, T.; Wu, W.; Huang, Y.; Zhang, X.; Tang, T.; Dai, K. Multiple biomarkers analysis for the early detection of prosthetic aseptic loosening of hip arthroplasty. *Int. Orthop.* **2013**, *37*, 1025–1031. [CrossRef]
119. Moreschini, O.; Fiorito, S.; Magrini, L.; Margheritini, F.; Romanini, L. Markers of connective tissue activation in aseptic hip prosthetic loosening. *J. Arthroplast.* **1997**, *12*, 695–703. [CrossRef]
120. López-Anglada, E.; Collazos, J.; Montes, A.H.; Pérez-Is, L.; Pérez-Hevia, I.; Jiménez-Tostado, S.; Suárez-Zarracina, T.; Alvarez, V.; Valle-Garay, E.; Asensi, V. IL-1 β gene (+3954 C/T, exon 5, rs1143634) and NOS2 (exon 22) polymorphisms associate with early aseptic loosening of arthroplasties. *Sci. Rep.* **2022**, *12*, 18382. [CrossRef]
121. Tang, F.; Liu, X.; Jiang, H.; Wu, H.; Hu, S.; Zheng, J.; Guo, H.; Yan, L.; Xu, C.; Lin, Y.; et al. Biomarkers for early diagnosis of aseptic loosening after total hip replacement. *Int. J. Clin. Exp. Pathol.* **2016**, *9*, 1954–1960.

122. Trehan, S.K.; Zambrana, L.; Jo, J.E.; Purdue, E.; Karamitros, A.; Nguyen, J.T.; Lane, J.M. An Alternative Macrophage Activation Pathway Regulator, CHIT1, May Provide a Serum and Synovial Fluid Biomarker of Periprosthetic Osteolysis. *HSS J.* **2018**, *14*, 148–152. [CrossRef]
123. Morakis, A.; Tournis, S.; Papakitsou, E.; Donta, I.; Lyritis, G.P. Decreased tibial bone strength in postmenopausal women with aseptic loosening of cemented femoral implants measured by peripheral quantitative computed tomography (pQCT). *J Long Term Eff. Med. Implants* **2011**, *21*, 291–297. [CrossRef] [PubMed]
124. Wilkinson, J.M.; Hamer, A.J.; Rogers, A.; Stockley, I.; Eastell, R. Bone mineral density and biochemical markers of bone turnover in aseptic loosening after total hip arthroplasty. *J. Orthop. Res.* **2003**, *21*, 691–696. [CrossRef] [PubMed]
125. Antoniou, J.; Huk, O.; Zukor, D.; Eyre, D.; Alini, M. Collagen crosslinked N-telopeptides as markers for evaluating particulate osteolysis: A preliminary study. *J. Orthop. Res.* **2000**, *18*, 64–67. [CrossRef]
126. Savarino, L.; Avnet, S.; Greco, M.; Giunti, A.; Baldini, N. Potential role of tartrate-resistant acid phosphatase 5b (TRACP 5b) as a surrogate marker of late loosening in patients with total hip arthroplasty: A cohort study. *J. Orthop. Res.* **2010**, *28*, 887–892. [CrossRef]
127. Lawrence, N.R.; Jayasuriya, R.L.; Gossiel, F.; Wilkinson, J.M. Diagnostic accuracy of bone turnover markers as a screening tool for aseptic loosening after total hip arthroplasty. *HIP Int.* **2015**, *25*, 525–530. [CrossRef]
128. Ovrenovits, M.; Pakos, E.E.; Vartholomatos, G.; Paschos, N.K.; Xenakis, T.A.; Mitsionis, G.I. Flow cytometry as a diagnostic tool for identifying total hip arthroplasty loosening and differentiating between septic and aseptic cases. *Eur. J. Orthop. Surg. Traumatol.* **2015**, *25*, 1153–1159. [CrossRef]
129. Papagiannis, S.; Tatani, I.; Kyriakopoulos, G.; Kokkalis, Z.; Megas, P.; Stathopoulos, C.; Grafanaki, K.; Lakoumentas, J. Alterations in Small Non-coding MicroRNAs (miRNAs) and the Potential Role in the Development of Aseptic Loosening After Total Hip Replacement: Study Protocol for an Observational, Cross-Sectional Study. *Cureus* **2024**, *16*, e72179. [CrossRef]
130. Noshahr, R.M.; Omrani, F.A.; Chari, A.Y.; Roudsari, M.S.; Madadi, F.; Jousheghan, S.S.; Manafi-Rasi, A. MicroRNAs in Aseptic Loosening of Prosthesis: Pathophysiology and Potential Therapeutic Approaches. *Arch. Bone Jt. Surg.* **2024**, *12*, 612–621. [CrossRef]
131. Malik, M.H.A.; Jury, F.; Bayat, A.; Ollier, W.E.R.; Kay, P.R. Genetic susceptibility to total hip arthroplasty failure: A preliminary study on the influence of matrix metalloproteinase 1, interleukin 6 polymorphisms and vitamin D receptor. *Ann. Rheum. Dis.* **2007**, *66*, 1116–1120. [CrossRef] [PubMed]
132. Stołtny, T.; Dobrakowski, M.; Augustyn, A.; Rokicka, D.; Kasperczyk, S. The concentration of chromium and cobalt ions and parameters of oxidative stress in serum and their impact on clinical outcomes after metaphyseal hip arthroplasty with modular metal heads. *J. Orthop. Surg. Res.* **2023**, *18*, 225. [CrossRef] [PubMed]
133. Parvizi, J.; Suh, D.-H.; Jafari, M.S.; Mullan, A.; Purtill, J.J. Aseptic loosening of total hip arthroplasty: Infection always should be ruled out. *Clin. Orthop. Relat. Res.* **2011**, *469*, 1401–1405. [CrossRef] [PubMed]
134. Mertens, M.T.; Singh, J.A. Biomarkers in Arthroplasty: A Systematic Review. *Open Orthop. J.* **2011**, *5*, 92–105. [CrossRef]
135. Hart, A.J.; Sabah, S.A.; Bandi, A.S.; Maggiore, P.; Tarassoli, P.; Sampson, B.; Skinner, J.A. Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. *J. Bone Joint Surg. Br. Vol.* **2011**, *93-B*, 1308–1313. [CrossRef]
136. Ettinger, M.; Calliess, T.; Kielstein, J.T.; Sibai, J.; Brückner, T.; Lichtinghagen, R.; Windhagen, H.; Lukasz, A. Circulating Biomarkers for Discrimination Between Aseptic Joint Failure, Low-Grade Infection, and High-Grade Septic Failure. *Clin. Infect. Dis.* **2015**, *61*, 332–341. [CrossRef]
137. Qin, L.; Du, C.; Yang, J.; Wang, H.; Su, X.; Wei, L.; Zhao, C.; Chen, C.; Chen, H.; Hu, N.; et al. Synovial Fluid Interleukin Levels Cannot Distinguish between Prosthetic Joint Infection and Active Rheumatoid Arthritis after Hip or Knee Arthroplasty. *Diagnostics* **2022**, *12*, 1196. [CrossRef]
138. Alotaibi, H.F.; Perni, S.; Prokopovich, P. Nanoparticle-based model of anti-inflammatory drug releasing LbL coatings for uncemented prosthesis aseptic loosening prevention. *Int. J. Nanomed.* **2019**, *14*, 7309–7322. [CrossRef]
139. van Duren, B.H.; Firth, A.M.; Berber, R.; Matar, H.E.; James, P.J.; Bloch, B.V. Revision Rates for Aseptic Loosening in the Obese Patient: A Comparison Between Stemmed, Uncemented, and Unstemmed Tibial Total Knee Arthroplasty Components. *Arthroplast. Today* **2025**, *32*, 101621. [CrossRef] [PubMed]
140. Layson, J.T.; Hameed, D.; Dubin, J.A.; Moore, M.C.; Mont, M.; Scuderi, G.R. Patients with Osteoporosis Are at Higher Risk for Periprosthetic Femoral Fractures and Aseptic Loosening Following Total Hip Arthroplasty. *Orthop. Clin. N. Am.* **2024**, *55*, 311–321. [CrossRef] [PubMed]
141. Patel, S.K.; Dilley, J.E.; Carlone, A.; Deckard, E.R.; Meneghini, R.M.; Sonn, K.A. Effect of Tobacco Use on Radiolucent Lines in Modern Cementless Total Knee Arthroplasty Tibial Components. *Arthroplast. Today* **2023**, *19*, 101082. [CrossRef] [PubMed]
142. Teng, S.; Yi, C.; Krettek, C.; Jagodzinski, M.; Katoh, M. Smoking and Risk of Prosthesis-Related Complications after Total Hip Arthroplasty: A Meta-Analysis of Cohort Studies. *PLoS ONE* **2015**, *10*, e0125294. [CrossRef] [PubMed]

143. Kapadia, B.H.; Issa, K.; Pivec, R.; Bonutti, P.M.; Mont, M.A. Tobacco use may be associated with increased revision and complication rates following total hip arthroplasty. *J. Arthroplast.* **2014**, *29*, 777–780. [CrossRef]
144. Khatod, M.; Cafri, G.; Namba, R.S.; Inacio, M.C.S.; Paxton, E.W. Risk Factors for Total Hip Arthroplasty Aseptic Revision. *J. Arthroplast.* **2014**, *29*, 1412–1417. [CrossRef]
145. Apostu, D.; Lucaciu, O.; Berce, C.; Lucaciu, D.; Cosma, D. Current methods of preventing aseptic loosening and improving osseointegration of titanium implants in cementless total hip arthroplasty: A review. *J. Int. Med. Res.* **2018**, *46*, 2104–2119. [CrossRef]
146. Safavi, S.; Yu, Y.; Robinson, D.L.; Gray, H.A.; Ackland, D.C.; Lee, P.V.S. Additively manufactured controlled porous orthopedic joint replacement designs to reduce bone stress shielding: A systematic review. *J. Orthop. Surg. Res.* **2023**, *18*, 42. [CrossRef]
147. De Meo, F.; Cacciola, G.; Bellotti, V.; Bruschetta, A.; Cavaliere, P. Trabecular Titanium acetabular cups in hip revision surgery: Mid-term clinical and radiological outcomes. *HIP Int.* **2018**, *28*, 61–65. [CrossRef] [PubMed]
148. Cacciola, G.; Giustra, F.; Bosco, F.; De Meo, F.; Bruschetta, A.; De Martino, I.; Risitano, S.; Sabatini, L.; Massè, A.; Cavaliere, P. Trabecular titanium cups in hip revision surgery: A systematic review of the literature. *Ann. Jt.* **2023**, *8*, 36. [CrossRef]
149. Chen, Y.-L.; Lin, T.; Liu, A.; Shi, M.-M.; Hu, B.; Shi, Z.-L.; Yan, S.-G. Does hydroxyapatite coating have no advantage over porous coating in primary total hip arthroplasty? A meta-analysis. *J. Orthop. Surg. Res.* **2015**, *10*, 21. [CrossRef]
150. Morano, C.; Garofalo, S.; Bertuccio, P.; Sposato, A.; Zappone, I.; Pagnotta, L. A Comprehensive Literature Review of Total Hip Arthroplasty (THA): Part 1—Biomaterials. *J. Funct. Biomater.* **2025**, *16*, 179. [CrossRef]
151. Soliman, M.; Chowdhury, M.E.H.; Islam, M.T.; Musharavati, F.; Nabil, M.; Hafizh, M.; Khandakar, A.; Mahmud, S.; Nezhad, E.Z.; Shuzan, N.I.; et al. A Review of Biomaterials and Associated Performance Metrics Analysis in Pre-Clinical Finite Element Model and in Implementation Stages for Total Hip Implant System. *Polymers* **2022**, *14*, 4308. [CrossRef]
152. Savin, L.; Pinteala, T.; Mihai, D.N.; Mihailescu, D.; Miu, S.S.; Sirbu, M.T.; Veliceasa, B.; Popescu, D.C.; Sirbu, P.D.; Forna, N. Updates on Biomaterials Used in Total Hip Arthroplasty (THA). *Polymers* **2023**, *15*, 3278. [CrossRef]
153. Isaacson, B.M.; Jeyapalina, S. Osseointegration: A review of the fundamentals for assuring cementless skeletal fixation. *Orthop. Res. Rev.* **2014**, *6*, 55–65. [CrossRef]
154. McCormick, K.L.; Mastroianni, M.A.; Kolodychuk, N.L.; Herndon, C.L.; Shah, R.P.; Cooper, H.J.; Sarpong, N.O. Complications and Survivorship After Aseptic Revision Total Hip Arthroplasty: Is There a Difference by Surgical Approach? *J. Arthroplast.* **2025**, *40*, 203–207. [CrossRef] [PubMed]
155. Lindgren, V.; Garellick, G.; Kärrholm, J.; Wretenberg, P. The type of surgical approach influences the risk of revision in total hip arthroplasty: A study from the Swedish Hip Arthroplasty Register of 90,662 total hipreplacements with 3 different cemented prostheses. *Acta Orthop.* **2012**, *83*, 559–565. [CrossRef]
156. Steiness, J.; Hägi-Pedersen, D.; Lunn, T.H.; Overgaard, S.; Brorson, S.; Graungaard, B.K.; Lindberg-Larsen, M.; Varnum, C.; Lundstrøm, L.H.; Beck, T.; et al. Non-opioid analgesic combinations following total hip arthroplasty (RECIPE): A randomised, placebo-controlled, blinded, multicentre trial. *Lancet Rheumatol.* **2024**, *6*, e205–e215. [CrossRef] [PubMed]
157. García-Martínez, O.; De Luna-Bertos, E.; Ramos-Torrecillas, J.; Manzano-Moreno, F.; Ruiz, C. Repercussions of NSAIDS drugs on bone tissue: The osteoblast. *Life Sci.* **2015**, *123*, 72–77. [CrossRef] [PubMed]
158. Luo, J.D.; Miller, C.; Jirjis, T.; Nasir, M.; Sharma, D. The effect of non-steroidal anti-inflammatory drugs on the osteogenic activity in osseointegration: A systematic review. *Int. J. Implant. Dent.* **2018**, *4*, 30. [CrossRef] [PubMed]
159. Birrell, F.; Lohmander, S. Non-steroidal anti-inflammatory drugs after hip replacement. *BMJ* **2006**, *333*, 507–508. [CrossRef]
160. Friedl, G.; Radl, R.; Stihsen, C.; Rehak, P.; Aigner, R.; Windhager, R. The effect of a single infusion of zoledronic acid on early implant migration in total hip arthroplasty. A randomized, double-blind, controlled trial. *J. Bone Jt. Surg.* **2009**, *91*, 274–281. [CrossRef]