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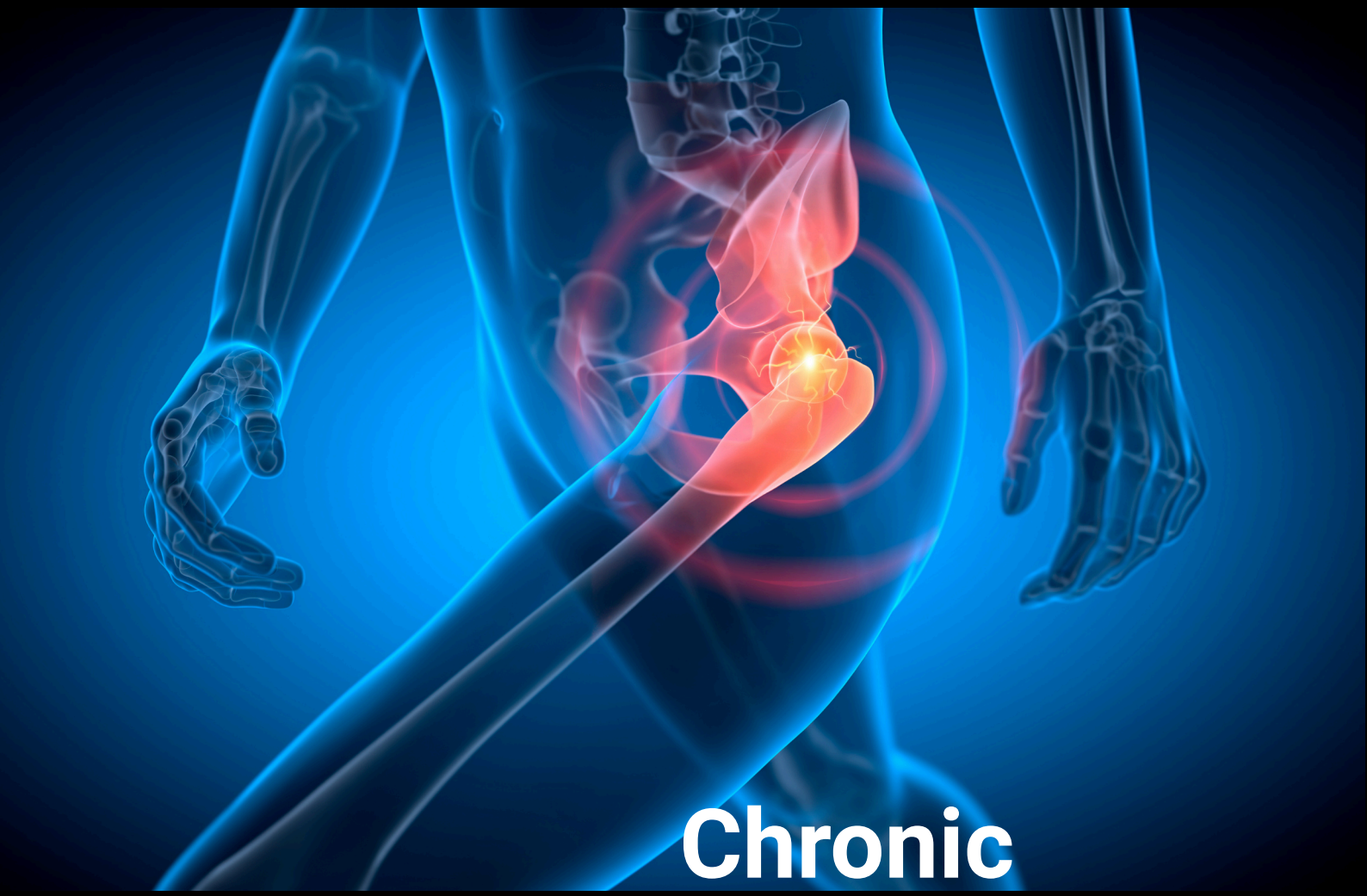

Chronic Inflammation

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From the Editor

Chronic Challenges in Joint Replacement

Prof. Alister Hart FRCS (Orth)
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The awareness of the impact of chronic inflammation around orthopedic implants in the medical community and the public has grown due to the increase in the incidence of hip and knee osteoarthritis after World War II, the use of orthopedic implants worldwide, types of implant materials, manufacturing methods and post-processing techniques, patients' and providers' desire for the best possible and longest-lasting outcomes after implant surgery, and use of digital media technology to rapidly and widely disseminate the issues involving implant surgery.

Many different materials are used in orthopaedic implants: metal alloys, metal coatings, polymers, ceramics, 3D printed titanium alloy, bone inductive materials, and anti-bacterial agents. It is no surprise that the continuous release of an implant derived material causes peri-prosthetic chronic inflammation; however, it is of great importance to understand the mechanisms of the complex relationship between particulate material and host response causing chronic inflammation to prevent the occurrence of adverse events.

The expansion of implant science as a field has increased the workload for regulators. In Europe, this is particularly difficult because the new MDR regulations have already strained the relationship between implant manufacturers and regulators. These groups benefit from improved outcome assessment of implants because of mature joint registries in search of long-term true success and early failure signals. However, registries are susceptible to data quality issues for linking primary to revision operations, use failure as their only endpoint, and for most registries the reason for revision is often poorly understood because culture and histopathology results are not known, and closed reduction of dislocations are not recorded.

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This series of articles provides an update on the state-of-the-art in the fields of chronic inflammation, the human inflammatory reaction to implant-derived material, and the terminology and definitions used to describe peri-implant inflammation on bone and soft tissues.

Dr. Ina Lackner reviews and explains the latest implant science on the human mechanical and biological and worn bearings. The unraveling of the biological response to polyethylene is a long and fascinating story. The loosening of cemented femoral stems in the 1970s was wrongly attributed to "cement disease" rather than polyethylene-particle- induced inflammation. However, this helped advance uncemented implant technology. In the 1990s, the use of metal-on-metal (MoM) bearings was based on the need to avoid polyethylene

induced osteolysis. However, this resulted in adverse reaction to metal debris which incorporates both soft tissue and bone inflammation and sometimes greater osteolysis than produced by polyethylene. In the 2000s there were many articles on the problem of taper junction corrosion of large diameter MoM hips which led to their prohibition in 2012. This was followed in the 2010s with tribocorrosion problems with dual modular neck THA implants with CoCrMo neck and Ti alloy femoral stems.

Prof. Catherine van der Straeten explains how our understanding of the risk factors involved in chronic inflammation were accelerated by the COVID-19 pandemic because morbidity and mortality was driven by the host response to the virus through cytokine release. We now better understand how chronic inflammation affects the musculoskeletal system, its role in joint inflammation and osteoarthritis, and risk factors for inflammation in general, including peri-implant inflammation.

For example, we now understand that adipose tissue acts as an endocrine organ with a source of cytokines such as adipokines that can increase inflammation anywhere in the body, including synovial joints. This may explain why synovial inflammation is often found in the early stages of osteoarthritis, challenging the long-held belief that the cartilage degradation precedes joint inflammation.

Adding to this rich discussion, I present three case reports focusing on adverse reactíons in hip replacements involving different material pairings: metal-on-metal (MoM), metal-on-polyethylene (MoP), and ceramic-on-ceramic (CoC). These cases illustrate the diagnostic complexities and highlight the necessity for accurate assessment and management of adverse reactions. The third case, involving ceramic-on-ceramic implants, particularly emphasizes the importance of differential diagnosis in cases initially suspected of ARMD but ultimately attributed to other causes. Each case contributes to our understanding of adverse reaction, reinforcing the importance of precise definitions and thorough clinical evaluations. The terms pseudotumour, ALTR, and metallosis often overlap in clinical presentations, making clear and accurate communication essential for managing patient expectations and treatment outcomes.

Through these insights, we aim to enhance the orthopedic community's understanding of implant-related reactions, fostering better patient outcomes through improved knowledge and collaborative regulatory practices.

Happy Reading!

Alister Hart

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Under the Microscope:

Inflammation is a natural whole-body response triggered by the immune system, which in turn can be generally divided into the innate and the adapted or acquired immune system. Both the innate and the adaptive immune system consist of different cell types, molecular signaling pathways, and cascades, all of which play specific roles during the immune response.

The **innate immune system** is a rudimentary first line of defense, responsible for initiating the inflammatory response.

The **adaptive immune system** is more highly evolved. Designed to learn and create memory as the organism is exposed to antigens throughout its life.[1]

The immune system performs multiple essential tasks. It is a defense mechanism to recognize, fight, and eliminate pathogens and foreign material from the body. The immune response is crucial for the initiation of wound and fracture healing, tissue repair- and reconstitution, and the re-establishment of tissue homeostasis after injury.[2-4]

In general, the inflammatory response can be divided into three phases:

- **acute,**
- **subacute,**
- **and chronic inflammation**.

These phases differ in their cellular content and inflammatory signaling pathways as well as in their duration. Acute inflammation is triggered immediately by a stimulus and usually lasts only a few days.

Chronic inflammation can last months or even years when the acute inflammatory response is not resolved. The subacute phase describes a transitional period from acute to chronic inflammation and typically lasts several weeks.[5,6]

The acute inflammatory response: A quick, strong, and efficient process to re-establish tissue homeostasis after injury

Acute inflammation is triggered by the innate immune system. In case of tissue injury, it maintains tissue integrity and aids in the reconstitution of the tissue's structural and physiological form and function. The acute inflammatory response is activated immediately after tissue injury and clinically characterized by five cardinal signs:

- **heat (calor),**
- **redness (rubor),**
- **swelling (tumor),**
- **pain (dolor),**
- **and loss of function (functio laesa)**[1].

The **cardinal signs of inflammation** (calor, rubor, tumor, and dolor) were first described by the Roman writer Aulus Cornelius Celsus, and the fifth sign, (functio laesa), was added by the Roman physician Galen.[7,8]

One example is the injury of the skin caused by a scratch or stitch (Figure 1).

The tissue injury initiates the release of transmitters such as histamine from mast cells, which stimulate the dilation of blood vessels. This dilation reduces blood flow velocity and increases the movement of blood in extremities, resulting in local heat and redness due to an enhanced number of red blood cells passing.[1,9] Furthermore, the dilated blood vessels become more permeable, thus increasing the passage and accumulation of fluids in the surrounding tissues, which is manifested by swelling (edema). Release of specific mediators and edema-induced stretching of sensory nerves increases pain sensitivity in tissues containing nerve endings. The loss of function refers to either simple loss of mobility in a joint due to edema and pain or to the replacement of functional tissue with scar tissue.[1,9,10]

At this point it is important to mention that with

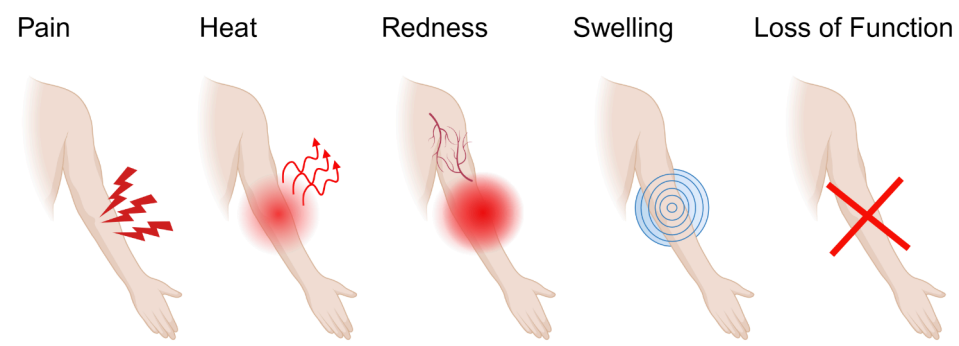

Fig. 1: The five cardinal signs of inflammation. The acute inflammatory response is activated immediately after tissue injury. The above figure shows tissue injury in an example of a skin injury on the forearm. The clinical symptoms of the acute inflammatory response are pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (functio laesa).

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tissue injury external (exogenous) pathogens such as bacteria, viruses, and other microorganisms can enter the site of injury. Intruding pathogens also release specific mediators and molecules to activate the immune system.[11] Once pathogens are involved, it is called an infection.[12]

Immune cells are the main actors during the acute inflammatory response following tissue injury.

With the initiation of the acute inflammatory response in the example of a penetrating skin injury, a cellular reaction cascade is triggered in the injured tissue, with immune cells being the main actors. During acute inflammation, various immune cells, cellular and molecular signaling pathways, and cascades aim to clear the site of tissue injury from damaged cells and/or pathogenic or foreign material and to induce tissue healing.[13,14]

At the site of tissue injury, local resident immune cells (so-called **tissue macrophages**) are activated. Macrophages are scavenger cells that play a crucial role in the inflammatory response. These cells have specific receptors on their surface which help them to identify external (exogenous) and internal (endogenous) material such as damaged tissue particles and cells (DAMPs), pathogens and their products (PAMPs), and other foreign material. When macrophages identify and recognize exogenous or endogenous particles by their specific surface receptors (PRRs), they become activated.[3,13,15]

Once activated, they start to engulf, digest, and degrade the particle by a process called phagocytosis, efficiently eliminating particles from the tissue. Macrophages also present parts of the digested particle on their surface to other immune cells, thus supporting and accelerating particle recognition.[1,16] Furthermore, macrophage activation results in the release of pro-inflammatory mediators (cytokines and chemokines) into the tissue and blood, attracting more immune cells to the site of injury. This process is called **chemotaxis**.[3,13]

The dilation of blood vessels and their increased permeability facilitate the migration of additional immune cells into the injured tissue. Circulating

neutrophils are attracted to the site of tissue injury, efficiently eliminating invading pathogens by the release of toxic material and by phagocytosis.[13,17] Neutrophils are immune cells that survive only a couple of days, which later becomes important to the resolution of acute inflammation.[13] Once damaged tissue, dead cells, pathogens, or foreign material are removed from the injured tissue, macrophages initiate the resolution of the inflammatory response.

Following the inflammatory phase, anti-inflammatory mediators and growth factors are released to suppress inflammation and initiate the proliferative phase.[18] During the proliferative phase, several tissue repair events, including *angiogenesis* (formation of new blood vessels), *granulation tissue* (new tissue) formation, and *re-epithelialization* (re-establishment of surface layer) are initiated. New connective tissue is formed with *neovascularization* (new vessel formation), with fibroblasts being the key cells accountable for constructing granulation tissue to fill in the wound gap.[13] Figure 2 shows the acute inflammatory response using the example of a penetrating skin injury .

From acute to chronic inflammation: The undesired immune response

The acute inflammatory response is a highly coordinated process, with different immune cells and various pro- and anti-inflammatory cascades tightly controlled in an equilibrium. Thus, the acute inflammatory response is a quick, strong, highly efficient process which usually lasts only a few days. In some cases, however, the acute inflammation does not resolve and progresses from subacute to chronic inflammation (Figure 3).[5]

Chronic inflammation is characterized by continuous, unresolved, and uncontrolled activation of inflammatory cells and mediators, which differ from those of the acute inflammatory response. Chronic inflammation is referred as slow, long-term inflammation which can last for prolonged periods (months to years[6]). The causes of chronic inflammation can vary and are due to (but not limited to) failure of eliminating the agent causing the inflammation (infectious organisms), to constant low-level exposure of a foreign material, to an autoimmune disorder, to a defect in cells responsible for mediating the inflammatory response, to recurrent episodes of acute inflammation and to other inflammatory mediators.[6]

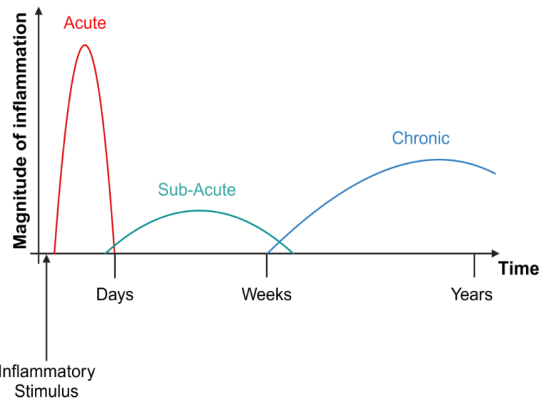

Fig. 3: Phases of inflammation.

Generally, inflammation can be divided into three phases: acute, sub-acute and chronic inflammation. After an inflammatory stimulus, the acute inflammatory response is immediately activated, a strong phase that usually lasts only a couple of days. If the acute inflammatory response does not resolve, it progresses from the sub-acute to the chronic stage, which can persist for a varying length of time.

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Most features of acute inflammation continue as the inflammation becomes chronic such as the dilation of blood vessels, increased blood flow, capillary (blood vessel) permeability, and migration of immune cells into affected tissue.[6] However, the composition of immune cells changes drastically, and short-lived immune cells are replaced by cells from the adaptive immune system (macrophages, lymphocytes, and plasma cells). Thus, the hallmarks

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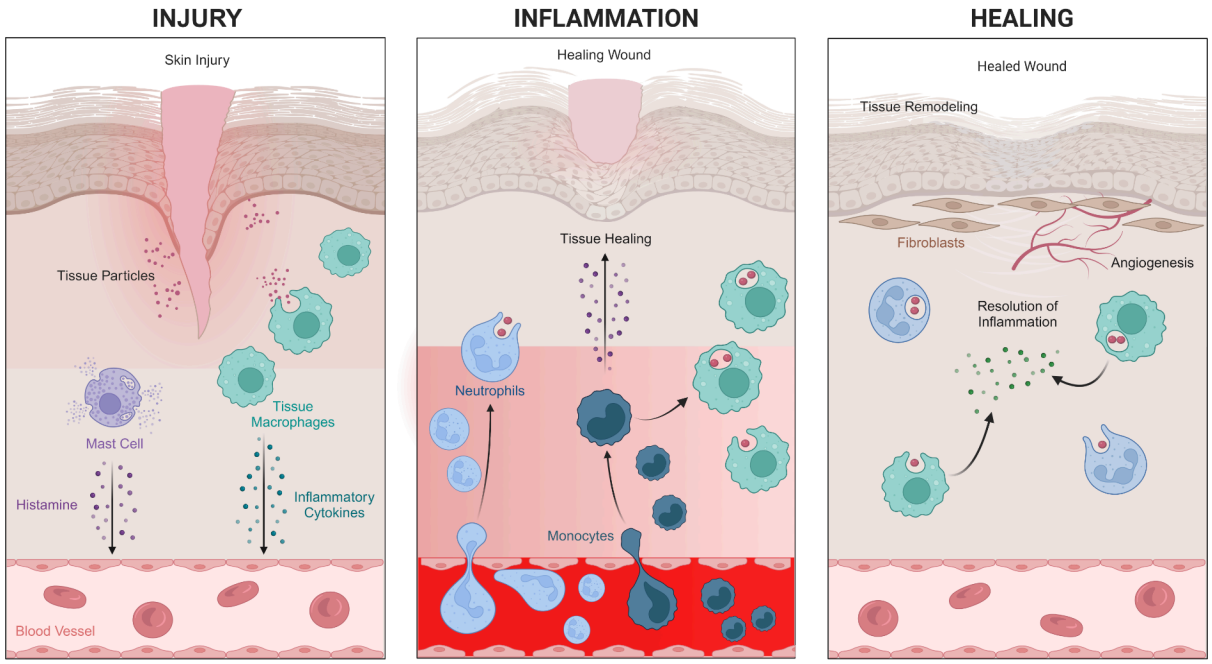

Fig. 2: The acute inflammatory response is exemplified by a skin injury. Injury to cutaneous and sub-cutaneous tissue immediately triggers an acute inflammatory response.

Injury: Mast cells (*purple cells*) in subcutaneous tissue are activated and release transmitters such as **histamine (*purple dots*)**, stimulating the dilation of blood vessels. Also, tissue-resident **macrophages (*green cells*)** become activated by particles from **injured tissue and damaged cells (DAMPs) (*pink dots*)**. Activation of macrophages triggers the release of inflammatory **cytokines (*green dots*)** into the tissue. Also, the macrophages start to engulf the damaged tissue particles.

Inflammation: Inflammatory cytokines and DAMPs attract additional immune cells to the site of tissue injury. Circulating **neutrophils (light blue cells)** migrate into injured tissue and start to remove tissue particles. Circulating **monocytes (dark blue cells)** also migrate into injured tissue and differentiate into macrophages. Neutrophils and macrophages engulf, digest, and remove damaged tissue particles, then release factors stimulating **tissue healing (dark purple dots)**.

Healing: Macrophages release **anti-inflammatory mediators (green dots)**, resulting in the resolution of the tissue inflammation. New blood vessels are formed **(angiogenesis)**. **Fibroblasts (brown cells)** form new connective tissue. *This figure is adapted from "The Inflammatory Response," created by Danielle Penk using BioRender.com, 2024. Retrieved from https://app.biorender.com/biorender-templates.*

of chronic inflammation are infiltration of immune cells into affected tissue, which constantly release pro-inflammatory mediators, growth factors, and enzymes.[6] Despite ongoing attempts at tissue repair, the constant and chronic activation and infiltration of immune cells lead to tissue damage (necrosis), granuloma (aggregate of immune cells) formation, and fibrosis (scar formation), eventually resulting in damaged or non-functional fibrotic tissue.[3,6] Irreversible tissue damage can further fuel inflammatory processes, weaken the immune system, and potentially predispose the body to other disease and infection.[2]

Under the Microscope:

The body's immune response to biomaterials and medical devices

The ability of a biomaterial to perform its intended function in the body depends on many factors, but the ultimate determinant of its success or failure is the host response.[19] The host reaction begins immediately after implantation and consists of the reaction to the surgically induced tissue injury and to the material itself. Usually, the response to surgery-related tissue injury resolves quickly as part of the wound healing process.[19] The reaction to the material lasts as long as the material is present in the body and depends on several factors related to either the material or the host.[19] Inflammation, healing, and foreign body reaction (FBR) are the earliest host responses following implantation.[20,21]

The process of wound healing after total joint arthroplasty surgery

Total joint arthroplasty (TJA) is a successful technique to replace and preserve the form and function of major joints such as hip, knee, and shoulder. The majority of today's orthopedic implants have good biocompatibility and osseointegration potential and a controlled implantation-induced inflammatory response. Wound healing is a normal biological process that takes place in four precisely programmed phases:

1. **Hemostasis,**
2. **inflammation,**
3. **proliferation,**
4. **and remodeling.**[22]

For proper wound healing, all four phases must occur in the correct order and time frame.[22] Here, we focus particularly on the inflammatory phase during wound healing after TJA.

After TJA, surgery-related tissue injury triggers an inflammatory response and a sequence of events in the surrounding tissue with the aim of wound healing and proper reconstitution of tissue at the implant site.[23] Table 1 lists the sequence of the host events following tissue injury in periprosthetic soft- and bone tissue. It is important to mention that the inflammatory response and wound healing process after biomaterial implantation is dependent on the tissue- and site of implantation. Therefore, the wound healing process and FBR of subcutaneously implanted materials can differ from those that take place in the periprosthetic soft and bone tissue after TJA.[20,23,24] In this review we are focusing on the latter. The process of periprosthetic soft and bone tissue are demonstrated in figure 4 and 5.

Table 1: Periprosthetic tissue reaction after implantation: A comparison between soft tissue and bone

PERIPROSTHETIC SOFT TISSUE REACTION	PHASE	PERIPROSTHETIC BONE TISSUE REACTION
Formation of a provisional matrix	1	Formation of a provisional matrix
Acute inflammation	2	Acute inflammation
Chronic inflammation	3	Chronic inflammation
Early macrophage response to particles of wear debris	4	Woven bone formation
Joint capsule healing and formation of neo-synovium	5	Lamellar bone formation. Remodeling of the bone-implant interface

Phases of wound healing in the periprosthetic soft tissue

Formation of a provisional matrix: After the implantation of a periprosthetic device, blood-material interactions occur with protein adsorption on the biomaterial surface and the development of a thrombus-blood clot at the tissue-material interface. An injury to the vascularized tissue during the implantation procedure immediately activates the innate immune system and initiates blood coagulation. Complex reaction cascades of blood coagulation and the innate immune response result in the formation of a thrombus on the implant surface. This thrombus is considered a provisional matrix, providing structural, biochemical, and cellular

components, which are important for the processes of wound healing and foreign body reaction. The formation of a provisional matrix is usually completed within a week, followed by the phases of acute and chronic inflammation in a sequential fashion.[20,23,25]

Acute inflammation: The acute inflammatory phase is characterized by the infiltration of short-living immune cells and mast cell degranulation. These immune cells release pro-inflammatory mediators and vasoactive substances, attracting and recruiting other immune cells, particularly macrophages to the site of injury. The phase is usually completed within a week.[20]

Chronic inflammation and joint capsule healing: The phase of chronic inflammation follows the acute inflammatory phase. It is important to mention that this phase is specific for the tissue wound healing process and differs from the clinical definition, describing a slow, long-term inflammation which can last up to several years. Chronic inflammation during periprosthetic wound healing typically lasts two to three weeks. This phase is characterized by the infiltration of monocytes, which differentiate in the tissue into macrophages, and of other white blood cells (lymphocytes). The phase of chronic inflammation is followed by the formation of granulation tissue. Granulation tissue is a specific kind of tissue which is the hallmark of healing. It derives its name from the pink, soft, granular appearance on the surface of healing wounds. This tissue is characterized by formation of new small blood vessels and by the presence of macrophages and fibroblasts, which produce new connective tissue. The formation of granulation tissue eventually results in healing of the joint capsule.[23]

Importantly, the persistence of an inflammatory response beyond three weeks may indicate an infection, the onset of an abnormal reaction to the implant, or a combination.

Early macrophage response to particles of wear debris: This phase is unusual during the wound healing process in the joint. The formation of so-called foreign body giant cells (FBGCs) will be addressed later in this review. It is important to mention that, during the process of periprosthetic wound healing, this cellular reaction only occurs in presence of orthopedic cement. The formation of FBGCs usually starts later in the presence of wear particles from the implant. Nanoparticulate wear debris may be present earlier in periprosthetic tissue after joint implantation but is difficult to quantify due to the limited availability of clinical samples.

Phases of periprosthetic bone reaction

Generally, peri-implant bone healing is analogous to intramembranous bone healing after fracture. It is composed of two phases: an **early phase** (consisting of phases 1-4) and a **late phase** (consisting of phase 5). The phases of periprosthetic bone healing after joint implantation have mostly been investigated in experimental but not in clinical studies.

Formation of a provisional matrix and acute inflammation: Both phases are similar to those occurring in periprosthetic soft tissue and last up to two weeks.

Chronic inflammation: Similar to the periprosthetic tissue, the phase of chronic inflammation is characterized by the presence of monocytes, which differentiate into macrophages. Additionally, various signaling molecules such as pro-inflammatory mediators, growth factors, and angiogenic factors are released into the peri-implant space. Thisresults in the recruitment, migration, and differentiation of mesenchymal stem cells (MSCs), which are important for woven (**primary**) bone formation.[26]

Woven bone formation: MSCs differentiate either into bone-forming cells (osteoblasts), forming immature primary (woven) bone or into fibroblasts, forming fibrous membrane at the implant surface.[27] Two types

of bone formation (**osteogenesis**) occur: a) contact osteogenesis directly on the surface of the implant, and b) distance osteogenesis from the tissues surrounding the implant.[28]

Late remodeling of bone-implant interface: After formation of woven bone, bone remodeling occurs through specific bone cells (osteoclasts and osteoblasts), gradually transforming the provisional woven bone into the lamellar bone. This dynamic process occurs for one year or longer and is necessary for successful long-term fixation[27].

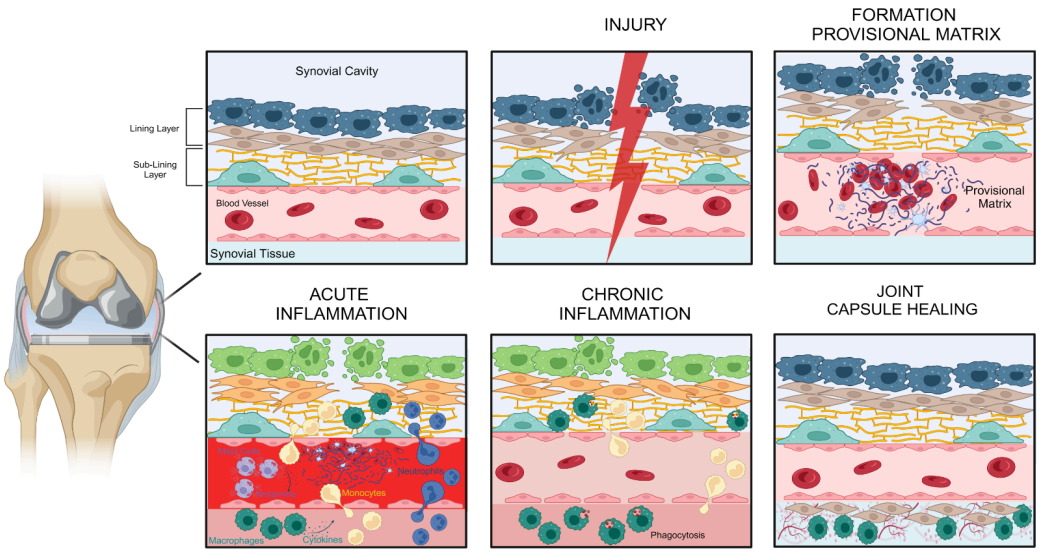

Fig. 4: Periprosthetic soft tissue reaction after TJA.

After total or partial joint arthroplasty, surgery-related tissue injury triggers an inflammatory response and thus a sequence of events in the surrounding tissue with the aim of wound healing and proper reconstitution of tissue at the implant site. Periprosthetic soft tissue healing is exemplified in the synovial membrane and the synovial soft tissue of a knee joint. The synovial membrane comprises a lining layer with lining **macrophage-like synoviocytes (dark blue cells)** and lining fibroblast-like synoviocytes **(brown cells)**. The sub-lining layer comprises extracellular matrix (yellow scaffold) and telopode-bearing telocytes **(mint green cells)**. The inflammatory status in the synovial membrane before partial or total joint arthroplasty surgery is presented in an oversimplified way. Patients receiving partial or total joint arthroplasty due to osteoarthritis usually exhibit varying degrees of chronic inflammation in the synovium before surgery.

Injury: During surgery, the synovial membrane and the synovial tissue with blood vessels get disrupted, resulting in tissue injury.

Formation of provisional matrix: Following injury, the immune system and the coagulation system get immediately activated and a **blood thrombus** (***blue scaffold***) with **erythrocytes** (***red blood cells***) and **activated platelets** (***light blue cells***) is formed, which provides a provisional matrix.

Acute inflammation: **Mast cells** (***purple cells***) are activated, releasing **histamine** (***purple dots***) into tissue, stimulating dilation of blood vessels. **Tissue-resident macrophages** (***dark green cells***) become activated, releasing **inflammatory cytokines** (***green dots***) into **tissue. Neutrophils** (***blue cells***) and **monocytes** (***yellow cells***) are attracted and migrate into injured tissue. **Lining macrophages** (***light green cells***) and **fibroblasts** (***brown cells***) become activated in synovial membrane. Macrophages and neutrophils in injured tissue start to engulf and digest damaged tissue particles.

Chronic inflammation: Monocytes migrate into injured tissue, differentiating into macrophages. Macrophages digest and remove damaged tissue particles and induce tissue healing.

Joint capsule healing: **Granulation tissue** (***pink tissue with pink dots***) is formed by **fibroblasts** (***brown cells***). New blood vessels are formed (angiogenesis).

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Adverse Local Tissue Reactions (ALTRs)

Although orthopedic implants have good biocompatibility and osseointegration potential, **adverse local tissue reactions** (ALTRs) can occur. With imaging techniques, ALTRs appear as thickened pseudocapsules and extraarticular fluid extensions.[29,30] ALTRs comprise a range of histological patterns, ranging from purely macrophagic to mixed lymphocytic and macrophagic with or without features associated with hypersensitivity, and predominant sarcoid-like granulomas.[31]

The main symptoms of ALTR are pain and swelling. ALTR can result in extensive destruction of joint tissue, challenging the prognosis for further clinical solutions.[32-34] ALTRs are described as soft or solid masses, in which the loss of the synovial surface with or without fibrin deposition, is accompanied by sub superficial necrosis, mononuclear cell infiltration and variable number of immune cells and giant multinucleated cells (FBGCs), in a thickened synovial membrane composed of dense connective tissue.[34-37] ALTRs are associated with aseptic loosening and implant revision. The immune system, particularly the chronic inflammatory response to a foreign implant material, plays a critical role in the development of ALTR.[34] The term chronic inflammation used in the context of ALTR describes the process of persistent, low-grade, long-term inflammation which can last several years. The pathogenesis of chronic inflammation and ALTR can depend on the host immune reaction to the implant material itself and, to implant wear particles.[38,39] Other factors, such as, surgery[40,41], infection, the patient's underlying condition and patient-related risk factors can further contribute to and/or aggravate the development of ALTR.[42]

Orthopedic wear particles trigger an inflammatory response in the periprosthetic environment

Despite the biocompatibility of the materials used and the improvements in implant design, material, and surgical techniques, factors such as mechanical forces, chemical reactions, material degradation, and biological interactions in the joint space can generate micro- and/or nano-scale wear debris originating from the implant bearing surface and junctions, which can trigger an inflammatory response.

Macrophages play a crucial role in wear particle-induced periprosthetic tissue inflammation and bone resorption

Macrophages are the key immune cells responsible for the elimination of wear particles.[43] Macrophage activation by wear particles is the dominant mechanism of wear particle-induced periprosthetic soft tissue- and bone inflammation.[44] The macrophage reactivity is dependent and driven by chemical and physical features of the particles themselves.[45] Macrophages recognize wear particles as foreign material by specific receptors on their cell surface. The wear particles are then engulfed by the cells in processes called endocytosis and phagocytosis, removing them from the tissue. Once engulfed by macrophages, the wear particles either degrade or accumulate in the cell cytoplasm. The activation of the macrophages results in the release of pro-inflammatory mediators, which recruit further immune cells to the site of wear particle accumulation, triggering a local tissue inflammation. Moreover, the release of pro-inflammatory mediators and other factors from macrophages activate bone-resorbing cells (osteoclasts), inducing osteolysis.[46,47] Osteolysis is the process of progressive destruction of periprosthetic bone tissue.[48] Histopathologic observations from clinical samples and experimental studies indicate that particle-laden macrophages might also be able to directly induce osteolysis by migrating into the bone microenvironment and interacting with osteoclasts.[49-51] The macrophages also interact with stroma, endothelial cells of the capillary vessels, and other cell types associated with inflammation.[45,52] Depending on particle size, material, and tissue concentration, this reaction can

Under the Microscope:

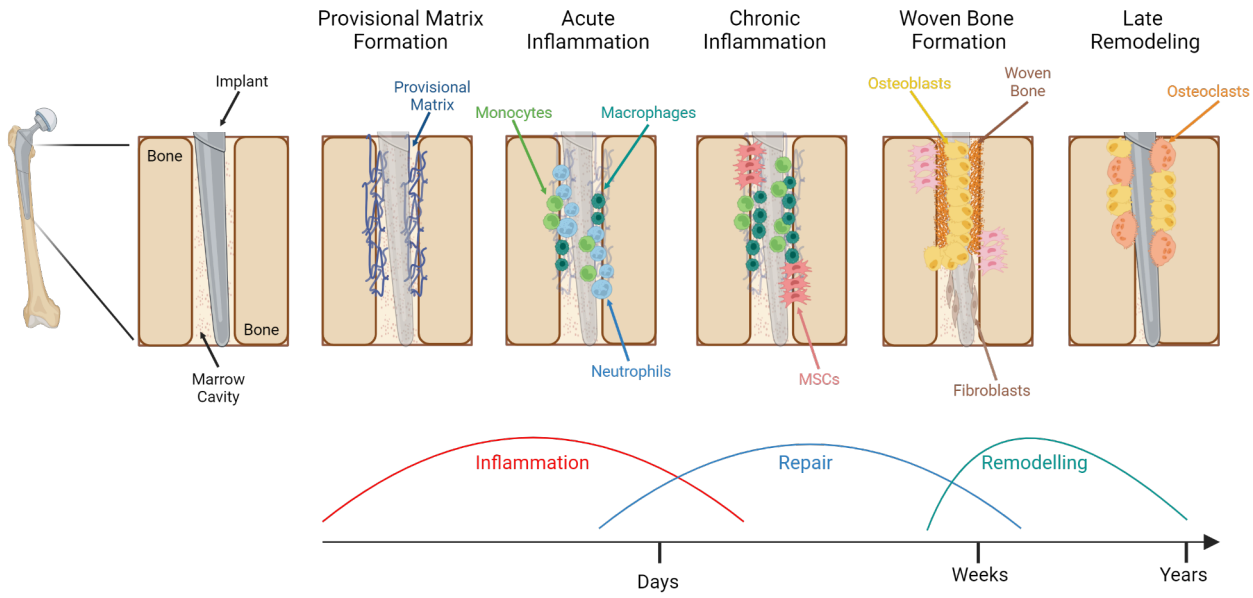

Fig. 5: Periprosthetic bone reaction after TJA.

After TJA, periprosthetic bone healing occurs between the implant and the bone surface, properly integrating the implant into bone tissue. The process of periprosthetic bone healing is exemplified with a hip implant in the femoral shaft.

Provisional matrix formation: Following TJA, a **provisional matrix (*blue scaffold*)** is formed in the peri-implant space.

Acute inflammation: **Macrophages (*dark green cells*)** are activated and release inflammatory cytokines into peri-implant space. **Neutrophils (*blue cells*)** and **monocytes (*light green cells*)** are attracted and migrate into peri-implant space. Damaged tissue particles are removed.

Chronic inflammation: Monocytes infiltrate into peri-implant space and differentiate into macrophages. M**esenchymal stromal cells (*MSCs, pink cells*)** are recruited.

Woven bone formation: MSCs differentiate into **osteoblasts (*yellow cells*)**, forming immature primary woven bone. **Fibroblasts (*brown cells*)** adhere on implant surface, forming a fibrous membrane.

Late remodeling: Bone remodeling through osteoblasts and **osteoclasts (*orange cells*)**, eventually transforming the woven bone into lamellar bone.

Figure created with BioRender.com, 2024.

lead to constant activation of macrophages, release of pro-inflammatory mediators, and cell recruitment, resulting in a prolonged and chronic periprosthetic tissue inflammation, periprosthetic osteolysis, and bone resorption.[53] Wear particle-induced chronic inflammation and osteolysis are associated with long-term implant failure and aseptic loosening, particularly at later stages after arthroplasty, and can result in revision surgery.[45,53,54] Figure 6 depicts a macrophage reaction to wear debris.

In cases of hypersensitivity, the adaptive immune system is activated primarily in response to metal ions, causing an inflammatory response.[55-57]

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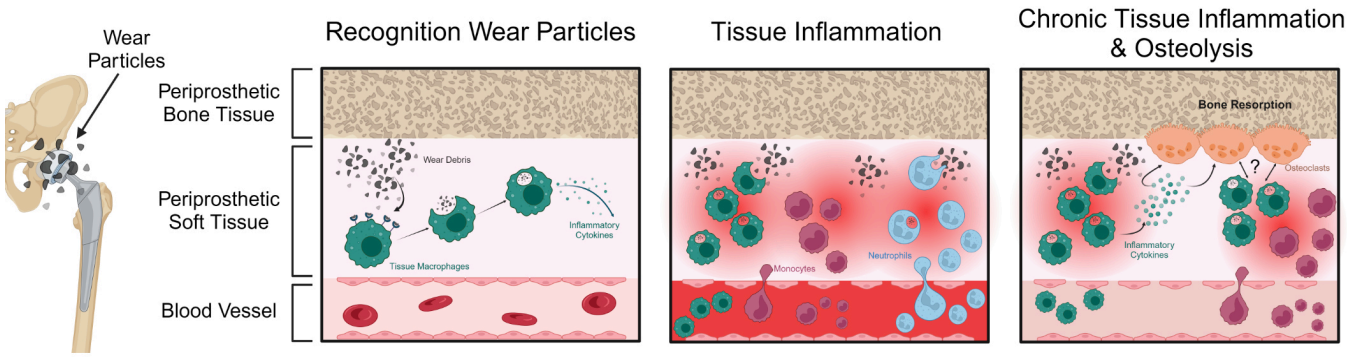

Fig. 6 : The macrophage reaction to wear debris is exemplified by a hip implant. Wear debris from implant bearing surface is generated and released into joint space.

Recognition wear particles: **Tissue-resident macrophages (*green cells*)** in periprosthetic soft tissue recognize wear debris particles by specific receptors on their surface and become activated. Macrophages start to engulf and digest wear particles by phagocytosis and release **inflammatory cytokines (green dots)** into the periprosthetic tissue.

Tissue inflammation: Inflammatory cytokines attract other immune cells to the site of wear particle accumulation. **Neutrophils (*light blue cells*)** and **monocytes (*dark red cells*)** migrate into tissue. Monocytes differentiate into macrophages. Macrophages and neutrophils engulf and digest wear particles.

Chronic tissue inflammation and osteolysis: Depending on size/shape, material and tissue concentration of wear particles, the acute inflammatory response does not resolve and progresses into a chronic tissue inflammation. Monocytes constantly migrate into tissue, differentiating into macrophages. Activated, particle-laden macrophages persistently release pro-inflammatory cytokines into periprosthetic tissue, maintaining chronic tissue inflammation. Furthermore, the released cytokines as well as particle-laden macrophages themselves activate **osteoclasts (*orange cells*)**, which then start to resorb the periprosthetic bone, resulting in periprosthetic osteolysis.

Figure created with BioRender.com, 2024.

Wear particle-induced formation of Foreign Body Giant Cells (FBGCs)

As mentioned, the formation of so-called **foreign body giant cells** (FBGCs) is part of the **foreign body response** (FBR) to an implant during wound healing in subcutaneous tissue but is extremely unusual during periprosthetic wound healing in the joint after TJA. However, FBGCs can form in later stages of wear particle-induced periprosthetic inflammation. They are the consequence of macrophage–macrophage fusion, resulting in a giant cell with multiple cell nuclei. Usually, small wear particles are efficiently degraded and eliminated by macrophages. FBGCs form either when phagocytosis is an insufficient primary mechanism of material degradation or when wear particles or when agglomerates/aggregates are in a size range between 10-100 µm.[20,58,59]

The term **'frustrated phagocytosis'** describes the formation of FBGCs in presence of orthopedic cement or very large particles, which impair FBGC function and thus inhibit phagocytosis of these large particles. Importantly, FBGCs have also been found in granulomatous diseases in absence of any particulate debris. Figure 7 shows the formation of FBGCs.

Under the Microscope:

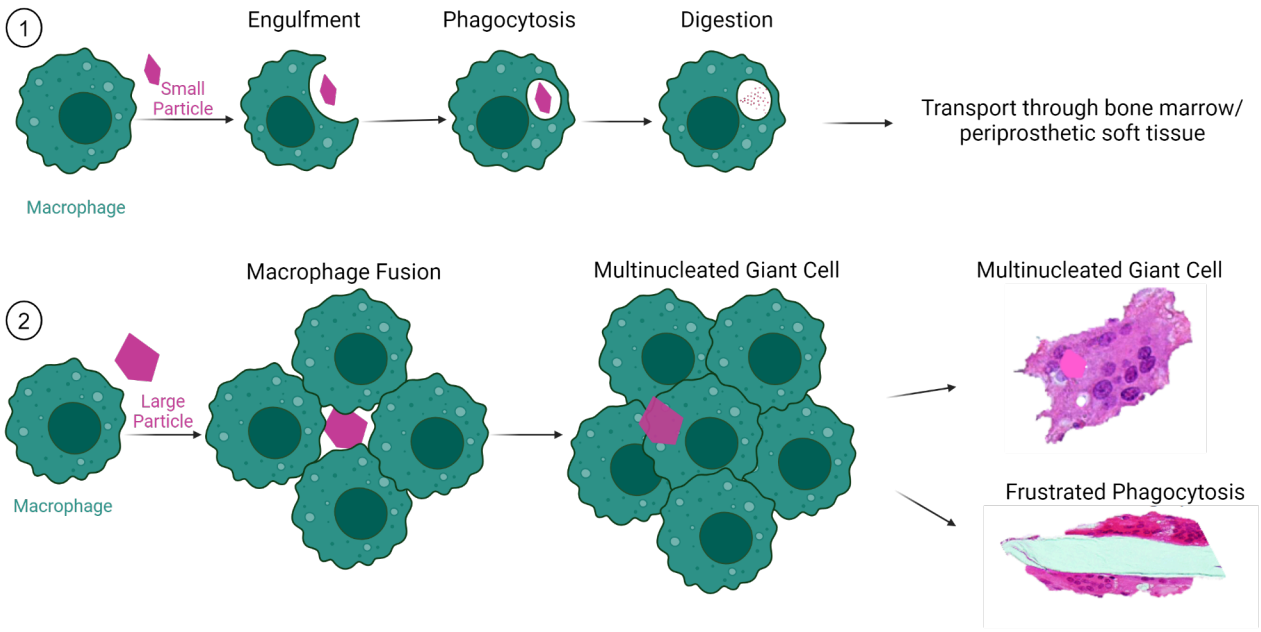

Fig. 7: Formation of Foreign Body Giant Cells (FBGCs).

The formation of FBGCs is presented in a simplified way.

1: A **small debris particle (purple particle)** is recognized by a macrophage (green cell). The macrophage starts to engulf and phagocytose the particle, resulting in the digestion of the particle. These particle-laden macrophages are further transported in periprosthetic bone tissue and marrow and in periprosthetic soft tissue.

2: A **large debris particle** is recognized by a macrophage but cannot be digested because of its size. This leads to the accumulation and fusion of multiple macrophages around the large particle. The fusion of multiple macrophages results in the formation of a multinucleated giant cell, and in some cases in frustrated phagocytosis.

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The immunological profile of different orthopedic wear particles

Wear particles from orthopedic implants have been shown to cause an inflammatory response in the periprosthetic tissue (Figure 8).[60] Determination of implant wear (particulate and non-particulate state) in soft tissue and in bone or bone marrow is important to link the observed adverse tissue reactions to the implant. Local particle presence has mostly been studied in the peri-implant membrane and synovial fluid, but not comprehensively in the adjacent bone and bone marrow due to limited availability of clinical samples.

The shape and type of released wear particles influence the inflammatory response,[45,61] and tissue alterations and morphology differ macroscopically and microscopically.[62] The type of implant material is the driving factor for the development of chronic inflammation. There are differences in the immuno-compatibility of orthopedic materials, which appear to differently shape the peri-implant microenvironment.[49] The following section describes different orthopedic implant materials and the immunological profile of their wear particles:

Polyethylene (PE) wear debris: Ultra-high-molecular-weight polyethylene (UHMWPE) particles activate

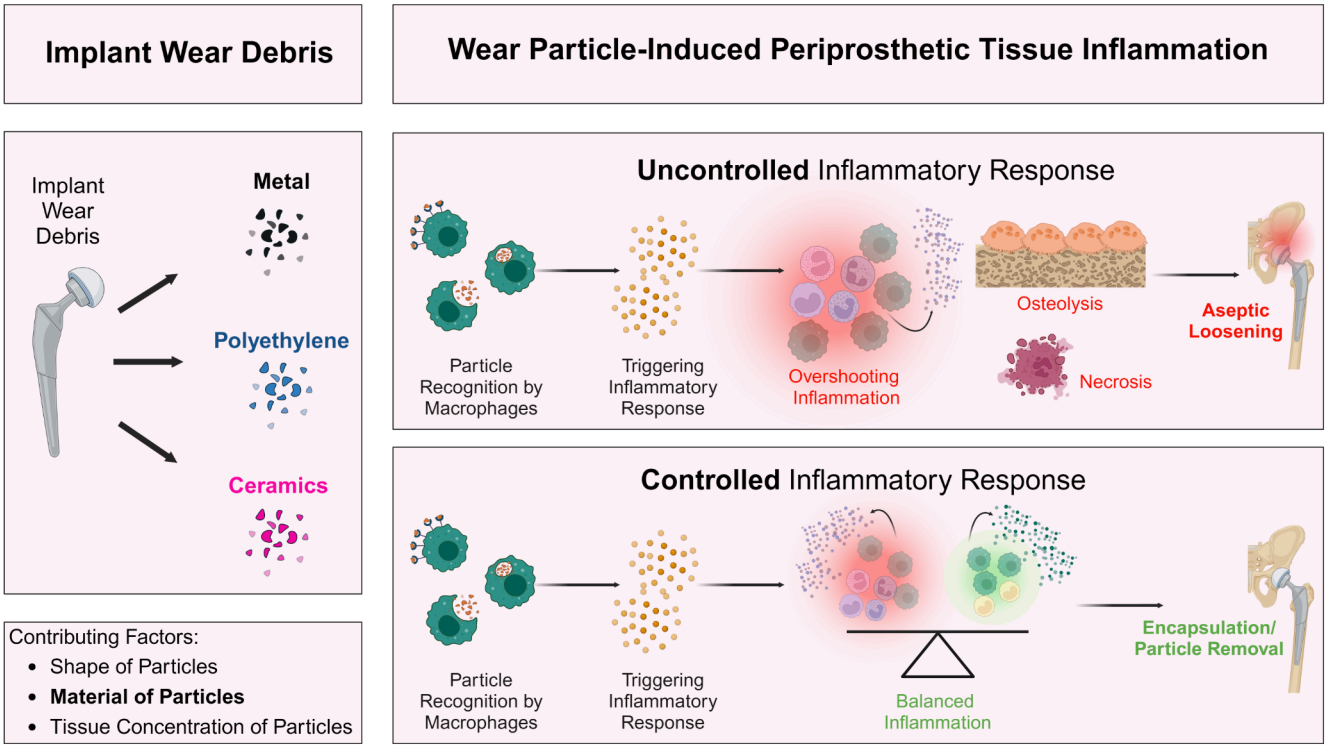

Fig. 8: Implant wear debris and wear particle-induced periprosthetic tissue inflammation.

Wear debris is generated from the bearing surface of an implant. Based on the bearing surface, the wear debris can be of different material, such as metal, polyethylene, or ceramics. The contributing factors for the development of wear particle-induced periprosthetic tissue inflammation are the particles' shape and size, tissue concentration, and material. The material isthe driving force for tissue inflammation. Wear particles in periprosthetic tissue are considered foreign bodies and thus trigger an inflammatory response. **Wear debris particles (orange particles)** in periprosthetic tissue are recognized by **macrophages (green cells)** via specific surface receptors. Macrophages are activated and phagocytose these particles. Activated macrophages release inflammatory **cytokines (orange dots)**, triggering an inflammatory tissue response. Depending on particle shape/size, tissue concentration, and material, this can result in an overshooting and chronic inflammatory response, causing tissue necrosis and osteolysis. An uncontrolled inflammatory response is associated with aseptic loosening of the implant. A controlled wear debris-induced inflammatory response is characterized by a well-balanced pro- and anti-inflammatory response, which eventually results in encapsulation of the implant and in particle removal.

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macrophages by different inflammatory signaling pathways[63] and initiate the release of pro-inflammatory mediators, causing osteoclastogenesis and bone resorption.64

UHMWPE generates relatively large amounts of volumetric wear when interfacing with the metallic head of hip implants. Therefore, carbon crosslinking methods such as gamma irradiation, chemical induction, and addition of antioxidant agents have been implemented to increase material wear resistance[65] in an attempt to minimize the pro-inflammatory response and incidence of complications.[66]

Polymethylmetacrylate (PMMA) wear debris: PMMA particles from radiographic contrast material have been shown to activate macrophages via multiple inflammatory signaling pathways.[67,68]. Consequently, PMMA particles can cause inflammation, osteoclastogenesis, and osteolysis.[69]

Metal wear debris: The generation of metallic debris is still a matter of great concern regarding periprosthetic osteolysis. Cobalt, nickel, and titanium implant particles were shown to activate macrophages via different inflammatory signaling pathways,[70-74] resulting in periprosthetic chronic inflammation and osteolysis. As mentioned above, metal ions were also shown to cause a delayed type of hypersensitivity by activating cells of the adaptive immune system (T-cells), which may also contribute to aseptic loosening.[55,57,75-77] However, only experimental studies have been performed so far. Whether the adaptive immune system additionally contributes to metal particles/ions-induced aseptic loosening is still a matter of intense debate, and more studies are needed for clarification.

Ceramic wear debris: Ceramic-on-ceramic implants have been proposed as the best option for young and active patients.[78,79] These implants display minimal wear-debris generation, with limited incidence of osteolysis and long-term survival rates.[78,79] Alumina has been shown to have a low cellular immunotoxicity. Alumina particles were further demonstrated to have only limited capacity to stimulate the release of pro-inflammatory mediators from human macrophages[80], and high concentrations of alumina ceramic particles induced only a weak up-regulation of mediators for osteoclastogenesis.[81] Also, pathogenic reactions to ceramic wear particles are considered as unlikely.[82] Moreover, alumina is considered hypoallergenic material, providing a valuable alternative for patients with metal hypersensitivity.[83,84]

Conclusion

In conclusion, inflammation is an essential, multifactorial but complex whole-body response that can have harmful effects under certain conditions. Inflammation plays a crucial role in wound healing after TJA but is also associated with the development of adverse local tissue reactions (ALTRs), which can lead to implant revision. While early-stage ALTRs are related to surgical techniques, implant material and design, and patient-related risk factors and predispositions, late-stage ALTRs are associated with chronic inflammation caused by wear debris from the implant. The best solution to avoid multiple revisions due to ALTR is prevention by avoiding the use of biomaterials that promote ALTR. This can be achieved by choosing biomaterials with low toxicity, high biocompatibility, hypoallergenic properties, and low pro-inflammatory potential, such as (for example) ceramics.

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Summary

Inflammation is a natural, whole-body response triggered by the immune system. The immune system performsessential functions such as combating pathogens, eliminating foreign bodies, initiating wound and fracture healing, initiating tissue repair and reconstitution, and re-establishing tissue homeostasis after injury. The inflammatory response is a complex but tightly regulated process involving many cells and signaling pathways. The acute inflammatory response is a strictly regulated but temporarily limited process; butit can turn into long-term, low-grade chronic inflammation, which is an undesirable and harmful process.

One must take caution when talking about chronic inflammation. The term is often used for different inflammatory processes, which is why it is very important to specify the respective process. As explained, chronic inflammation during wound healing after TJA differs from chronic inflammation to implanted materials as part of FBR.

TJA is the ultimate solution to replace and preserve the form and function of major joints. The inflammatory response is an indispensable process of wound healing after TJA and the proper reconstruction of tissue at the implant site, which usually resolves within a few weeks. However, patient-related risk factors, pathologic predispositions, surgical techniques, hypersensitivity, orthopedic material, and the presence of implant wear particles can trigger an adverse local tissue reaction (ALTR) associated with low-grade chronic inflammation in periprosthetic tissue, osteolysis and bone resorption. This can result in aseptic loosening, periprosthetic implant failure, and revision surgery.

Wear particles from various orthopedic implant materials have been shown to trigger a local inflammatory reaction, with ceramic particles being the least reactive and therefore only triggering a mild and controlled pro-inflammatory reaction.

The best solution to avoid ALTR-related multiple revisions is prevention by avoiding the use of biomaterials that promote ALTR. Some orthopedic implant materials have a higher likelihood of triggering ALTR due to their physicochemical properties or may lead to potential exacerbation in combination with other material and patient-related risk factors.

Tackling Chronic Inflammation in Joint Replacement

Inflammation is part of the innate biological response to infectious or non-infectious agents. It is a non-specific, essential defense mechanism against injury or intrusion by pathogenic micro-organisms, endogenous (e.g., gout crystals) or exogenous (e.g., implant wear debris) non-biological products.

In autoimmune diseases, this so-called immune system is even activated against the body's own cells, proteins, or other molecules. Local clinical signs of inflammation include heat, redness, swelling, pain, and loss of function.

Based on the onset and duration of the symptoms, inflammation can be categorized as acute, sub-acute, or chronic. Acute inflammation starts immediately after a specific injury or infection and typically lasts only a few days. It is characterized by the release of soluble immune mediators including acute phase proteins such as C-reactive protein, cytokines, and

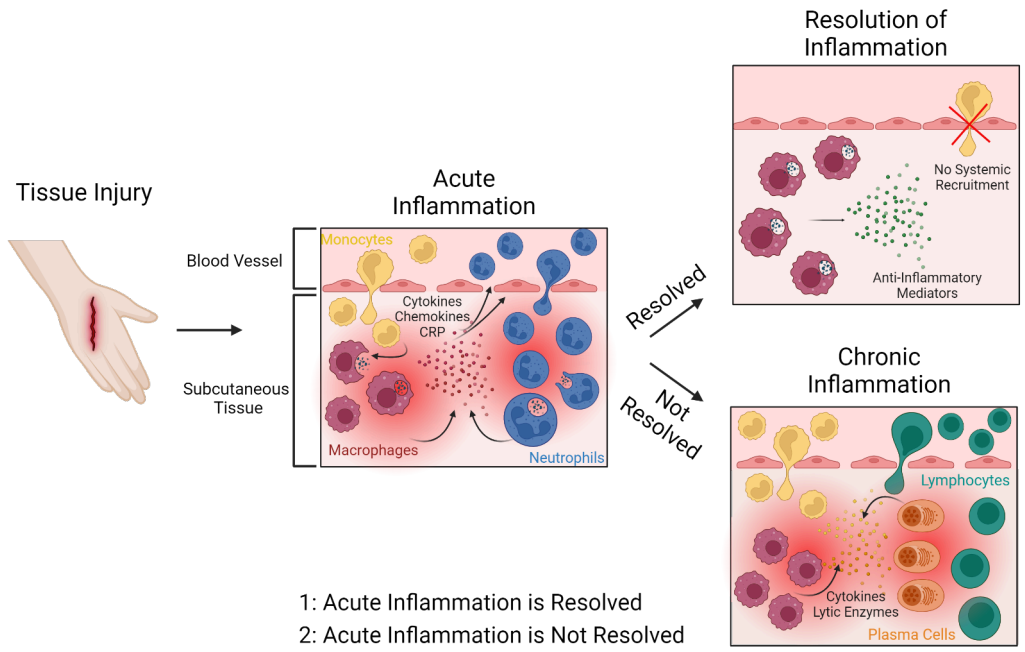

Fig. 1: Acute inflammation, chronic inflammation, and resolution of inflammation. Acute inflammation, chronic inflammation and the resolution of inflammation are demonstrated by an example of skin tissue injury of the hand.

Acute inflammation: Skin injury results in the disruption of subcutaneous tissue and blood vessels. Tissue-resident macrophages (dark red cells) recognize damaged tissue particles and become activated. Activated macrophages start to engulf and digest damaged tissue particles. Furthermore, they release pro-inflammatory mediators such as cytokines, chemokines, and acute phase proteins such as C-reactive protein (CRP) (red dots) into the injured tissue. These pro-inflammatory mediators attract other immune cells to the site of tissue injury. Monocytes (yellow cells) and neutrophils (blue cells) migrate into injured tissue. Monocytes differentiate into macrophages. Neutrophils start to engulf and digest damaged tissue particles. Once damaged tissue particles are removed, tissue healing, and resolution of inflammation are induced. Resolution of inflammation: For the resolution of inflammation, macrophages release anti-inflammatory cytokines (green dots), stopping the pro-inflammatory response and the systemic recruitment of immune cells into the tissue. However, if the acute inflammatory response does not resolve it may progress from sub-acute to chronic inflammation.

Chronic inflammation: Chronic inflammation is characterized by permanent migration of immune cells such as monocytes, lymphocytes (green cells) and plasma cells (orange cells) into the tissue, constantly releasing lytic enzymes and cytokines (yellow and orange dots), thus resulting in a non-resolving, persistent, chronic tissue inflammation. *Figure was created with BioRender.com, 2024.*

chemokines attracting neutrophils and macrophages to the area of injury. These cells initiate the healing process or the elimination of the infectious or non-infectious intruder. The resolution of the inflammatory process involves the controlled production of mediators, and the decrease of chemokine concentrations to reduce and stop the recruitment of white blood cells.[1] If the acute inflammation does not resolve, it may evolve from sub-acute (two to six weeks) to chronic inflammation, which may last for months or even years. Chronic inflammation is sustained by the continued recruitment and infiltration of mononuclear leucocytes such as macrophages, lymphocytes, and plasma cells releasing cytokines and lytic enzymes which may damage the tissue again, thus prolonging the tissue injury followed by secondary repair often associated with fibrosis and granulomatous reactions.[2]

Causes of dysregulation and prolongation of the inflammatory process include failure to eliminate the causative agent, which is either a resistant microbial pathogen or a substance that cannot be phagocytosed or broken down enzymatically (such as wear debris from articulating surfaces) as well as factors causing oxidative stress (increased release of free radicals, advanced glycation end products (AGEs), urate crystals, oxidized lipoproteins, etc.).

In the context of orthopaedic implants, the pathogenesis of chronic inflammation often involves a complex, intricate and multifactorial cascade of immune reactions related to the implant material, to the surgery, to an associated (low-grade) infection, and/or to the patient's underlying condition. Discerning an aseptic chronic inflammatory syndrome from a chronic low-grade infection is difficult, as they are often concomitant and related. The presence of the implant itself as a foreign body constitutes a major risk factor for the onset, prolongation, and persistence of both inflammation and infection. As described above, the protracted inflammatory process may cause tissue damage, fibrosis, and granulomatosis. The natural immunological defense may fail to eliminate microorganisms in this compromised environment. Additionally, bacteria are attracted to implant surfaces to which they may attach, and subsequently colonize and form biofilms, acting as a physical barrier protecting the bacteria from immunocytes and antibiotics.[3] These biofilms may also prohibit osseointegration and eventually lead to implant loosening. Again, the differentiation between aseptic and low-grade septic loosening is often difficult and interrelated.

Clinical symptoms and diagnostic tests for chronic Inflammation

Symptoms of chronic inflammation may vary from local pain, swelling, and dysfunction to more generalized arthralgia, myalgia, and malaise. Systemic symptoms may include subfebrile fever, fatigue, weight loss or gain, neurological and gastrointestinal symptoms, higher susceptibility to infection, insomnia, anxiety, and depression. Chronic inflammation represents a threat to the global health of the individual and is associated with higher morbidity and mortality.

Currently there are no specific laboratory tests for the diagnosis of chronic inflammation. Good serum markers of inflammation include hs (high-sensitivity) C-reactive protein and fibrinogen but are not specific to chronic inflammation; they are also elevated in cases of acute inflammation or infection. These standard tests are inexpensive and can be performed in routine medical laboratories. Specific tests of proinflammatory cytokines such as interleukin 6 (IL-6) are more expensive, not routinely available, and sometimes difficult to interpret.

Imaging techniques may play an important role in the diagnosis and monitoring of chronic inflammation.[4] Besides the conventional and widely used X-ray, CT, MRI, PET/CT, and the more specialized FDG-PET-CT scintigraphy with Tc, Ga, or

Tackling Chronic Inflammation in Joint Replacement

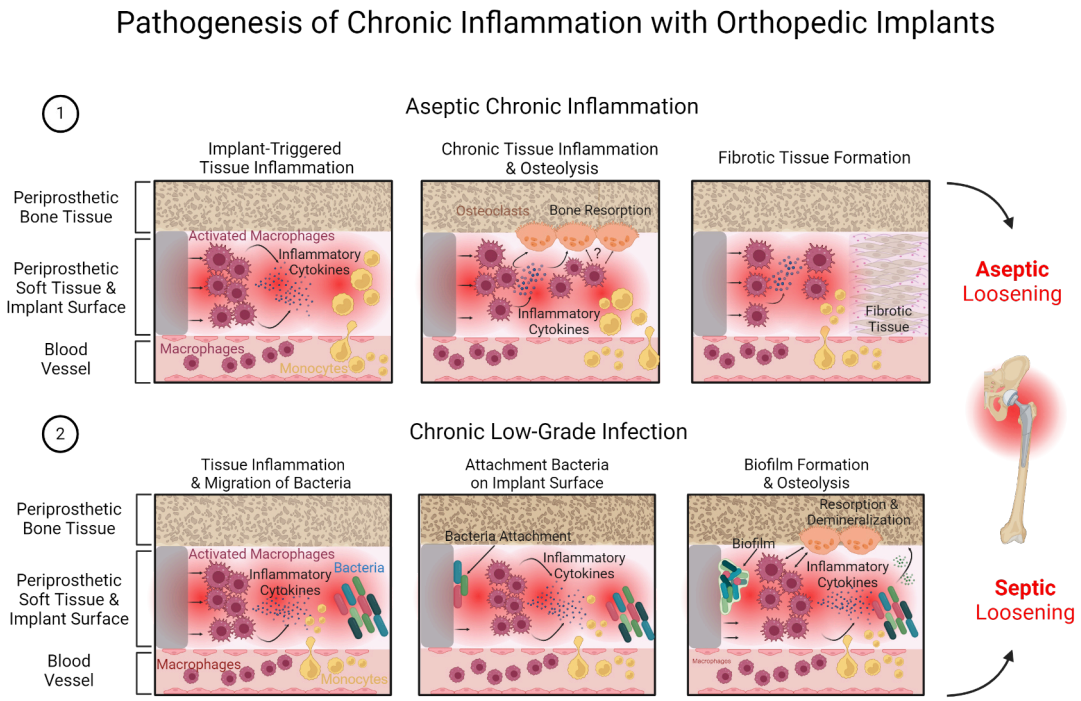

Fig. 2: Pathogenesis of chronic inflammation with orthopedic implants. The pathogenesis of chronic inflammation with orthopedic implants is exemplified by a hip implant. It is very important to distinguish between aseptic chronic inflammation and chronic low-grade infection. 1: Aseptic chronic inflammation. During aseptic chronic inflammation tissue-resident macrophages (dark red spiky-shaped cells) in periprosthetic tissue are permanently activated by the implant material surface. The activated macrophages release pro-inflammatory cytokines (blue dots) and trigger chronic tissue inflammation. Monocytes (yellow cells) are permanently attracted and migrate into periprosthetic tissue. Monocytes differentiate into macrophages, which are then getting activated by material surface promoting the chronic tissue inflammation. During chronic tissue inflammation, the released pro-inflammatory cytokines and activated macrophages themselves activate osteoclasts (orange cells), which then cause bone resorption and periprosthetic osteolysis. Furthermore, chronic inflammation results in the generation of fibrotic tissue (pink tissue, with pink dots), thus replacing functional periprosthetic soft tissue with fibrotic tissue. Aseptic chronic inflammation with implant-triggered tissue inflammation, osteolysis and fibrotic tissue formation is associated with the development of aseptic implant loosening. 2. Chronic low-grade infection. During chronic low-grade infection, macrophages in periprosthetic tissue (dark red spiky-shaped cells) are constantly activated by the implant material surface and release pro-inflammatory cytokines (blue dots). Monocytes (yellow cells) permanently migrate into periprosthetic tissue and differentiate into macrophages. The chronic and compromised tissue inflammation favors the migration of bacteria into periprosthetic tissue, additionally fueling tissue inflammation. The compromised inflammatory response in the tissue is not able to clear bacteria, which then allows them to attach to the implant surface. Once attached to the implant surface, bacteria form a biofilm, which makes them resistant to immune cells and to antibiotic treatment. Activated macrophages and pro-inflammatory cytokines furthermore activate osteoclasts, which then start to resorb bone, resulting in periprosthetic osteolysis. Additionally, bacteria from biofilm release acidic factors (green dots), which cause bone demineralization. Chronic low-grade infection with chronic tissue inflammation, bacteria migration, biofilm formation, osteolysis and bone demineralization is associated with the development of septic implant loosening.

Figure was created with BioRender.com, 2024.

Understanding the Immune Dynamics of Joint Replacement

In-white blood cells, new, highly sophisticated imaging techniques are being developed, to localize sites of inflammation in detail and monitor activity during treatment. These techniques include molecular and multimodal imaging, optical imaging of immune cell trafficking, photoacoustic imaging, MRI sensors for biomarkers, and hyperpolarized MRI for the detection of oxidative stress.[5] These new techniques are expected to facilitate the differential diagnosis between chronic inflammation and low-grade infection in the future.

Patient-related risk factors associated with chronic inflammation.

To mitigate adverse inflammatory effects following an orthopedic intervention such as arthroplasty, it is important to identify certain patient-related risk factors which promote a sustained inflammatory response.

These include:

Age: Advanced age is often associated with increased levels of several inflammatory molecules. The chronic, aseptic, low-grade inflammation occurring in older people is known as **"inflammaging."**
Causes include senescence of cells and of the immune system, with increased circulating cell debris such as mitochondrial DNA associated with mitochondrial dysfunction, accumulation of pro-coagulation factors, free radicals, and reactive oxygen species (ROS), but also the increase in visceral body fat and the disruption of the gut microbiome. All these factors may lead to a chronic stimulation of the innate immune system with continuous release of proinflammatory molecules. Inflammaging is a risk factor for age-related morbidity, including cardiovascular diseases and mortality.[6]

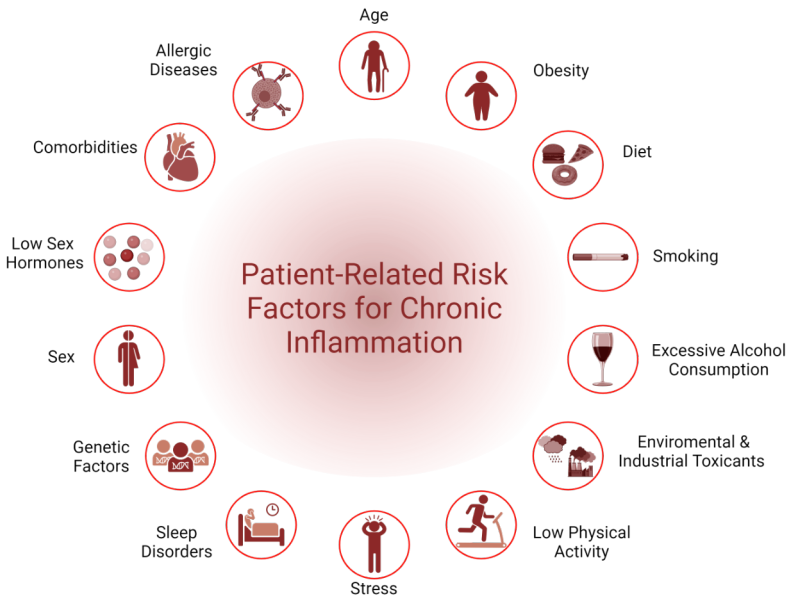

Fig. 3: Patient-related risk factors for chronic inflammation.

The demonstrated patient-related risk factors can sustain the development of chronic inflammation in general.

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Tackling Chronic Inflammation in Joint Replacement

Obesity: Adipose tissue is now recognized as an endocrine organ, with adipocytes secreting metabolically active mediators called adipokines and other inflammatory cytokines and chemokines when stimulated by the excess of macronutrients, especially carbohydrates and fat. Several studies have also demonstrated a predominance of proinflammatory M1 macrophages in the fat tissue of obese people in contrast with the dominance of anti-inflammatory M2 macrophages in non-obese people.[7] Concomitantly, the production of the hormone adiponectin by the adipocytes is reduced. Adiponectin plays an important role in lipid metabolism and insulin sensitivity and is also involved in immune responses and inflammation. Low levels of adiponectin levels are a significant predictor of cardiovascular mortality and have been associated with type 2 diabetes, cancer, stroke, and metabolic abnormalities. Reduced adiponectin levels in combination with the elevated secretion of pro-inflammatory molecules such as IL-6 from adipose cells, may lead to chronic inflammation (also called **"metaflammation**,") the metabolic syndrome associated with obesity (including insulin resistance, type 2 diabetes, coagulation, and cardiovascular disorders) and atherosclerosis.8 Obesity also has a detrimental effect on cartilage leading to osteoarthritis, in both weight-bearing joints and non-weight bearing articulations. Adipokines, including adiponectin and leptin, are important downregulators of inflammatory responses in cartilage, while other catabolic cytokines may inhibit the synthesis of proteoglycans and collagen type II, inducing cartilage degradation and bone resorption. Degradation products will elicit new inflammatory reactions, thus perpetuating the inflammatory process.[9]

Diet: Chronic inflammatory diseases have been associated with an unbalanced diet, rich in saturated fat and carbohydrates. As explained, increased intake of macronutrients may lead to higher production of pro-inflammatory molecules by the adipocytes.[10] Additionally, unhealthy diets are often high in toxic contaminants (e.g., in thermally processed foods) and low in antioxidants (found in fruit, vegetables, and tea), which protect the cells from increased oxidative stress. Finally, the diet may have an impact on the composition and metabolism of the gut bacteria, the so-called microbiome. The gut microbiome consists of a diversity of microorganisms and performs important functions related not only to digestion and metabolization but to immune modulation. Gut microbiome dysbiosis, i.e. a disturbance in the composition and the ratio of microbial species, may cause breaches in the intestinal barrier, letting potentially harmful components into systemic circulation, thus stirring up an immune inflammatory response that may become chronic.[11] The importance of diet cannot be underestimated as it is demonstrated to be the number one risk factor in death and disability-adjusted life statistics.[12] Diets high in fruits, vegetables and fibers reduce inflammation and have a positive effect on global health and longevity.

Smoking: Cigarette smoking is associated with chronic lung and cardiovascular disease, stroke, and cancer but is also generally recognized as a major risk factor for chronic inflammation.[13] Toxins in cigarette smoke activate the secretion of proinflammatory molecules from mucosal cells in the oral cavity and the airways thereby inducing and sustaining inflammation. Cigarette smoke also contains trace amounts of bacterial lipopolysaccharides and other components triggering the immune response and leading to chronic inflammation.[14] Blood samples of smokers have significantly higher levels of CRP, IL-6 and other inflammatory biomarkers.[15] On the other hand, some elements of cigarette smoke may suppress the innate and adaptive defense against bacteria and neoplastic cells, thus

increasing the risk of infection and cancer.

Excessive alcohol consumption: In large amounts, alcohol and its metabolites affect the liver, cause intestinal inflammation, alter the composition of the intestinal microbiome, impair its function, and damage the intestinal mucosal barrier. This leads to an additional inflammatory response, creating a vicious circle of chronic inflammation.[16] Toxins such as gut microbiome-derived lipopolysaccharide (LPS) may also enter systemic circulation through breaches in the intestinal linings, causing inflammatory reactions and eventually irreversible organ damage.[17]

Environmental or industrial toxicants: Long-term exposure to even low doses of chemical pollutants such as heavy metals, industrial chemicals, pesticides, food additives, or microplastics may lead to accumulation in the body and induce oxidative stress associated with chronic inflammation and cell and organ damage, as well as an impaired immune defense against microbial pathogens. Studies have shown that cocktails of pollutants are associated with an increase in systemic pro-inflammatory cytokines and activation of immune cells.[18]

Low physical activity: Sedentarism and physical inactivity may lead to abdominal adiposity and visceral fat accumulation which is associated with chronic systemic inflammation as described above.[19] However, physical inactivity is also related to chronic inflammation independent of obesity. Researchers hypothesize that muscle disuse caused by inactivity disturbs the release of myokines from skeletal muscle affecting immune regulation and promoting a proinflammatory pathway.[20]

Stress: Studies have demonstrated that stress activates neuroinflammatory responses in the brain. As stress activates the hypothalamo-pituitary-adrenal (HPA) axis, immune responses are normally suppressed through the secretion of glucocorticosteroids.[21]Glucocorticosteroids have also been shown to activate the innate immune pathways to address danger signals. Prolonged and intense stress may thus overstimulate the immune system and lead to elevated pro-inflammatory cytokines, and accumulation of peripheral monocytes and macrophages in the brain and peripherally, causing chronic inflammation.[22] The effect of stress on chronic inflammation is multifactorial and is still under investigation.

Stress and sleep disorders: Sleep disorders and irregular sleep schedules have been associated with a greater risk of inflammatory cytokine release and chronic inflammation. It is hypothesized that sleep disorders are correlated with other types of stress and with alterations of the circadian rhythm (e.g., in workers with night shifts) and the release of glucocorticosteroids.[23]

Genetic factors: The genetic determinants of chronic inflammation have not been elucidated; but, for some chronic inflammatory diseases such as Crohn's disease and diabetes type 1, shared genome loci have been identified.[24] Two extensive genome-wide association studies have identified 58 loci for chronic inflammation related to CRP secretion.[25]

Gender: The relationship between gender and inflammation is well-known. Females are more often affected by autoimmune diseases but have fewer infections and more circulating antibodies. These findings may be associated with genes located on the X chromosome which are related to the immune system and may be overexpressed in females compared to males.[26] On the other hand, there are relevant gender differences in oxidative stress mechanisms. In males, higher levels of ROS and other

inflammatory markers have been associated with more oxidative cell damage and higher basal inflammation, possibly even accounting for higher mortality in comparison with females whose antioxidant mechanism and specific immune responses seem more efficient.[27,28]

Low sex hormones: In addition to gender differences, research has demonstrated that sex hormones like testosterone and estrogen may suppress the production and secretion of pro-inflammatory markers. Decreased production of sex hormones (e.g., in postmenopausal women) is often associated with the onset of inflammatory disorders, while maintaining sex hormone levels reduces the risk of several inflammatory diseases.[29]

Co-morbidities such as inflammatory polyarthritis, inflammatory bowel diseases, other autoimmune diseases, diabetes, and cancer are additional triggers and perpetuators of inflammationy.

Allergic disease: Allergic disease is one of the most common chronic health disorders, affecting about 30% of the world's population. People with a family history of allergies are at risk of developing allergic disease. In allergic people, exposure to otherwise harmless substances (called **antigens** or **allergens**) may elicit hypersensitivity responses, mediated by antibodies, immune complexes, or delayed lymphocytic cellular responses attacking the antigen. These types of adaptive immunity responses have been classified in four hypersensitivity classes (Type I-IV Gell and Cooms classification) and may result in chronic inflammation in cases of persistent or repetitive exposure to the allergens. About 4,000 different substances have been identified as potential allergens. Hypersensitivity to metals, including contact dermatitis, constitutes one of the prevalent forms of allergy. Sensitization to allergenic metals (about 45 of the 92 metal elements)[30] may generate any of the four types of hypersensitivity responses, depending on the metal and the route of entry into the body. In addition to hypersensitivity reactions, metals may be immunotoxins and lead to the development of local inflammatory reactions, such as the adverse local tissue reactions (ALTR) associated with excessive metal wear from orthopedic implants,[31] which usually involve innate immune mechanisms including the recruitment of macrophages rather than lymphocytes.[32]

Chronic inflammation in the context of joint replacement.

Since joint replacements are subject to repetitive use, loading, and weight-bearing, the generation of wear products is inevitable. Materials used in orthopedic surgery, and more specifically in arthroplasty (including different metals, polymers, ceramics, and bone cements), will produce particulate debris and in some cases metal ions and corrosion products.[33]

All these byproducts activate the innate immune system and even the adaptive immune system in patients with hypersensitivity to certain materials, usually metals. The development of chronic inflammation in the tissues surrounding a joint implant is often multifactorial and may be connected to the implant material and its wear products, to the surgery, and/or to patient-related risk factors. As described above, the role of patient-related risk factors in the outcome of a joint replacement cannot be underestimated and is receiving more attention in the fields of personalized medicine and personalized arthroplasty.[34] However, the importance of the implant material and the surgical technique and accuracy must be taken into account. Regarding the implant material, extensive fundamental and clinical studies have identified different volumetric wear rates and wear debris in association with specific bearing couples in total joint replacements.[35] Determinants of the bioreactivity of wear debris (i.e., the potential

Understanding the Immune Dynamics of Joint Replacement

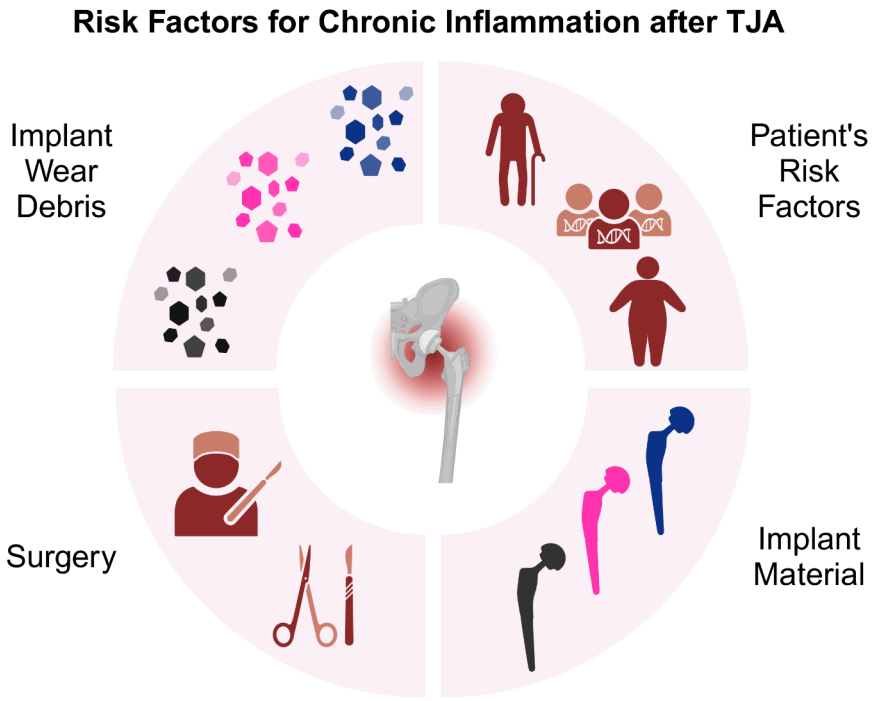

Fig. 4: Risk factors for chronic inflammation after TJA.

The demonstrated risk factors can cause or aggravate the development of chronic inflammation after TJA.

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immunological reaction to particles, metal ions, and even metal corrosion products) include the quantity, size, morphology, and chemical composition of the particles. These factors are related to the wear mechanism, namely the severity, rate, mode, and source of the wear.[36] Large conventional polyethylene wear particles have been associated with extensive foreign body reactions and massive macrophage recruitment, as well as osteoclast activation causing osteolysis.[37] In cases of excessive wear of metal-on-metal hip implants, the smaller metal particles have led to cases of ALTR.[38] In addition, the chemical composition of the particles and the occurrence of metal ions and corrosion products may cause additional toxic reactions featuring cell death and tissue necrosis.[39] Newer material combinations for articulating surfaces, such as crosslinked polyethylene and zirconia-toughened alumina, have exhibited much less generation of wear particles, resulting in lower implant failure and revision rates.[40]

Regarding the surgical factor, several aspects need to be considered. Firstly, every surgical intervention causes a tissue injury and will inevitably elicit an inflammatory reaction. In normal circumstances this inflammatory response is moderate and resolves after 2-14 days. In some cases, however, the surgical procedure triggers systemic inflammation and/or chronic postoperative pain.[41] Secondly, in arthroplasty, surgical skills and accuracy of implant positioning are paramount to preventing articulating components' dislocation, impinging, or exhibiting excessive wear. The latter occurs in hip resurfacing

in cases of steep acetabular cup positioning, leading to edge-loading on the femoral head, which in turn inevitably leads to higher wear-generating particles and other wear debris such as metal ions from metal-on-metal articulations.[42]

In cases of high wear with an overload of particulate debris following component malpositioning, the immune system will not be able to eliminate the causative agents, leading to a continuous cytokine activation and recruitment of mononuclear leucocytes, eventually resulting in chronic inflammation, osteolysis, fibrosis, and granulomatosis.

This chronic inflammation is associated with clinical symptoms such as pain and dysfunction and possibly prosthetic failure. Additionally, dormant bacterial biofilms on implant and particle surfaces may be activated in the compromised environment and lead to a low-grade infection, complicating, and perpetuating the chronic inflammation. The differences in diagnosis between aseptic chronic inflammation and low-grade infection is also important regarding the choice of therapeutic interventions. While extensive osteolysis, prosthetic loosening, or clear-cut periprosthetic infections necessitate revision surgery, non-surgical therapeutic interventions with osteogenic, cellular, and immunotherapeutic agents may be used in the future to disrupt the inflammatory vicious cycle and salvage an otherwise well-functioning implant.[43]

Conclusion

From a preventive point of view, several factors are paramount: careful surgical technique and implant positioning; preference of materials exhibiting low wear, low immunogenicity, and low bacterial adherence; and potential risk-associated host factors. Evidently, patient- risk factors are often interrelated. Arthroplasty patient populations' risk factors for chronic inflammation can include advanced age, obesity, and low physical activity. They are more susceptible to the development of adverse inflammatory effects after the implantation of a prosthetic joint. During the preoperative and postoperative period, patients should be encouraged and supported to adopt a healthy lifestyle including a balanced diet, weight loss if necessary, and physical exercise. The good news is that the arthroplasty itself will enhance the patient's quality of life and enable them to establish habits that promote a more active lifestyle. Successful hip and knee replacements can be life-changing interventions, associated with less overall morbidity and lower mortality.[44,45]

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About Complex Hip Surgery

ComplexHipSurgery.com is a comprehensive free educational resource for surgeons, patients and technologists. It began as a face-to-face international surgical course run by professor Alister Hart and Johann Henckel.

Professor Hart has been a consultant orthopaedic hip surgeon since 2006 and in 2009 was nicknamed the "hip detective" by the BBC for his work on treating painful hip replacements. This website is a collection of cases involving Professor Hart's patients with hip problems. 90% of his NHS referrals are from other consultant orthopaedic surgeons to him at the Royal National Orthopaedic Hospital NHS Trust. He also receives private referrals from GPs, physios and other surgeons to him at Cleveland Clinic London. Over the years a whole range of new technologies have been incorporated into the care complex hip problems.

Today, Professor Hart uses 3-D imaging to plan every operation. By doing this homework before the operation he is able to take on more complex cases with greater certainty of an excellent outcome. He uses 3-D printed models to assess the complexity before the operation, 3-D printed Guides to position the implants optimally and 3-D printed implants when the shapes are complex and he wants to minimise removal of bone.

Key Areas of The Cases:

Implant Failures: Research focuses on identifying the causes of implant failures, including wear, loosening, and hypersensitivity reactions like ALVAL.

Surgical Techniques: Exploration of innovative surgical methods for revision and reconstruction.

Patient Outcomes: Studies assess the impact of surgery on patients' quality of life and functional outcomes.

Implant Retrieval Centers: These facilities analyze failed implants to understand the causes of failure and provide recommendations for improved designs.

Prof. Alister Hart has contributed significantly to this field, leading initiatives like the London Implant Retrieval Centre, which offers data-driven insights into implant performance (RNOH NHS) (Cleveland Clinic). His research emphasizes the importance of comprehensive analysis and dissemination of findings to enhance clinical practice globally.

Clinical challenges of ALTRs caused by orthopedic implants

Even though orthopedic implants have a good biocompatibility, adverse local tissue reactions (ALTRs) can occur. Historically, ALTRs were first associated with failed metal-on-metal (MoM)[1, 2] bearings and were recorded as early as 1988[3]. However, ALTRs have also been described with other implant modifications such as metal-on-polyethylene (MoP)[4], ceramic-on-polyethylene (CoP)[5], ceramic-on-ceramic (CoC)[6] and ceramic-on-metal (CoM)[7], disproving the hypothesis that ALTRs are only caused by MoM bearings, emphasizing the complexity of this clinical topic.

The terms pseudotumor, aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL), trunnionosis and metallosis have been interchangeably used in the literature to describe ALTRs in the clinical setting[8]. A pseudotumor describes the presence of benign aseptic masses and bursae, whereas ALVAL is a histologic description for a specific tissue appearance. Trunnionosis refers to tribocorrosion damage at the femoral head-neck junction, whereas metallosis describes the stained appearance of the joint capsule and periprosthetic tissues due to large amounts of metal debris[8,9]. The term adverse reaction to metal debris (ARMD) is a subset of ALTR but only refers to adverse reactions to metallic debris[8]. However, all the above listed terms are primarily descriptive terms from evidence-based observations in the clinical setting but cannot be validated as clinical coding systems for specific diagnoses of ALTR-related revision surgeries.

Based on major national arthroplasty registries, ALTR in periprosthetic soft- and bone tissue can be defined as an inflammatory tissue reaction, which is often accompanied by aseptic loosening and osteolysis of the periprosthetic bone. The development of ALTRs can be multifactorial but is mostly associated with the implant material itself and with the presence of corrosion- and implant wear particles in periprosthetic tissue. Cellular responses to wear and corrosion particles in periprosthetic tissue are driven by either the innate or adaptive immune system, leading to chronic tissue inflammation. Implant wear particles activate macrophages, which form multinucleated foreign body giant cells and trigger an inflammatory tissue response, leading to the migration of further immune cells, especially lymphocytes in the state of chronic inflammation. In addition, T lymphocytes have been described to trigger a delayed type IV hypersensitivity reaction to metal debris. Other factors such as surgical procedures and patient-related factors may further favor and/or exacerbate the development of ALTR[10-12].

The development of ALTRs in periprosthetic tissues is multifactorial, and the underlying causes and mechanisms are often complex and difficult to understand. The presence of implant debris and metal corrosion products is usually, but not exclusively the cause for the development of chronic inflammation and ALTRs. The choice of implant material is crucial but does not guarantee the prevention of ALTRs. Furthermore, the usage of implant modifications with different materials further complicates the prediction of ALTR development. Moreover, because there is no consensus on the definition and terminology of ALTRs, their clinical diagnosis and the decision for revision surgery are difficult to make. Additionally, tissue inflammation and intoxication as well as severe osteolysis pose a major clinical challenge for the revision surgeon.

This article presents three case reports of ALTRs with different implant materials and modifications that demonstrate the complexity of ALTRs and the clinical challenges for the revision surgery.

Case 1: Revision of a Metal-on-Metal (MoM) hip

The story

The patient, a 49-year-old woman, underwent metal-on-metal (MoM) hip resurfacing procedure in 2001 due to a unilateral hip dysplasia (DDH). 17 years later, she presented with mild hip pain but extensive loss of bone in the pelvis which was presumably caused by an inflammatory reaction to metal wear debris. Her blood metal ion levels were 100 times higher (cobalt 188 bbp and chromium 126 bbp) than from patients with well-functioning MoM hips.

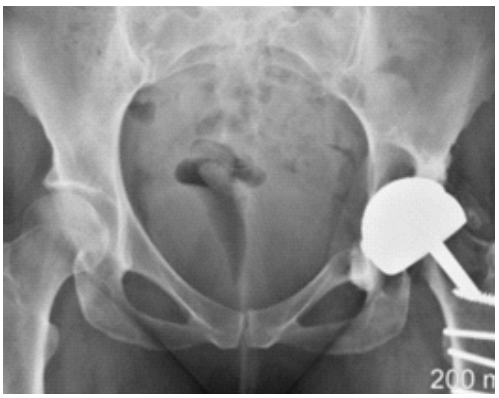


Fig. 1: Anteroposterior plain radiograph demonstrates radiographic features of osteolysis around the acetabular and femoral components.

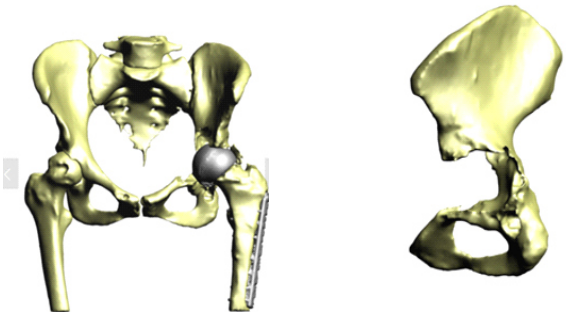


Fig.2: 3D construction showing the hemipelvic defect.

Clinical challenge

The case posed multiple challenges. The patient was at imminent risk of pelvic fracture without surgery. However, surgery itself also risked fracture of the pelvis during implant removal. Furthermore, the remaining pelvic bone was poisoned by metal debris and thus the patient's bone integrity was compromised, which could affect the stability of a new implant.

Investigation & Diagnosis

Detailed imaging, including plain radiographs and MRI, revealed extensive osteolysis and muscle wasting around the hip.

Surgical plan

A multidisciplinary team decided that revision surgery was necessary due to the risk of fracture and very high metal ion levels. The plan involved removing the existing MoM implant and fitting a custom 3D-printed acetabular cup. The procedure required meticulous care to avoid causing fractures during implant removal. The new cup would only be effective if the pelvis remained intact.

Case 1: Revision of a Metal-on-Metal (MoM) hip

Outcome

The operation was successful, with minimal bone loss during implant removal. A custom-made titanium acetabular cup was fitted and stabilized with screws. Postoperative imaging confirmed correct implant positioning and satisfactory fixation. The patient's recovery was positive, with significant reductions in metal ion levels and the restoration of pain-free hip function.

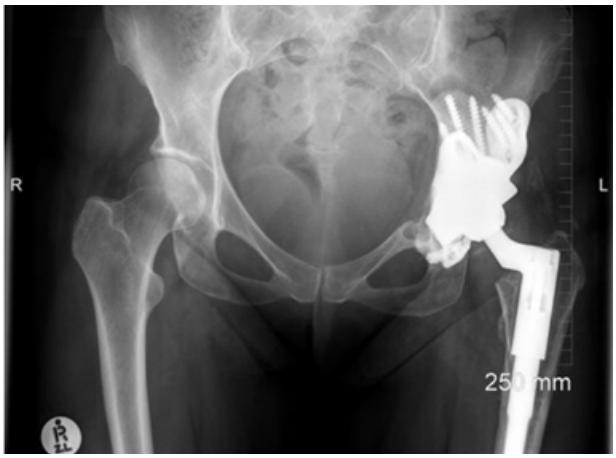


Fig. 3: Anteroposterior plain radiograph taken at one year after the operation. No evidence of implant migration.

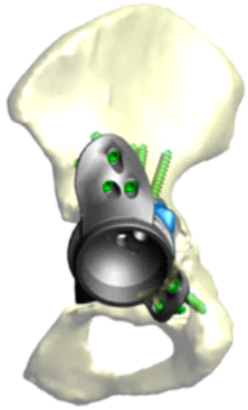


Fig. 4: Implant design showing the custom acetabular implant design around the patient's bony anatomy.

Conclusion

This case represents ALTR with MoM, which was characterized by extensive osteolysis of pelvic bone, which was presumably caused by metal wear debris. Elevated blood levels of chromium and cobalt further supported this hypothesis.
This case demonstrates the importance of precise surgical planning and execution in complex hip revision surgeries. The use of 3D-printed implants tailored to the patient's anatomy greatly improved the chances of successful fixation despite significant bone loss. Update at 6 years post operative is that the patient living a full and active life with excellent hip function. More details about this type of surgery has been published by Professor Hart:

Di Laura, Anna PhD; Henckel, Johann MD; Hart, Alister FRCS(Orth)a. Custom 3D-Printed Implants for Acetabular Reconstruction: Intermediate-Term Functional and Radiographic Results. JBJS Open Access 8(2):e22.00120, April-June 2023. | DOI: 10.2106/JBJS.OA.22.00120

Source: Revision of a metal on metal hip with massive acetabular osteolysis and previous femoral osteotomy using a custom 3D-printed cup in a mid-life woman — Complex Hip Surgery - CASE 10

Case 2: Revision of a Metal-on-Polyethylene (MoP) hip

The story

This case involves a 67-year-old gentleman who faced a series of complications due to hip trauma he had experienced over 50 years ago. After his primary and revision surgeries, and subsequent three hip replacements, he was left with a failing hip implant. His most recent hip replacement lasted 13 years before massive circumferential acetabular osteolysis caused the cup to loosen. Imaging revealed anterior and medial wall deficiencies, while the posterior column remained intact. The patient had a metal-on-polyethylene (MoP) bearing, which over time led to the wear of the polyethylene liner, triggering an inflammatory reaction and bone loss due to polyethylene debris.

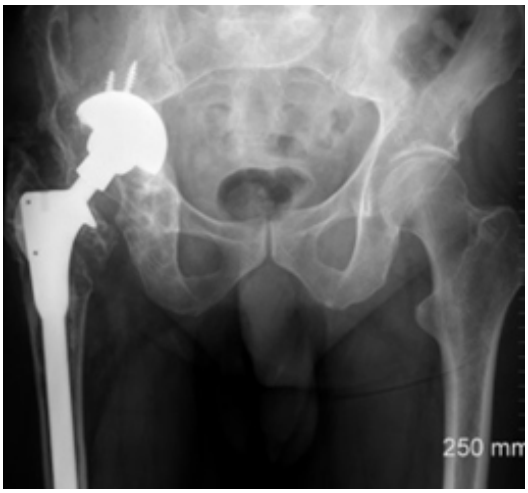


Fig. 1: Pre-operative radiograph demonstrating the medial migration of the acetabular cup into the pelvis

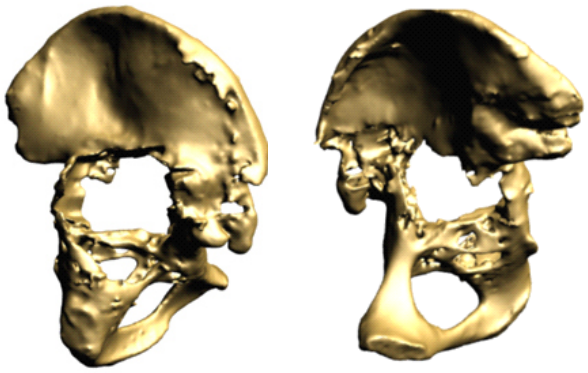


Fig. 2: 3D reconstruction of patient's right hemipelvis created from CT scans. Complete loss of the medial acetabular wall was observed.

Clinical Challenge

The loosening of the acetabular cup was exacerbated by the significant osteolysis, which had severely compromised the structural integrity of the acetabulum.

Investigation & Diagnosis

Imaging, including preoperative radiographs and CT scans, revealed the extent of acetabular migration and bone loss. A 3D reconstruction showed a complete loss of the medial acetabular wall, leading to a diagnosis of a Paprosky 3B acetabular defect.

Case 2: Revision of a Metal-on-Polyethylene (MoP) hip

Surgical Plan

The surgical plan required a custom 3D-printed acetabular cup, designed specifically for the patient's anatomy. The implant was designed with three flanges for optimal fixation. The surgery involved a posterior approach, with meticulous bone preparation to minimize further bone loss and ensure the custom implant fit securely.

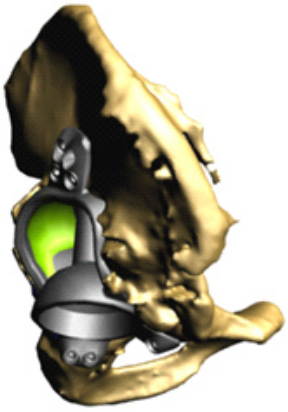


Fig. 3: 3D reconstruction of implant design. The design has three flanges, one to the ischium, one to the pubic bone and one to the iliac crest.

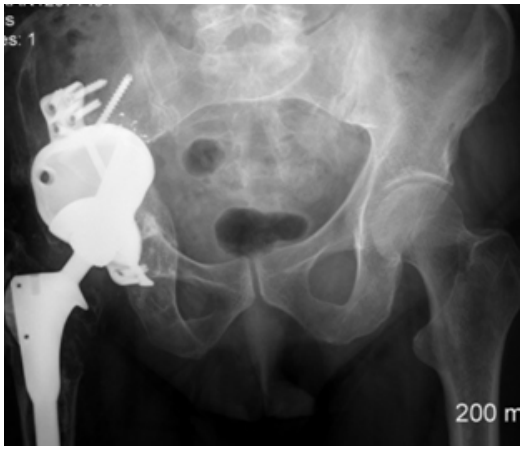


Fig. 4: 6 weeks post operation radiograph. No migration present on the radiograph

Outcome

The surgery was a success, with the patient able to mobilize with a single crutch and resume exercising nine months postoperatively. Postoperative imaging confirmed excellent positioning of the implant with successful bone integration and the restoration of leg length.

Conclusion

This case represents ALTR with MoP. ALTR was characterized by massive osteolysis of the pelvic bone, which was most likely caused by polyethylene wear debris. This case underscores the complexity of revision hip surgeries and highlights the value of custom 3D-printed implants for achieving secure fixation and improving patient outcomes despite significant bone loss. Update at 7 years post operative is that the patient has excellent hip function and more can be seen in this paper:

Durand-Hill, M., Henckel, J., Di Laura, A., & Hart, A. J. (2020). Can custom 3D printed implants successfully reconstruct massive acetabular defects? A 3D-CT assessment. Journal of Orthopaedic Research®, 38(12), 2640-2648.5. https://doi.org/10.1002/jor.24752

Source: Revision of a loose cup due to massive circumferential acetabular osteolysis from polyethylene wear, using a custom 3D-printed cup - Complex Hip Surgery - CASE 15

Case 3: Revision of a Ceramic-on-Ceramic (CoC) hip

The story

A middle-aged patient came to the clinic with severe pain and limited mobility in his left hip. Previously, he had undergone bilateral hip replacements that included modular necked femoral stems with ceramic-on-ceramic (CoC) bearings. However, the modular design led to corrosion between the titanium femoral stem and the cobalt-chromium neck, causing metal debris and an adverse tissue reaction in his left hip.

Clinical Challenge

The challenge was in addressing the corrosion-related inflammation without exacerbating the damage to the surrounding bone, as the femoral stem was well fixed. Unlike cases with pseudotumors, the patient's problem originted from metal debris due to the interaction of different alloys in the modular components.

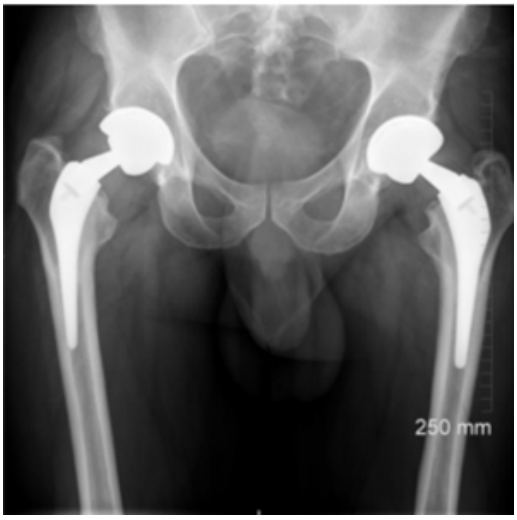


Fig. 1: Anteroposterior plain radiograph demonstrating bilateral hip replacement with modular necks. No radiographic evidence of stem loosening on either side

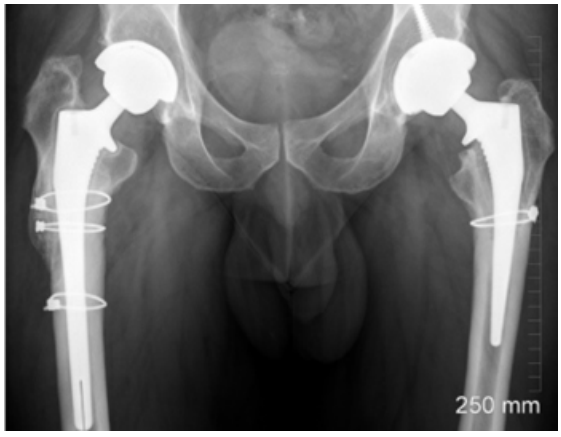
Investigation & Diagnosis

Imaging studies confirmed the presence of metal debris and inflammation around the implant, particularly affecting the left hip. Despite the ceramic-on-ceramic bearing being intact, the corrosion at the modular junction between the neck and the stem was the main culprit. The diagnosis was an adverse reaction to metal debris, secondary to modular neck corrosion.

Case 3: Revision of a Ceramic-on-Ceramic (CoC) hip

Surgical Plan

The surgical plan involved removing the well-fixed stem with minimal bone loss. The surgeons aimed to use a Corail primary stem to preserve the femoral bone stock. The modular neck junction was carefully disassembled using flexible osteotomes to prevent further damage.



Fig, 2: Anteroposterior plain radiograph of the pelvis taken two years after the left revision procedure. Radiographic evidence of osseointegration surrounding the left sided Corail stem was present.

Outcome

The surgery was successful, and at his six-week follow-up, the patient reported pain-free mobility and had resumed his daily activities. Imaging showed that the new primary stem had successfully integrated with the bone. At the two-year follow-up, the patient had a well-functioning hip, with no complications and clear evidence of bone growth around the implant, confirming the efficacy of the surgical approach.

Conclusion

This case represents ALTR with CoC. ALTR was characterized by tissue inflammation and extensive fluid accumulation around the ceramic implants. However, ALTR was not caused by the ceramic implant but by corrosion, which occurred between the titanium femoral stem and the cobalt-chromium neck.

Source: Revision of a well-fixed femoral stem with adverse reaction to metal debris from modular neck corrosion, using a non-modular stem — Complex Hip Surgery - CASE 24

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Case Reports

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