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Hypoxia and Type-IV Hypersensitivity – Dual Pathogenesis in Adverse Reactions to Hip Implants

Hipoxia e hipersensibilidad de tipo IV: patogenia dual en reacciones a implantes de cadera

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Abstract

Background Adverse local tissue reactions (ALTRs) to hip implants affect a high proportion of patients. Described initially in metal-on-metal joints, an increasing number of studies report their occurrence in other types of implants. Due to the huge number of patients with hip implants worldwide, it is urgent to fully understand the mechanisms that cause ALTRs to develop efficient options in terms of follow-up, diagnosis and therapy.

Scope and audience The present review, we analyze the corrosion and wear of the materials used in hip implants, as well as the cell and immunological mechanisms involved, with the aim of providing an updated view of the clinical and scientific contents in the literature for students, orthopedic surgeons and researchers.

Keywords
- pseudotumors
- synovium
- chromium and cobalt
- orthopedic implants
- hip arthroplasty
- implant corrosion

Resumen

Antecedentes Las reacciones tisulares adversas (RTAs) a implantes de cadera afectan a una alta proporción de pacientes. Si bien fueron inicialmente descritas en articulaciones de metal sobre metal, un creciente número de estudios señala su presencia en otros tipos de implante. El gran número de pacientes con prótesis de cadera en el mundo señala la urgencia de comprender cabalmente los mecanismos que dan origen a RTAs para el desarrollo de alternativas de monitoreo, diagnóstico y terapéuticas eficientes.

Ámbito de revisión y público objetivo En la siguiente revisión bibliográfica, abarcamos desde la corrosión y el desgaste de los materiales utilizados en implantes de cadera hasta los mecanismos celulares e inmunológicos involucrados, con el fin de ofrecer una visión actualizada de antecedentes clínicos y científicos a estudiantes, cirujanos ortopédicos e investigadores.

Palabras clave
- pseudotumores
- sinovia
- cromo y cobalto
- implantes ortopédicos
- artroplastía de cadera
- corrosión de implantes

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Introduction

Every year, approximately two million people worldwide undergo hip arthroplasty, mainly due to osteoarthritis. This procedure consists of the removal of joint tissues and their replacement with prosthetic implants.[1,2] The main goal of arthroplasty is to relieve pain and recover lost mobility resulting from degenerative articular conditions. Although it is a successful therapeutic tool,[3] a non-negligible percentage of patients will develop adverse local tissue reactions (ALTRs) to the implants.

Although the first description of ALTRs refers to metal-on-metal (MoM) implants, they also occur on metal-on-polyethylene (MoP) ones, although with a lower incidence.[4,5] Nowadays, MoM implants are rare, and MoP is the most widely used combination. We expect that ALTRs will remain a clinically relevant condition;[6] therefore, a thorough understanding of ALTRs is critical to orthopedic surgery.

The ALTRs are inflammatory lesions resulting in pain, swelling, articular and adjacent soft tissue destruction, disability, and increased dislocation risk. In addition, they hinder future therapeutic solutions.[7,8] Their etiopathogenesis is complex and not fully elucidated. Furthermore, the ALTRs are more common in joints with implants, with a higher incidence in MoM implants, suggesting metallic elements are the main cause.[9] The following work reviews the literature regarding metals in orthopedic implants and their cellular and immunopathological effects in ALTR pathophysiology.

Institutional approval mechanisms for the use of implants: 510K as the origin of the disaster

The main institution in charge of regulating drugs, equipment, and devices for medical use worldwide is the Federal Drug Administration (FDA) of the United States. The FDA has two basic mechanisms to approve the use and commercialization of intracorporeal medical devices (see more information at www.fda.gov/medical-devices): I) pre-market approval (PMA), in which a new device must undergo scientific tests, and exhaustive pre-clinical and clinical studies; and II) 510K, or "substantial equivalence", which determines that a new device is similar to a previously approved one, waiving the need for preclinical or clinical studies. This second mechanism is critical in highly competitive markets, in which time for innovation is essential. Most hip implants received a 510K approval for being "substantially equivalent" to previously approved implants.[10] Thus, most available implants have not been tested in pre-marketing clinical trials. Additionally, many received approvals as "equivalent" to pre-existing implants, which, in turn, were approved as "equivalent" to other pre-existing ones. As such, many tests validating hip implants date back to the 1980s, and the data used in most of them are not from clinical trials.[11]

Technological development in hip implants and its protagonists: Cobalt and modularity

Due to their mechanical properties, metal alloys are the most widely used material for implant design. Stainless steel and cobalt-titanium alloys are combined with polymers or ceramics to meet functionality and biocompatibility requirements.[12] Kenneth McKee and John Watson-Farrar introduced the original design in 1951, with an implant consisting of a femoral piece made of a 67% cobalt (Co), 25% chromium (Cr), and 8% molybdenum (Mo) (CoCrMo) alloy, and a direct articulation with an acetabular cup from the same alloy.[13] The choice for CoCrMo results from its good corrosion resistance and mechanical strength. Sir John Charnley improved this design in 1962 by introducing a polyethylene coating between the joint surfaces to substantially reduce friction.[14] Dr. Per Ingar Brånemark introduced titanium alloys in the 1970s, significantly improving biocompatibility.[15] In addition to an excellent resistance to corrosion, titanium presents a good mechanical resistance but a poor frictional resistance. As such, joint surfaces still consist of CoCrMo. Most of the hip implants from the 1970s to the late 1990s were composed of a titanium femoral stem and a CoCrMo femoral head, articulating with a polyethylene coating in a titanium acetabular cup. However, the mechanical resistance of polyethylene is low, and the wear and abrasion generate particles resulting in inflammatory osteolytic lesions in a large percentage of patients.[16] The 1990s saw the introduction of a second generation of MoM implants, which aimed to minimize wear and abrasion. The femoral head from these implants articulated directly in the acetabular cup, and both parts consisted of CoCrMo.[17] New technologies allowed for smoother surfaces that theoretically reduce wear and friction, which was later proven in vitro.[18,19] The FDA approved these systems for clinical use through the mechanism of "substantial equivalence" to previously approved devices (510k).[10]

The elimination of the polyethylene coating enabled the introduction of large femoral heads, avoiding joint dislocation (a frequent issue) by increasing the displacement required to dislodge the femoral head.[20,21] The size of these larger femoral heads would not increase friction when the space between surfaces diminished to 50 to 100 µm.[22,23] This also allowed the development of coated MoM prostheses with minimal bone removal.[1,24,25] Initially, the clinical performance of MoM implants was positive, with no higher risk of cancer or fetal malformations in patients with these devices, when compared to the general population.[26–30] Because of these advantages, 35% of hip prostheses used in the 2000s were MoM.[31,32] However, about 30% of the patients presented adverse reactions, constituting the greatest failure of orthopedic implant surgeries.[33,34] As such, most manufacturers stopped producing total MoM prostheses,[35] drastically reducing the use of coated devices.[1]

The introduction of modular parts selected individually and assembled during surgery resulted in an inventory reduction for the industry and hospitals. Furthermore,

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modularity offers a greater versatility when searching for more appropriate solutions for the sizes and angles of joint elements. Unfortunately, the higher contact surface and microfriction between parts increased the degree of corrosion in implants, as well as the presence of metallic elements in articular fluids and tissues. For this reason, it also contributes to the etiopathogenesis of ALTRs.[36–38]

General aspects of ALTRs

The ALTRs consist of the development and growth of cysts or solid fibrotic masses originating from the synovial membrane of patients with hip implants.[39–42] Their clinical manifestations range from asymptomatic to pain, discomfort, and compression of veins or nerves.[43,44] Histologically, ALTRs present ulceration and subsuperficial necrosis of the synovial membrane, which is thicker and has a large amount of dense connective tissue (►**Fig. 1**). Additionally, there is the infiltration of mononuclear cells and a variable number of eosinophils and multinucleated giant cells.[5,34,39,45]

Furthermore, ALTRs can present a variable leukocyte infiltration, ranging from reactions with macrophage predominance and small amounts of CD4+ and CD8+ T lymphocytes (TL) (►**Fig. 1A**), to lesions dominated by lymphocytes with large mononuclear perivascular aggregates, and few macrophages (►**Fig. 1B**) and CD3+ TL and CD20+ B lymphocytes (BL).[34,39] In addition, there are vascular-endothelial alterations (►**Fig. 1C**), macrophage fusion resulting in mononuclear giant cells (►**Fig. 1D**) or epithelioid cells (►**Fig. 1E**), and eosinophils (►**Fig. 1F**).

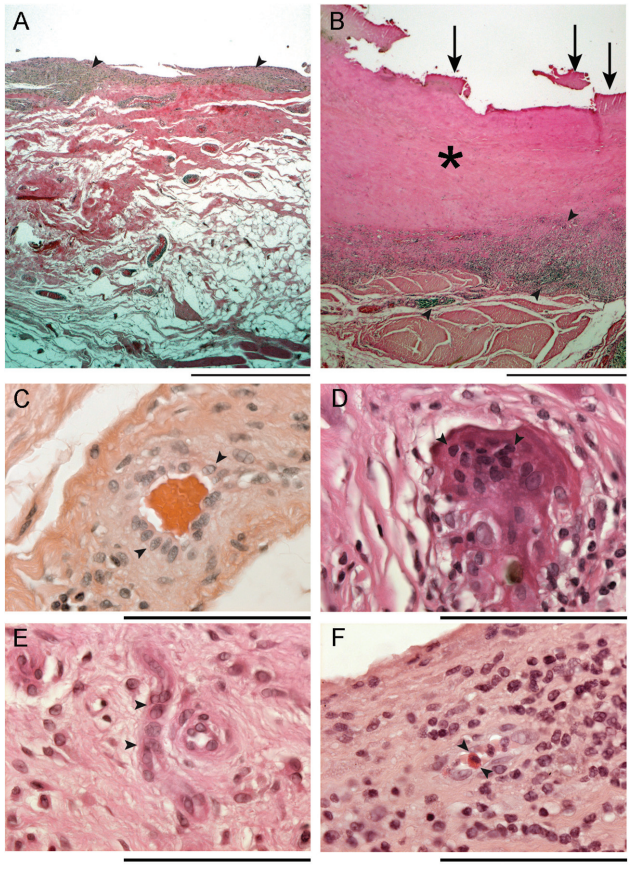

Fig. 1 Characteristic histology of adverse local tissue reactions (ALTRs). (**A**) Predominantly macrophagic ALTR, with macrophages clusters in the subsurface region (arrowheads) surrounding the synovial ulcer. (**B**) ALTR with lymphocyte predominance; superficial ulceration presents fibrin deposits (arrows) and a large area of subsuperficial necrosis (asterisk). Large lymphocytic accumulations and perivascular aggregates (arrowheads) surround the necrotic area. (**C**) Endothelial alterations in ALTR. Cubic or prismatic (instead of flat) endothelial cells in venules and capillaries (arrowheads). (**D**) Multinucleated giant cells and (**E**) epithelioid cells (arrowheads) are examples of monocytic cell fusion. (**F**) Eosinophil (arrowheads) in the inflammatory cell infiltrate. Hematoxylin-eosin staining; magnification bar = 1 mm in **A** and **B**; and = 100 µm in **C–F**.

Degradation of metal alloys in the pathogenesis of ALTRs: Particle formation and ion release

The degradation products released from implants, including metallic ions and some solid particles, play a significant role as etiological agents in ALTRs.[46] These degradation products result from two phenomena: I) modular joint corrosion and microfriction between the stem and the femoral head (►**Fig. 2A**), II) articular surface wear.[37,47] Although the latter

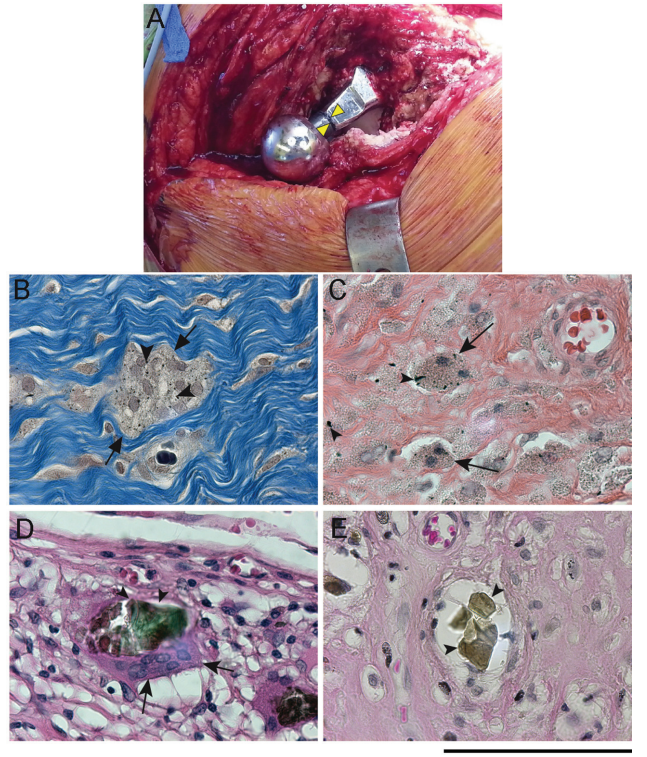

Fig. 2 Metallic particles in adverse local tissue reaction (ALTR). (**A**) Corrosion at the femoral head-stem junction (arrows). (**B–C**) Small metallic particles (0.25–1 mM) resulting from abrasion and wear, rich in Co and Cr (arrowheads), are common in macrophage cytoplasm (arrows). (**D–E**) Large Cr particles (10–100 mM) and corrosion products rich in Cr, oxygen (O), and phosphorus (P), but lacking Co (arrowheads) are commonly phagocytosed by multinucleated giant cells (arrow in **D**).

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has a higher incidence in MoM implants, potentially explaining the high prevalence of ALTRs, the friction of modular components is common in both MoM and MoP. The friction and wear of metal surfaces release metallic, crystalline particles, with sizes ranging from 0.1 to 1 µm, and an identical composition to the implant alloy.[36,48] These particles occur in periarticular tissues and synovial fluids from the affected joints (►**Fig. 2B-C**). This corrosion results in the release of Co^{2+}, Cr^{3+}, and Mo^{6+} ions, which are evident in the synovial fluid and blood plasma of patients with implants.[5] Additionally, this corrosion leads to the formation of particles in the synovial fluid and joint tissues (►**Fig. 2D-E**). These structures result from the clumping of nanoparticles from amorphous, insoluble salts, which are composed of Cr phosphate or Cr oxide but lack Co.[36,48]

The release of ions from the metallic surfaces of the implants generates high concentrations of Co and Cr, increasing the levels of these ions in the synovial fluid and plasma of patients with hip implants.[5,7,49] Furthermore, the strong association between plasma Co and Cr levels and ALTR led regulatory agencies, including the Medicines and Healthcare products Regulatory Agency (MHRA) from the United Kingdom, to include serum ion analysis in follow-up protocols for MoM implants.[50] Notwithstanding, there is no correlation between the corrosion level and the clinical severity of lesions.[51] This fact, along with the histological description of high lymphocyte count in ALTRs, provides ground for the most accepted hypothesis that ALTRs are delayed (type IV) hypersensitivity reactions to metals, in which their intensity is not necessarily proportional to the intensity of the stimulus.[34,52–54] However, hypersensitivity tests did not discriminate between stable and failed implants, so they have no predictive value for ALTRs.[55] Some questions remain: 1) What is the effect of metals on the joint cell populations that triggers the immune response? 2) If the main cause is hypersensitivity, why some lesions are characterized by macrophages and others by lymphocytes?

Cobalt ion-induced hypoxia triggers inflammation in peri-implant tissues

The association between the ALTRs and the levels of Co^{2+} and Cr^{3+} in plasma and synovial fluid suggests a directly toxic effect of these ions on joint tissues. Our recent study demonstrated that synovial fibroblasts which are exposed to clinically relevant doses of Co^{+2} experience hypoxia,[56] activating transcription factors, such as NF-κB, which trigger a cytokine storm, resulting in inflammation by promoting endothelial activation (adhesion molecule expression) and leukocyte migration. The evidence of autophagocytosis of mitochondria and the changes in mitochondrial distribution also confirm this fact. Similarly, Salloum et al. demonstrated a decrease in oxygen consumption in mononuclear cells exposed to Co^{2+} and an increase in glycolysis, as well as the generation of reactive oxygen species (ROS), leading to oxidative stress, which altogether compose a damage mechanism.[57] The subcellular mechanism of injury by metal ions has not been fully clarified.[58–60] However, it has recently been proposed that Co^{+2} would activate a mitochondrial permeability transition pore (mPTP) leading to the disappearance of the proton gradient and allowing adenosine triphosphate (ATP) generation.[58] According to this mechanism, the high concentration of Co ions in the synovial tissues would cause cellular alterations and ultimately result in joint inflammation.

Hypersensitivity in ALTRs: A partial coating model potentially associated with the presence of metals

Hypersensitivity is a pathological immune response, deemed exaggerated in comparison with the damage generated by the etiological agent. Type IV hypersensitivity is mediated by cells, instead of antibodies or immune complexes as in other types of hypersensitivity.[61] In a cell-mediated hypersensitivity reaction, cytokines secreted by LTs induce macrophages to fuse into multinucleated cells around the damaged areas, forming granulomas and resulting in tissue necrosis and fibrosis. Although cell-mediated hypersensitivity is mainly associated with chronic infections, such as tuberculosis or neoplastic-like conditions, ALTRs present all of its features (fibrosis, necrosis, multinucleated cells, granulomas, and LT infiltration), strongly supporting the theory of its participation in their development.[5,39,48,62]

The lymphocytic infiltrates, seen as perivascular aggregates with high structural and functional complexity, provide strong evidence of the involvement of hypersensitivity mechanisms in ALTRs.[63] Our recent analysis of gene expression in perivascular lymphocytic aggregates demonstrated their identical composition in response to MoM and MoP implants.[64] Interestingly, we did not find a Th17 component (typical of autoimmune or hypersensitivity diseases) in the perivascular lymphocyte aggregates but, instead, a predominant Th1 component and exhausted lymphocytes, opening up new immunotherapeutic perspectives.

Although the highly specific nature of T lymphocyte activation requires recognition by the T-cell receptor (TCR), the elements which trigger such recognition are unknown. Some authors proposed the presence of hapten-carrier complexes,[65] as in other hypersensitivity mechanisms: a metal ion or nanoparticle is bound to a host protein and generates a neoantigen. This neoantigen triggers a specific response after its presentation to the TCRs capable of recognizing it. The work of our collaborators at the University of British Columbia,[66] when describing risk genotypes in HLA class II genes that increase the chances of ALTR development, strongly supports this hypothesis. These results lead to the assumption that certain types of

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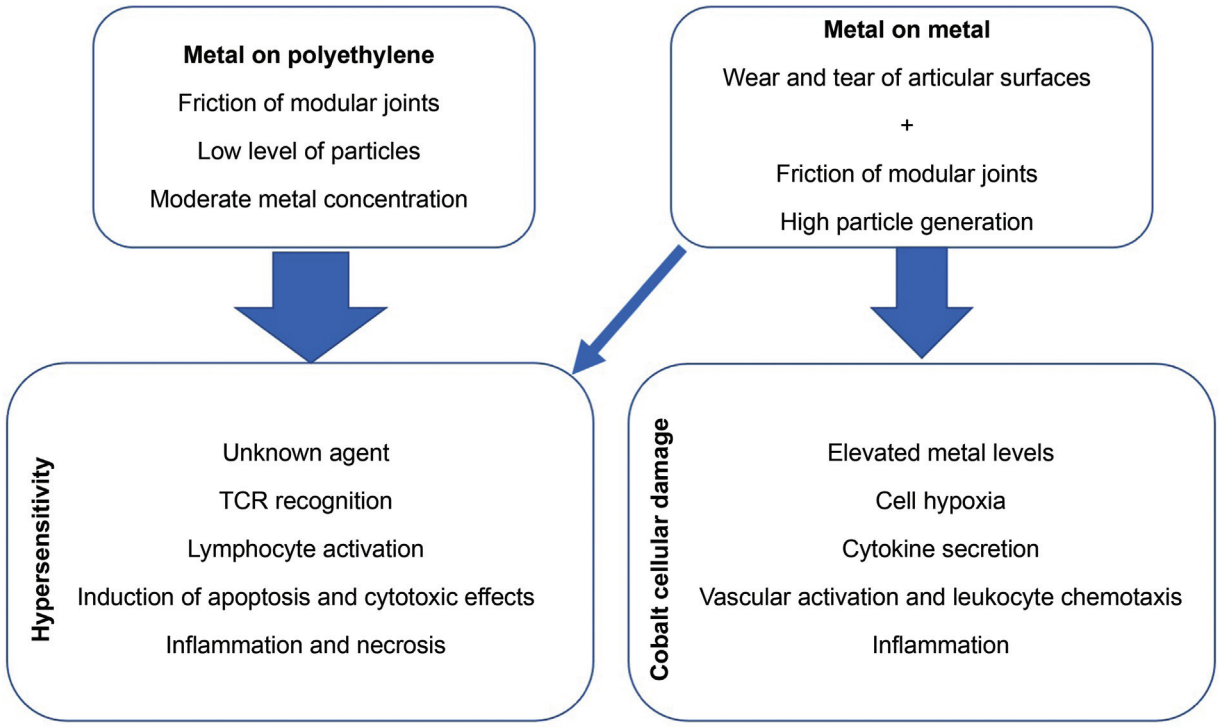

Fig. 3 Diagram of adverse local tissue reaction formation in MoP and MoM implants due to hypersensitivity reactions and/or cobalt-induced cellular cytotoxicity.

receptors would be more susceptible to activation by neoantigens composed of metal particles or ions, and highlighted the role of a genetic predisposition. This mechanism has been proposed to explain hypersensitivity to metals, including nickel.[67] However, there is no proven association between metal-induced hypersensitivity and ALTRs.[55] Furthermore, Kwon et al.[68] (2010) found no differences in lymphocyte activation in the presence of Co^{2+} and Cr^{3+} between patients with failed MoM implants and the control group, suggesting that hypersensitivity is not the only explanation for ALTR development. These observations, along with the high prevalence of ALTR in MoM systems, and its low prevalence in MoP systems, suggest a complex process with different pathogenic mechanisms, including direct cell damage by metal ions, metal ions immunogenicity, and genetic factors.[69]

Dual pathogenesis in ALTR: Cell damage caused by cobalt ions and type IV hypersensitivity

The presence of the two previously described damage mechanisms (cellular hypoxia induced by cobalt and type IV hypersensitivity) supposes complex pathogenesis for ALTRs. Dr. Giorgio Perino,[45,48] from the Hospital of Special Surgery in New York, United States, histologically describes two types of inflammatory responses: one with a prevalent macrophagic infiltration with little lymphocyte component and little necrosis; and another with a preferential lymphocytic infiltrate and necrosis but no macrophages. These findings suggest two pathological mechanisms. Furthermore, the quantitative descriptions of the same group[45,48] show macrophage-rich lesions in highly worn MoM implants, accompanied by a high number of metal particles and high blood levels of Co. In contrast, most ALTRs in MoP implants present lower Co levels and particle numbers, corresponding to hypersensitivity reactions with predominantly lymphocytic infiltration, a high degree of necrosis, and few macrophages. These findings are consistent with those from our group and other researchers.[5,70]

High levels of Co generate hypoxia and cell death, leading to an inflammatory condition characterized by macrophage infiltration. This type of response is predominant in MoM implants with a high level of articular surface wear and, consequently, a high Co concentration in periarticular tissues, affecting up to 30% of patients with these implants. A smaller group presents hypersensitivity reactions characterized by lymphocytic infiltration, perivascular aggregation of T lymphocytes, and high levels of necrosis; genetic factors potentially increase the susceptibility to this type of reaction. This group does not necessarily have high blood levels of Co or Cr, and account for a part of ALTRs in MoM implants and virtually all cases of ALTRs in MoP devices (►**Fig. 3**).

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Future perspectives

We still do not know the specific mechanism of lymphocyte activation or why the presence of metallic products induces adverse reactions in some patients alone. Although MoM implants are not in use anymore, the incidence of ALTRs in patients with MoP devices, the most widely employed today,[1,6] reinforces the significance of these reactions and demands a complete knowledge of their pathophysiology to design more effective preventive strategies. The increasing number of surgeons and patients opting for Co-free ceramic implants suggests a considerable reduction in ALTR prevalence. However, future research into the effects of metals may extend to areas where these materials remain in use.

Conflict of Interests

The authors have no conflict of interests to declare.

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