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REVIEW

Prosthetic Metals: Release, Metabolism and Toxicity

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Abstract: The development of metallic joint prostheses has been ongoing for more than a century alongside advancements in hip and knee arthroplasty. Among the materials utilized, the Cobalt-Chromium-Molybdenum (Co-Cr-Mo) and Titanium-Aluminum-Vanadium (Ti-Al-V) alloys are predominant in joint prosthesis construction, predominantly due to their commendable biocompatibility, mechanical strength, and corrosion resistance. Nonetheless, over time, the physical wear, electrochemical corrosion, and inflammation induced by these alloys that occur post-implantation can cause the release of various metallic components. The released metals can then flow and metabolize in vivo, subsequently causing potential local or systemic harm. This review first details joint prosthesis development and acknowledges the release of prosthetic metals. Second, we outline the metallic concentration, biodistribution, and elimination pathways of the released prosthetic metals. Lastly, we discuss the possible organ, cellular, critical biomolecules, and significant signaling pathway toxicities and adverse effects that arise from exposure to these metals.

Keywords: metallic joint prostheses, prosthetic metal release, potential toxicity and adverse effects

History and Characteristics of the Metallic Prosthesis

History of the Hip and Knee Prosthesis

The development of hip and knee replacement has continued for over a century as orthopedic surgeons and researchers strive to identify suitable materials to replace diseased joints (Figure 1). John Murray Carnochan attempted to complete the first mandibular arthroplasty by inserting an oak chip in 1840,[1] marking the introduction of prosthesis implantation. However, the implant failed immediately after, resulting in the loosening of the chip. In the 1860s, Verneuil introduced knee arthroplasty to treat diseased knee rigidity by establishing a septum in the joint space using surrounding soft tissue or fascia.[2] Gluck performed a total hip arthroplasty (THA) in 1891 using a femoral head and acetabular cup constructed from ivory, subsequently fixed with Nickel plated screws.[3] The significance of the stiffness and durability of implantations in bearing joints emerged over time, leading to the utilization of metallic insertion. Robert Jones designed a golden cover four years later to resurface a diseased femoral head.[4] Despite the subsequent utilization of prostheses made from rubber,[5] glass,[3] and stainless steel,[5] long-term outcomes indicated dissatisfaction with the implantations. Attempts to use materials like nylon and glass in diseased knees likewise failed.[2] Smith Peterson debuted the first acetabular cup in 1938 constructed using Cobalt-Chromium-Molybdenum alloy (Co-Cr-Mo), inspired by dental materials.[6] However, a single metallic cup worsened friction between itself and the femoral head, resulting in bone necrosis and pain. To address this, the Judet brothers designed an artificial head with a short stem or a long stem by Austin Moore.[6] Different types of metallic molds were also utilized as femoral or tibial hemiarthroplasties in knee replacements until the mid-twentieth century, inspired by the application of Co-Cr-Mo alloy in diseased hip joints.[2] After 1950, knee prosthesis development focused more on biomechanics than on materials. The transition from fully restrictive hinged prostheses to semi-restrictive and non-restrictive total condylar prostheses for total knee arthroplasty (TKA) today was a result of such focus.[7] On the other hand, John Charnley, regarded as the founder of modern hip replacement, used high molecular polyethylene and acrylic cement to anchor the artificial femoral head in 1958,[3]

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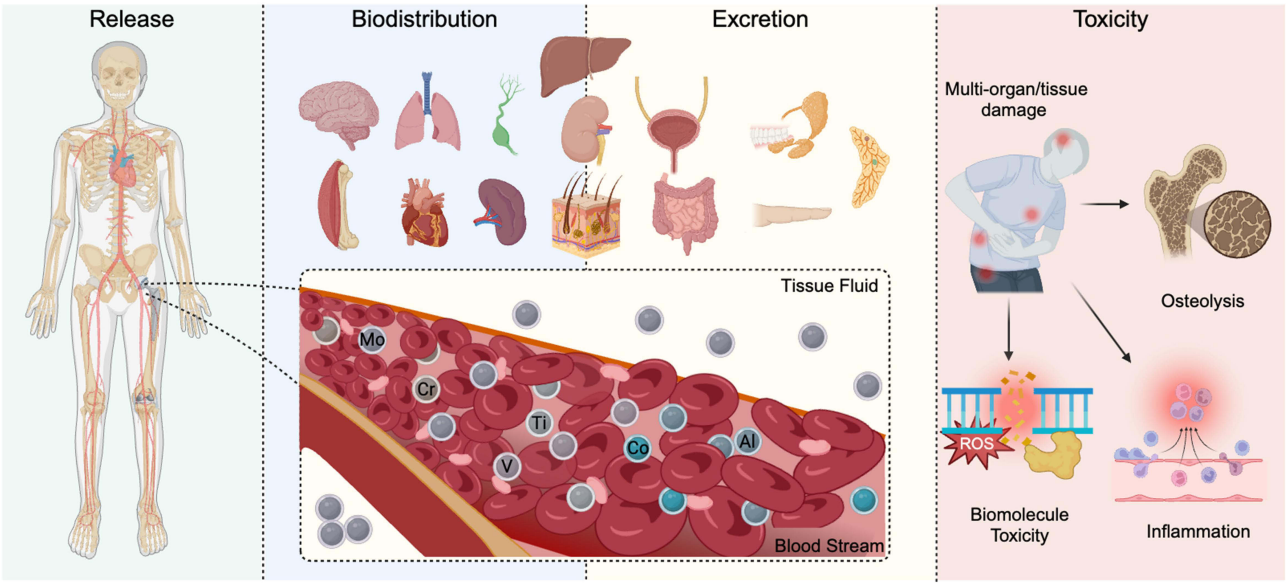
Graphical Abstract



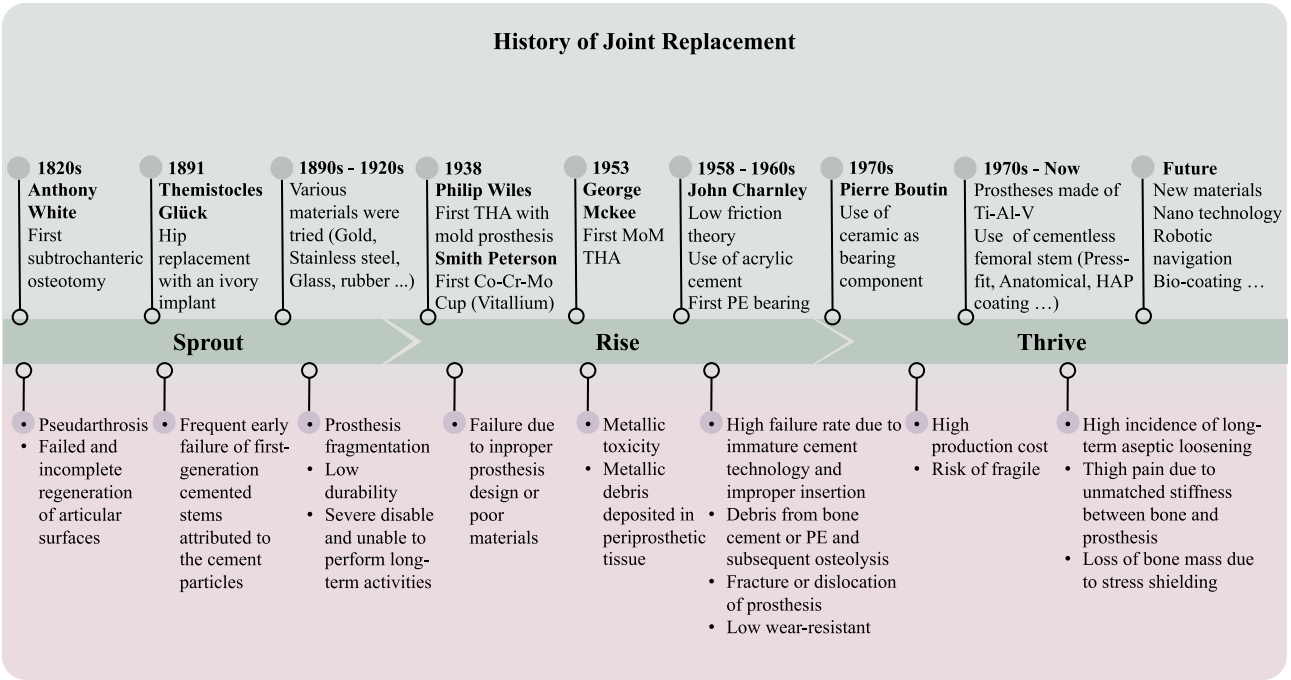


Figure 1 History of joint replacement.

a milestone in the low friction arthroplasty theory.[3] Since then, arthroplasty has been widely accepted and recognized as a standard treatment for adult joint diseases.[8] Nowadays, press-fit or anatomical prostheses have been developed, with some being modified further by hydroxyapatite coating to enhance stability or durability.[3]

Along with the continuous development of joint prostheses, arthroplasty is now being hailed as the greatest surgery of the 21st century and has become the premier solution for end-stage diseases such as osteoarthritis and osteonecrosis of

the femoral head. According to the 2022 American Joint Replacement Registry (AJRR) annual report, over 2.8 million hip and knee procedures was registered in the whole United States, representing a cumulative registered procedural volume growth of 14% compared to the previous year.[9] Undoubtedly, the solid development of joint prostheses has guaranteed total joint replacement as the most successful option for the treatment of end-stage joint diseases.

Major Characteristics of the Modern Metallic Prosthesis

The current mainstream in clinical applications for joint replacements has been shaped by advancements in alloy technology. Specifically, the Titanium-Aluminium-Vanadium (Ti-Al-V) and Co-Cr-Mo metallic prostheses are predominately utilized.[10] Ti-Al-V elements often feature as the tibial plateau in artificial knee systems or the femoral stem and acetabular cup in artificial hip systems.[11] Co-Cr-Mo, on the other hand, mainly consists of the bearing femoral head in an artificial hip or the femoral condyle in an artificial knee.[12,13] The exceptional biocompatibility, mechanical strength, and corrosion resistance ability of these alloys account for their broad applications.[11]

Biocompatibility

Biosafety concerns associated with Ti-Al-V and Co-Cr-Mo alloys are rare due to their biological inertia. Co, Cr, Mo, and V essentially participate in the metabolism of vitamins, glucose, or carbohydrate by contributing to the formation of several critical enzymes in vivo.[14–22] Although Ti, Ta, and Al are not considered essential for normal bio-functioning detected in the human body, they are detected in vivo, possibly through daily intake of food and water.[23,24] Generally, it is suggested that the aforementioned metals remaining at a physiologically acceptable level result in few adverse events. Additionally, the metals could be excreted through multiple organs. Table 1 summarizes the physiological function of these metals.[25–35]

Mechanical Strength

When treating weight-bearing joints, such as the hips and knees, appropriate mechanical strength is a key advantage of Ti-Al-V and Co-Cr-Mo alloys compared to other materials with lower elastic moduli. The elastic moduli of the Ti-Al-V alloy are approximately four to six times greater than those of cortical bone, allowing for stress-sharing with the

Table 1 Physiological Function Affected by Prosthetic Metals

Metals	Functions	Reference
Co	Cofactor of Vitamin B12 Participating in metabolism of purines, pyrimidines, amino acids, and fatty acids. Involving in the production of red blood cell Maintaining the normal functions of nervous system by creating a myelin sheath and other amino acids or proteins	[25,26,32,33]
Cr	Participating in the metabolism of lipid, carbohydrates, and protein Stimulating fatty acid and cholesterol synthesis Participating in insulin action and glucose breakdown A component of glucose tolerance factor	[29–31]
Mo	Cofactor of sulfite oxidase, xanthine oxidase, aldehyde oxidase, mitochondrial amidoxime-reducing component Catalyzing oxidation-reduction reactions Participating in the metabolism of purines/ pyrimidines amino acids, and fatty acids Enzymes containing Mo participate in the basic metabolism of carbon, sulfur and nitrogen cycles	[27,28]
Ti	–	–
Al	–	–
V	Inhibiting or activating phosphate-dependent enzymes Mimicking and potentiating effect of various growth factors such as insulin and epidermal growth factor Regulating the phosphate metabolism and phosphate-dependent energetic processes Vague function in osteogenic actions	[34,35]

Abbreviations: "-", No result; Co, Cobalt; Cr Chromium; Mo, Molybdenum; Ti, Titanium; Al, Aluminum; V, Vanadium.

periprosthetic bone and bearing the body weight as the femoral stem or tibial plateau.[36] The Co-Cr-Mo alloy, which has an elastic modulus approximately twice that of the Ti-Al-V alloy, is commonly used in grinding components such as the artificial femoral head and condyle.[36] The mechanical properties of mainstream medical metals was summarized in Table 2.[37] However, implants with extremely high elastic moduli can hinder osteointegration and result in an unstable state due to excessive stress sharing (known as the stress shielding effect), preventing adequate bone growth.[11]

Corrosion Resistance

The alloys possess excellent corrosion resistance characteristics, which are highly desired in ensuring long-term stability. Upon being implanted in vivo, gentle redox reactions start on the prosthetic surface, and a thin protective oxide membrane is known as a passivation film gradually forms.[38] This passivation film provides a clear antioxidant effect and shields the alloys from excessive redox reactions. Specifically, Ti-Al-V generates a stable Ti oxide film on their surface attributed to their strong affinity with oxygen, while Co-Cr-Mo produces a thin but denser protective oxide layer to avoid electrochemical corrosion.[39,40] These membranes can rapidly recover and resupply, even if the film is destroyed by fretting or wearing.[38]

Potential Mechanism of Metals Released from the Prosthesis

Both the hip and knee joints are load-bearing joints subjected to complex forces. In load-bearing conditions, the prosthesis must withstand the comprehensive effects of tension, compression, torsion, interface shearing, and repeated fatigue over many years. Despite the excellent corrosion resistance of Ti-Al-V and Co-Cr-Mo, metals in different forms (ions, particles, and debris) were detected in vivo under the combined effects mentioned above. The metals are released from prostheses as a result of diverse factors involving mechanical wearing, electrochemical corrosion, and inflammation.[41]

Mechanical wearing, a tribological effect of two surfaces in contact, generally includes fretting and impinging. Factors associated with fretting include the number of cycles, load to the interface, motion amplitude, frequency, and temperature. Such actions can cause abrasion of metallic particle fragments from the materials. These metallic microparticles have an irregular shape and a diameter of less than 400 μm.[42]

Electrochemical corrosion may occur on the partial or entire surface of the prosthesis, depending on the electric potential energy of the metals.[41] When active metals come into contact with other cations, the difference in electric potential energy causes electron flow, indicating the onset of corrosion. This phenomenon is more noticeable when different metals are used in alloy components, such as a Co-Cr-Mo femoral and a Ti-Al-V stem.[43] Although the passivation film mentioned earlier exists, the protective effect of the oxide membrane is cracked by the simultaneous action of electrochemical corrosion and mechanical wear. This cracking causes the continuous release of metallic debris or ions.[41]

The metallic debris and ions generated by wear and corrosion can lead to a series of cascading effects on multiple cells, including inflammation, necrosis, fibrosis, and osteolysis.[42] Macrophages play a central role in the cascade, phagocytosing the metals and releasing inflammatory mediators such as Interleukin (IL) and Tumour Necrosis Factor (TNF).[43] A specific phenotype, distinct from traditional M1 and M2 types of macrophages, has even been proposed to describe this situation.[43] Larger but non-degradable debris can be released after cell death and subsequently re-phagocytosed, triggering a negative feedback loop.[44] Furthermore, macrophages can attach to and affect the oxide surface of alloys, compromising the passivation

Table 2 Elastic Modulus of Prosthetic Metals and Natural Bone Tissues

Metals	Elastic Modulus (GPa)	Compressive Strength (MPa)	Tensile Strength (MPa)	Reference
Co-Cr-Mo	283	1976	1403	[37]
Ti-Al-V	114	1119	940	[37]
Cortical Bone	10–30	141.6	39.74	[37]
Cancellous Bone	4.5–23.6	2.270	4.5	[37]

Note: Adapted from Shanmuganantha L, Baharudin A, Sulong AB, Shamsudin R, Ng MH. Prospect of Metal Ceramic (Titanium-Wollastonite) Composite as Permanent Bone Implants: a Narrative Review. *Materials (Basel)*. 2021;14(2):2. Creative Commons.[37]
Abbreviations: Co-Cr-Mo, Cobalt-Chromium-Molybdenum alloy; Ti-Al-V, Titanium-Aluminum-Vanadium alloy.

films and accelerating corrosion.[45] Other cells, including osteoclasts and osteoblasts, are also influenced by the released metals and inflammatory mediators, amplifying the adverse events.[46,47]

Metabolism Profiles of the Prosthetic Metals

Elevation of Metals in vivo

The blood of the ordinary population contains very low levels of metals as a result of frequent exposure to metal products in their environment,[14,15,48] as indicated in Table 1. Therefore, a baseline metallic concentration was established in whole blood or serum using references from the Laboratory Test Information Guide of the London Health Sciences Centre and Mayo Clinic Laboratory data.[49–60] These measurements follow the guidelines from the Centre for Disease Control and Prevention of America (Table 3).[61]

Metallic prostheses can cause an increase in metal concentration in patients' blood that exceeds the baseline level. As indicated in a comprehensive systematic review of over 400 cases of Co-Cr hip prosthesis implantation, the mean Co concentrations were found to be 0.70 ~ 3.40 μg/L and 0.30 ~ 7.50 μg/L in the whole blood and serum, respectively.[80] Similarly, the average Cr concentrations were 0.50 ~ 2.50 μg/L and 0.80 ~ 5.10 μg/L, respectively, in the whole blood and serum, as shown by the study.[80]

Table 3 [62–79] presents evidence of increased levels of Co and Cr in the blood of patients with Co-Cr-Mo prostheses. The increased concentration persisted for 72 months, and the concentration of both Co and Cr exhibited two peaks, as observed at 24 months (6.20 μg/L of Co, 4.70 μg/L of Cr) and 60 months (8.42 μg/L of Co, 4.58 μg/L of Cr) following surgery.[81] The second peak may be attributed to secondary wearing and corrosion due to prosthetic dysfunction or patient factors, such as renal dysfunction.[82,83] However, others have suggested that after implantation of Co-Cr-Mo prostheses, the concentration of Co and Cr may initially soar before stabilizing or gradually decreasing over time.[84] The post-operative in-vivo fluctuations in Mo levels are still debatable Some studies have reported that Mo concentration peaked at 60 months following THA, reaching levels over 6 ng/mL.[81] However, other studies have shown that there was no notable rise in Mo levels detected in the blood.[85,86]

Individuals with Ti-Al-V prostheses exhibit obvious Ti accumulation (12 times higher than baseline) in their blood, peaking at 13.6 μg/L after 3 months post-surgery before declining. Ti concentration in a case with Ti-Al-V prostheses may even reach 50 times the baseline.[87] Al tends to bind to transferrin, albumin, and some low molecular weight compounds, primarily citrate,[88] in the blood, facilitating its penetration through biological barriers and subsequent clearance from the kidneys,[89] thereby producing a gentler rise compared to Ti. V primarily occurs as Vanadate or Vanadyl in the blood, binding also to transferrin, and it has a similar duration of peaking (3~6 months post-surgery) as Al.[90,91]

The release of metals into the body can be influenced by various factors that include prosthetic factors such as interfaces, designs, and manufacturing processes; patient-specific factors such as weight and physical activity; and operational factors such as instability and mismatched components. Additionally, the methods used to sample and detect metal ions in the body and the timing of these evaluations can also have an impact on the results. Specifically, the use of a Metal-on-Metal bearing interface tends to result in higher concentrations of metals in the body compared to the Metal-on-Polyethylene or the Metal-on-Ceramics bearings.[63–68,74,75,92] Moreover, higher levels of metals are commonly detected when the prosthesis is not functioning optimally.[72,93] Elevation in metallic concentration is more likely to occur when bilateral implantation is performed.[62,71,94] Other factors that can affect metal release include the surface coating,[77,78] the size of the femoral head,[66,73] and the design and manufacture of the prosthesis.[76,79]

Thus, long-term monitoring of the state of the prosthesis after implantation is essential. Prostheses in an abnormal state are more prone to severe wear and may result in a secondary surge in metal concentration following surgery. Continuous monitoring of metal concentration fluctuations, for example, at 3- or 6-month intervals following implantation, can aid in evaluating the state of the implanted prosthesis and predicting its lifespan. Therefore, postoperative metal concentration can be an essential indicator of the state of the implanted prosthesis. However, some aspects, including sensitivity, specificity, and the time lag between increased metal concentration and the occurrence of an unstable prosthesis, require further confirmation. The findings presented in this study may provide some insights; however, further detailed investigations are necessary.

Table 3 Reference Range and Postoperative Concentration of Prosthetic Metals in the Blood

Metals		Reference Range (μg/L)	Postoperative Metallic Concentration (μg/L)								Reference
			3 Months	6 Months	12 Months	18 Months	24 Months	36 Months	60 Months	72 Months	
Co	Serum/Plasma	0.000–0.900	–	0.650	0.130–1.700	0.760–5.160	0.140–0.770	0.780–1.620	0.180–2.930	0.240–0.860	[52,62–68]
	Whole Blood	0.000–1.000	0.900–1.900	0.850–2.650	0.360–3.400	–	0.360–6.200	0.850–3.650	0.340–8.420	–	[55,62,69–76]
Cr	Serum/Plasma	0.000–0.300	–	0.600	0.250–2.100	0.500–2.980	0.180–1.300	0.970–2.410	0.210–1.200	0.360–1.050	[51,62–68]
	Whole Blood	0.000–1.000	1.300–3.100	0.100–4.150	0.300–4.150	–	0.240–4.700	0.100–4.300	0.100–4.580	–	[54,62,69–76]
Mo	Serum/Plasma	0.300–2.000	–	–	0.250–0.970	–	–	0.890–0.930	–	–	[56,65,77,78]
	Whole Blood	0.000–4.000	–	–	–	–	–	–	–	–	[53]
Ti	Serum/Plasma	0.000–1.000	10.290–13.600	9.050–12.780	5.270–11.700	–	8.900–9.340	–	–	–	[50,68,79]
	Whole Blood	0.000–1.000	–	–	0.940–3.360	–	1.200–3.460	–	1.230–3.780	–	[60,69,76]
Al	Serum/Plasma	0.000–6.000	10.900–11.800	9.500–13.700	9.400–9.800	–	7.730–7.900	–	–	–	[49,79]
	Whole Blood	0.000–15.100	–	–	–	–	–	–	–	–	[59]
V	Serum/Plasma	0.032–0.088	0.550–0.720	0.710–0.920	0.600–0.630	–	0.490–0.560	–	–	–	[57,79]
	Whole Blood	0.026–0.106	–	–	–	–	–	–	–	–	[58]

Abbreviations: "-", No result; Co, Cobalt; Cr Chromium; Mo, Molybdenum; Ti, Titanium; Al, Aluminum; V, Vanadium.

Biodistribution and Deposition

Metals released from implanted prostheses eventually deposit in various organs and tissues through transportation via blood or interstitial fluid. Although direct detection of metal accumulation in tissues of THA or TKA patients remains lacking, the biodistribution or deposition of blood metals has been confirmed via experiments conducted in human or animal models, as well as biokinetic models. Figure 2 summarizes the biodistribution of these metals.

Bone and Muscle

Concentration of Co up to 380 ppm was detected in the mineralized periprosthetic bone two years after implantation of the prosthesis.[95] In an animal trial, Co distribution in muscle was also observed.[96] Although the Cr level in the mineralized periprosthetic bone exhibited no significant change,[95] a biokinetic investigation provided evidence of Cr distribution in bone.[97] Biopsy results from THA or TKA patients or animal models failed to present any relevant evidence of Mo accumulation.

While Ti deposition from prostheses was not detected in bone and muscle, Ti from dental implants was found in the jawbone and surrounding soft tissue.[95] Evidence of Ti retention in bone is also found in an animal trial.[98] Bone and muscle serve as the primary accumulation sites for Al, with 60% and 10%, respectively.[99,100] V is detectable in human muscle tissue, with elevated levels also found in rat bone after a long-term high V diet or intravenous injection.[101]

Kidney and Liver

The kidney and liver are organs that filter and purify blood flow. Biopsies from patients with bilateral THA have shown concentrations of Co, Cr, and Mo nearly fifty times higher than the standard value,[102] similar to findings from studies in rats with metallic implants.[103,104]

Elevated levels of Ti concentration in the liver of Metal-on-Metal bearing THA patients are confirmed 4 to 10 years post-implantation.[105] Both laboratory rats with hamster dose injections and New Zealand rabbits with proximal tibial

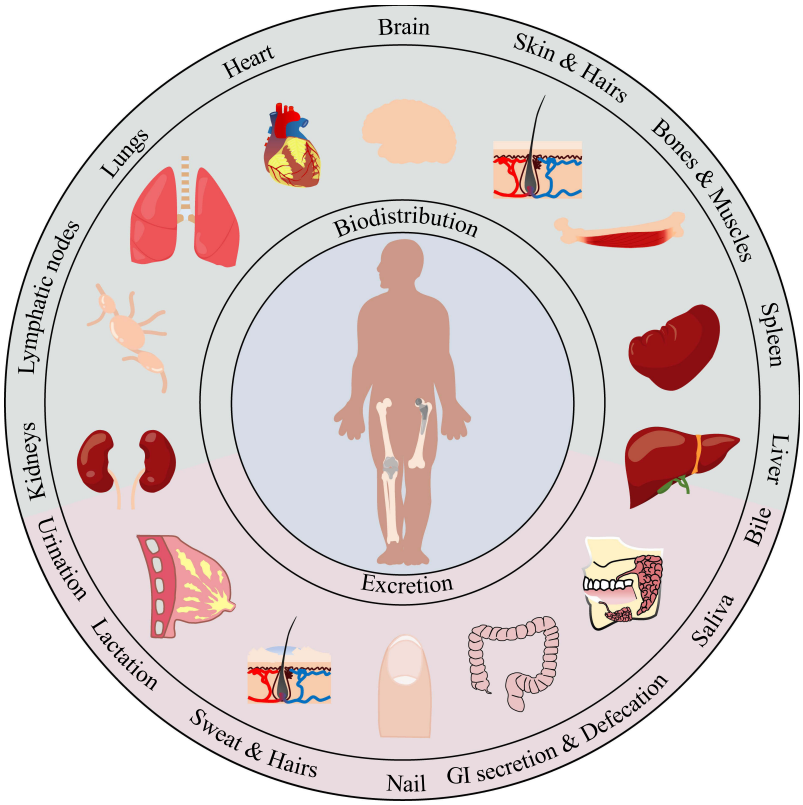


Figure 2 Biodistribution and excretion of prosthetic metals.

screw implants have experienced Ti accumulation in the liver and kidney.[24,105] Approximately 3% of the total body burden of Al is found in the liver,[99] whereas evidence of Al kidney retention is only present in rats in intravenous injection tests.[100] Limited evidence of V accumulation has been found in the kidney or liver of THA or TKA patients; however, biokinetic calculation suggests V tends to first accumulate in the kidneys, then the liver of rats treated with oral V administration.[106]

Brain

The ability of metals to permeate the brain depends on their ability to cross the blood-brain barrier (BBB). Ti dioxide nanoparticles have been reported to cause damage to the BBB ultrastructure and increase BBB permeability.[107] Elevated levels of Ti in brain tissue were found in laboratory rats after intravenous injection of Ti nanoparticles,[108] with the metal mainly concentrating in the hippocampus.[109] It is estimated that with the assistance of transferrin and citrate, approximately 1% of the total Al burden and 5% of the total V burden are deposited in the brain.[90,99] V dose-dependently accumulates primarily in the olfactory bulb, brain stem, and cerebellum,[110,111] while experimental studies show Al retention in cerebral tissue detected in rats treated with a dose of intravenous Al.[100] However, no significant increase in Ti, Al, and V has been reported in patients with metallic prostheses.

Co and Cr may enter the brains of THA patients through cerebrospinal fluid circulation,[112] with animal trials showing accumulation in cerebral tissue.[113,114] Evidence for Mo accumulation in brain tissue is limited.

Lung

Although few reports indicate the metal deposition of Co-Cr-Mo or Ti-Al-V in human lungs, elevated concentrations of Ti, Al, and V were found in the lungs of laboratory baboons with Ti-Al-V alloy implantation.[115] Furthermore, increased Co, Cr, and Mo levels were found in lung tissue after Co-Cr-Mo debris was implanted under rat skin, with peak concentrations recorded at 48 hours.[116]

Spleen

Studies have reported Co, Cr, and Mo deposition in the spleen of THA and TKA patients, with concentrations exceeding baseline values.[102,117,118] In an animal trial, Ti retention in the spleen of rats was detected after intraperitoneal or intravenous injection of Ti dioxide.[109] Biokinetic modeling based on multiple human and animal studies confirms Al accumulation in the spleen.[119] Accumulation of V in humans was confirmed in the spleen, a fact also evidenced in rats.[106]

Other Organs and Tissues

In addition to the previously mentioned organs, traces of these metals have been found in other tissues in the human body. Elevated levels of Co, Cr, Mo, Ti, and Al have been detected in the hair of patients that have prostheses.[120,121] A high level of Co was found in the heart of a patient after they experienced fatal cardiomyopathy due to severe wear of the Co-Cr-Mo alloy.[122] Additionally, an investigation showed higher levels of Co in the seminal plasma of implanted patients (2.89 μg/L) compared to control patients (1.12 μg/L).[123] An implantation model of metallic debris also suggested elevated levels of Co in the heart and testis.[116] In addition, deposition of Al in body fat and accumulation of Mo in lymph nodes were also confirmed in patients with THA.[124]

Excretion and Elimination

The kidneys were the primary excretion site for all the metals mentioned.[88,96,106,109,125–127] TKA or THA patients had high metal concentrations in their urine.[128–130] Strong evidence indicated high average Co concentrations in the urine of patients who had undergone THA.[81,92,131–139] An experiment administering Co intravenously in humans demonstrated that 40% was eliminated within the first 24 hours, 70% within a week, 80% within a month, and 90% within a year.[140] The geometric mean Mo level in the blood was 15.36 nmol/L, while the highest level in urine was 58.41 μmol/L.[141] Furthermore, a volunteer experiment demonstrated rapid Mo excretion,[142] which could explain the low Mo level in the blood and the low risk of adverse effects from Mo. Al and V are rapidly excreted by converting to hydrophilic forms (Vanadyl or Vanadate)[106] or combining with hydrophilic substances (citric acid, transferrin, or albumin).[89] These processes enhance penetration and improve kidney clearance, but only 10% can pass through the glomerular membrane

as free ions.[89] Nevertheless, due to the continuous metallic release in THA patients, the excretion of both metals gradually slows down after the initial rapid phase and persists for several years.[90,91,128]

In addition to urination, faecal excretion is an important elimination pathway for metals. Metals, including Cr, Al, V, and Ti, in the gastrointestinal tract primarily come from saliva, bile, and gastrointestinal secretions,[88,90,106,109,143,144] and due to their poor absorption rate, they are eliminated with feces.[90,125,145–148] Moreover, Cr and Ti can be eliminated through the shedding of nails, hair, sweat, and milk.[109,143] Ti particles can also be phagocytosed by cells and coughed up as sputum from the respiratory tract (Figure 2).[109]

Toxicity Induced by the Prosthetic Metals

Toxicity to Organs and Tissues

Continuously high concentrations of these metals can cause damage to multiple organs, with diverse clinical manifestations. Reports show that elevated Co in THA or TKA patients can cause various organ damages, including neurotoxicity (lethargy, hearing loss, numbness, paresthesia, tinnitus, visual and auditory abnormalities, and peripheral neuropathy), cardiomyopathy, pericardial effusion, hypothyroidism, hepatotoxicity, allergic dermatitis (rash) and polycythemia.[149–153] High levels of Co can also cause systemic toxicity that can lead to hard metal asthma, hard metal disease (pulmonary fibrosis) and myocardial toxicity better known as "Beer Drinkers' Cardiomyopathy".[25,154–157] Excess Cr can lead to similar systemic toxicity in the nervous and circulatory systems.[152]

Chronic accumulation of Al in the brain can cause neurological damage, including Alzheimer's and Parkinson's diseases, with symptoms such as brain degeneration, disorientation, memory impairment, dementia, and changes in personality and intelligence.[100,158] Al accumulation in the kidneys can cause fibrosis in glomeruli or Bowman's capsule,[100] leading to renal dysfunction and subsequent microcytic anemia.[159] Al systemic toxicity can also manifest as bone diseases such as osteomalacia due to interference with parathyroid hormone and bone calcium metabolism.[100] Excessive V deposition can cause systemic toxicity, including peripheral neuropathy, skin allergies, diarrhea, kidney damage, and reproductive system damage, as reported in several studies.[160–166] Systematic pathological changes from high Ti, and Mo levels after THA or TKA are uncommonly reported.[167–172]

Aside from causing systemic changes, accumulated metals in situ can also trigger adverse local tissue reactions (ALTRs) in the periprosthetic tissues, such as inflammatory pseudotumor, osteolysis, and tissue necrosis.[173–176] Excessive Ti, in the form of metallic oxide nanoparticles, can often cause periprosthetic osteolysis and inflammation.[24,109,146,177,178] Another possible localized adverse reaction known as aseptic lymphocyte-dominated vascular-associated lesions (ALVAL), may occur in patients with especially a Metal-on-Metal bearing prosthesis. ALVAL is resulted by activated cytotoxic T lymphocytes and macrophages induced via the T lymphocyte-mediated type IV hypersensitivity reactions, for the metal debris or ions released from the prosthesis diffuse into the surrounding tissue, complexing with natural proteins to form hemi-antigens and leading to the allergic reaction.[179] The histopathological manifestation of ALVAL is characterized as an aseptic and chronic perivascular inflammatory response dominated by lymphocytic infiltration.[179] ALVAL has been shown to have a positive correlation with elevated Co and Cr concentrations, but no evidence with Ti, Al, V, and Mo has been found.[180,181] The reported cases also focused only on the abnormally elevated levels of Co and Cr in the patients' blood.[181] Most patients with ALVAL manifest as persistent periarticular pain, especially persistent groin pain after THA, and further examination also reveals pathologic changes such as joint effusion and osteolysis.[180]

Metals are also known to pose considerable risks of both carcinogenicity and mutagenicity. Experimental evidence has confirmed the carcinogenic and mutagenic potential of Co, Cr, and both ionic and oxide forms of Ti,[177,182–196] and they are more likely to pose risks that are time-dependent rather than concentration-dependent.[197] The carcinogenicity of Al is yet to be confirmed, although a correlation has been observed between Al and breast cancer.[100] It is still unclear whether the metals act as a single causative factor or as a co-inducing factor with other substances during tumor development.[90]

Toxicity to Cells and Biomolecules

To gain a deeper understanding of metal toxicity like inflammation, osteolysis, and mutagenicity, researchers have studied their toxic effects on the cell and biomolecule aspects. Therefore, we will further discuss the potential mechanisms of how the

release of metals correlates with the regulation of the inflammatory cascade, the inhibition of osteoblasts, the activation of macrophages and osteoclasts, and the damage to the biomolecules and organelles.

Macrophage and Osteoclasts Activation

After the uptake of metals by macrophages and osteoclasts through phagocytosis, these cells get activated to release pro-inflammatory mediators, such as IL-1β, IL-6, TNF-α, and Prostaglandin E2 (PGE_2), which participate in the receptor activator of nuclear factor-kappa B/ligand (RANK/RANKL) signaling to provoke osteolysis and inflammation.[198–202] The larger non-degradable debris is re-phagocytosed after cell death, creating a closed circuit that promotes inflammation continuously.[44] Moreover, mature osteoclasts also produce acid and enzymes that erode the prosthetic surface and enable the uptake of dissolved metals, thereby compounding the damage.[203] The effects of metals on osteoclasts and macrophages vary according to the concentration.[200] Extremely high metal concentrations are believed to have a direct harmful effect on cell viability.[200]

Osteoblasts and Mesenchymal Cells Inhibition

Apart from macrophages and osteoclasts activation, osteoblasts and mesenchymal cells also have an essential role in the emergence of ALTR, given the imbalanced homeostasis of bone resorption and formation.[204] After internalizing prosthetic metals, osteoblasts are impacted, and their viability and proliferation are affected, which can cause cell death.[205–207] On the other hand, osteoblasts exhibit downregulation of the type-I collagen gene expression, while cytokines like IL-6 and TNF-α occur synchronously.[205,206] Factors derived from osteoblasts promote osteoclastogenesis by facilitating its progression.[207] Also, exposure to prosthetic wear products in vivo and in vitro reduced mesenchymal cells' alkaline phosphatase activity and matrix mineralization for osteogenesis.[208]

Inflammatory Cascade Regulation

Cytokines that metallic-activated cells release act as messengers that disperse the functions of different cells throughout the regulatory network of local osteolysis and inflammation. For instance, PGE_2, and TNF-α are essential activators of the RANK/RANKL pathway and suppressors of type-I collagen generation.[207,209–211] TNF-α production activates the osteoclast precursor through calcineurin/nuclear factor of activated T cells 1 (CaN/NFATc1) signaling[212–214] and upregulates the RANKL expression in osteoblasts.[213,215–219] Additionally, chemokines like granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF) enhance and accumulate inflammatory cells. Furthermore, the chemokines like monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) are responsible for osteoclasts migrating to periprosthetic tissues.[198,220–225]

The regulation of most cytokines is thought to occur following a metallic concentration and time-dependent pattern. Elevated levels of Co and Cr can lead to increased TNF-α upregulation.[226] Furthermore, Co promotes other cytokines and chemokines, such as IL-1β, IL-6, IL-8, PGE_2, INF-γ, MCP-1, MIP-1α and vascular endothelial growth factor-a (VEGF-A),[227–229] while Cr is believed to promote IL-1β, MCP-1, and MIP-1α.[228,230] Promotion of cytokines by Mo includes IL-1β, IL-6, and TNF-α.[231] Ti causes upregulation of cytokines, including IL-1β, IL-6, IL-8, TNF-α, and PGE_2.[232–234] Moreover, M-CSF and GM-CSF are promoted by Ti to induce the maturation and gathering of inflammatory cells.[235] V upregulates TNF-α, IL-6, and IL-8 expression, while suppressing IFN-γ and IL-10 expression.[236–239] Besides, common inflammatory cytokines such as IL-1β, IL-8, and TNF-α, Al promotes cytokines including MIP-1α.[240,241] Figure 3 and Table 4 summarize the cytokine profiles that were upregulated. Contrarily, metals such as Co, Cr, and Ti are known to downregulate transforming growth factor-β (TGF-β), the factor that promotes anti-inflammation and type-I collagen synthesis.[242,243]

Toxicity to Biomolecules

Studies have shown that excess metals can cause molecular-level hazards such as structural damage to DNA and chromosome abnormalities (including aberrations, translocations, and aneuploidy), which can increase the risk of genotoxicity and carcinogenicity.[268,269] In summary, the study of toxicology can be classified into three basic categories: i. metals binding directly to molecules and influencing their functions or structure; ii. metals generating free radicals and oxidative species that lead to significant damage; iii. metals interfering with signaling molecules in specific pathways.

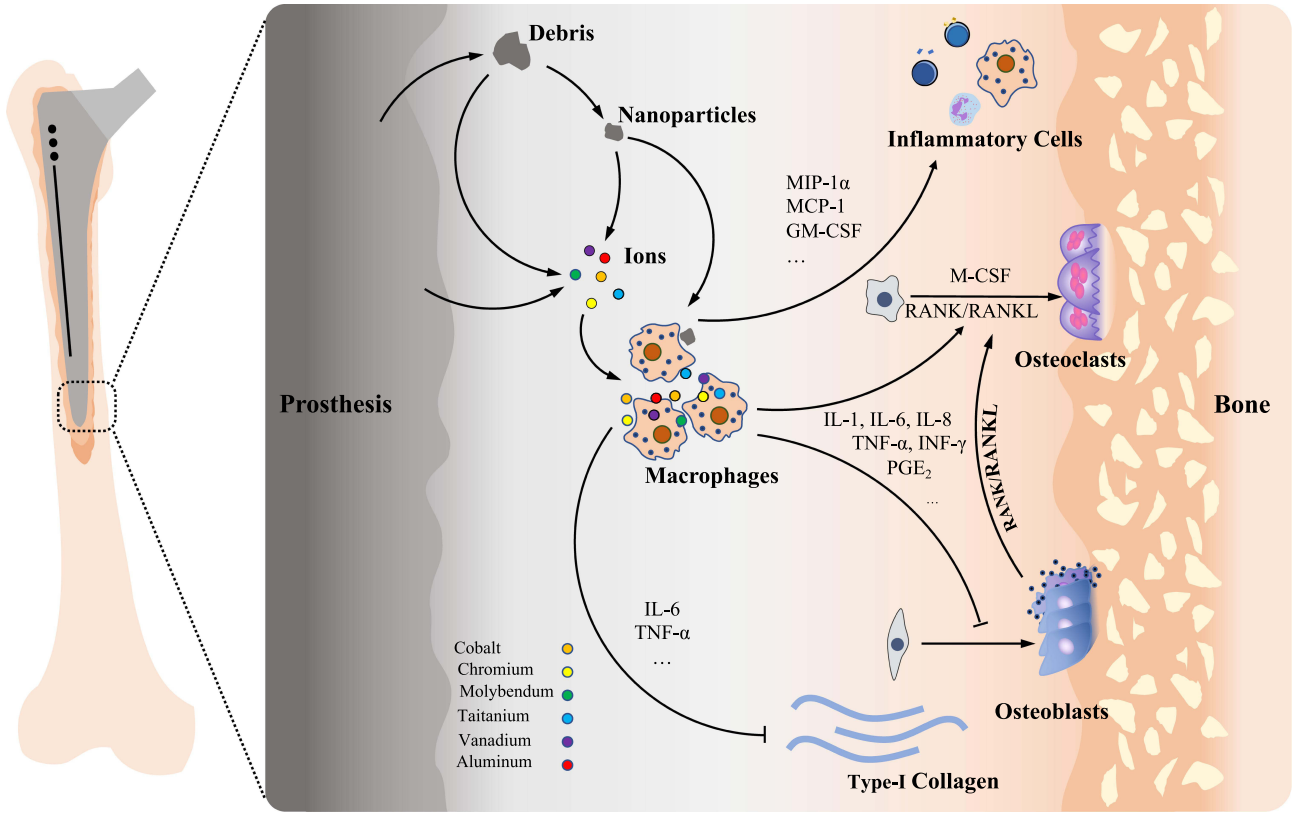


Figure 3 Macrophage, osteoblasts and osteoclasts influenced by prosthetic metals.

The damage induced by direct combination mostly emerges in the ionic metals through the direct combination with negatively charged components due to ionic interactions. The toxicity is strengthened with the higher charges of the cations.[270] Toxicity of bivalent Co (Co^{2+}) is attributed to their notable capacity to interact with Zinc finger motifs, which mediates the interactions between proteins themselves and nucleic acids,[271] thus resulting in DNA single-strand break, DNA repairing interruption, DNA-protein cross-linkage and sister chromatid exchange.[272–276] The decreased function of the osteogenic-related alkaline phosphatase due to the direct substitution of Zn^{2+} by Co^{2+} has also been reported.[277] Furthermore, the high affinity to sulfur atoms enables Co^{2+} to suppress the antioxidation of lipoic acid in mitochondria, subsequently blocking the citric acid cycle, the core of adenosine triphosphate (ATP) production,[275] which has been evidenced by the Co-dose-dependent ATP depletion and the consequently decreased mitochondrial membrane potential.[258] Trivalent Cr (Cr^{3+}) can be directly combined with DNA to form a stable Cr^{3+}-DNA admixture and DNA-DNA cross-linkage. Hence, the single or double-strand structure of nucleic acid is destroyed.[278,279] As the Cr^{3+} concentration significantly increases, enzyme activity is directly inhibited, where the active center is restricted by Cr^{3+}, leading to the more pronounced toxicity.[280] The primary toxicology of ionic Ti is its direct combination with cellular structures, including phosphorylated proteins, phospholipids, and nucleotides,[203] consequently hindering cellular functions. The combination of Trivalent Al (Al^{3+}) with phospholipids, the chief component of the membrane of a cell or organelle, can render the peroxidation and alter membrane fluid dynamics.[159] Once the mitochondrial membrane is affected, cytochrome c can be released, initiating cell apoptosis.[159] V appears more as Vanadate and Vanadyl, rather than in the ionic form. The metallic salt is proven to be able to inactivate a series of bioligands, including Glutathione, ATP, adenosine diphosphate (ADP), nicotinamide adenine dinucleotide (NAD), amino acids and some enzymes (phosphatases and dynein ATPase), after the direct combination.[239,281]

Reactive oxygen species (ROS) is a group of oxygen-free radicals typically generated by neutrophils and macrophages during inflammation or by metal-catalyzed reactions.[282] ROS can be hazardous if they overwhelm the body's antioxidant protection, leading to interference with DNA bases, enhanced lipid peroxidation, and changes in calcium and sulfhydryl homeostasis.[282] The generated hydroxyl radicals play a major role in later intensive oxidative damage to

Table 4 Inflammatory Cytokines, Chemokines and Signaling Related to Prosthetic Metals

Metals	Increased Cytokines	Decreased Cytokines	Chemokines	Signaling Molecule	Reference
Co	TNF-α, PGE2, INF-γ, VEGF-A IL-1β, IL-6, IL-8	TGF-β	MCP-1 MIP-1α	HIF-1, PI3K, AKT, mToR, RhoA	[244–246]
Cr	IL-1β TNF-α	TGF-β	MCP-1 MIP-1α	Ca^{2+}/CaMK, SRC, Ras, AMPK, PGC-1α	[247–249]
Mo	IL-1β, IL-6 TNF-α	–	–	JNK, ERK1/2, AMPK	[250,251]
Ti	IL-1β, IL-6, IL-8 TNF-α, PGE2	TGF-β	M-CSF GM-CSF	PI3K, AKT, p38MAPK, ERK1/2, PKCε, NF-κB, GSK-3β, β-catenin, MAPK, JNK, HIPPO, YAP	[252–257]
Al	IL-1β, IL-8 TNF-α	–	MIP-1α	JNK, Ca^{2+}/CaMK, Wnt, β-catenin, PI3K, AKT, DDX3X, NLRP3, PHF8, H3K9me2, BDNF	[258–266]
V	IL-6, IL-8 TNF-α	INF-γ IL-10	–	PLA2, SRC, EGFR, PKC, MAPK, NF-κB, JNK	[267]

Abbreviations: "-", No result; Co, Cobalt; Cr, Chromium; Mo, Molybdenum; Ti, Titanium; Al, Aluminum; V, Vanadium; TNF-α, Tumor Necrosis Factor α; PGE2, Prostaglandin E2; IFN-γ, Interferon-γ; IL, Interleukin; VEGF-A, Vascular Endothelial Growth Factor A; TGF-β, Transforming Growth Factor-β; MCP-1, Monocyte Chemoattractant Protein-1; MIP-1α, Macrophage Inflammatory Protein-1α; M-CSF, Macrophage Colony Stimulating Factor; GM-CSF, Granulocyte- Macrophage Colony Stimulating Factor; HIF-1, Hypoxia-Inducible Factor-1; PI3K, Phosphoinositide 3-Kinase; AKT(PKB), Protein Kinase B; mToR, Mammalian Target of Rapamycin; RhoA, Ras homolog gene family-member A; CaMK, Ca^{2+}/Calmodulin-Dependent Protein Kinase; AMPK, Adenosine 5'-Monophosphate-Activated Protein Kinase; PGC-1α, Peroxisome Proliferator-Activated Receptor-Gamma Coactivator-1α; JNK, c-Jun N-terminal Kinase; ERK1/2, Extracellular Regulated Protein Kinases 1/2; p38MAPK, p38- Mitogen-Activated Protein Kinase; PKCε, Recombinant Protein Kinase Cε; NF-κB, Nuclear Factor κB; GSK-3β, Glycogen Synthase Kinase 3β; YAP, Yes-Associated Protein; DDX3X, DEAD (Asp-Glu-Ala-Asp) Box Polypeptide 3; NLRP3, NOD-like Receptor Thermal Protein Domain Associated Protein 3; PHF8, PHD Finger Protein 8; H3K9me2, trimethylation of lysine 4 of the third subunit of histones; BDNF, Brain-Derived Neurotrophic Factor; PLA2, Phospholipase A2; EGFR, Epidermal Growth Factor Receptor.

biomolecules (DNA, chromosomes, proteins, and polyunsaturated fatty acids) and cell organelles (such as mitochondria and lysosomes) due to the concentration-dependent result of Co^{2+},[275] Cr^{3+},[278,279,283] and Mo[283] overload. Detectable elevation of superoxide dismutase (SOD)[283] and catalase activity[280] is further evidence of metal-induced oxidative stress caused by ROS. The hexavalent (Cr^{6+}) form is often used for prosthetic fabrication.[284] However, Cr^{6+} has a transient biological half-life due to its high potential energy, which tends to switch to the more stable Cr^{3+} form - The most common oxidation form found in humans. This means that the hexavalent form is likely to be reduced to trivalent swiftly by redox reactions in cells, potentially leading to intensive oxidation damage to biomolecules and organelles.[285]

For Ti-Al-V alloys, ROS is generated by Ti dioxide (TiO_2) nanoparticles.[286] The following oxidative stressing leads to repeated cell damage and proliferation, indirect DNA damage, and finally, abnormal cell growth behavior.[287] Trivalent Al (Al^{3+})-associated with oxidative damage affects the mitochondria functioning,[288] inducing p53 elevation, chromosome translocation and DNA fragmentation, followed by the activation of caspase-3 and caspase-12.[159] This implies genomic instability, the hallmark of tumorigenesis and a prerequisite condition for malignant transformation.[289] A series of oxide compounds of V (V_2O_5, V_2O_3, V_2O_4) and Vanadyl and Vanadate is the source of ROS, which is dose- or time-dependently.[239,290–293] The consequences are upregulation of cyclooxygenase-2,[294] activation of p21 and p53,[295] and inhibition of a cyclin named Cdc25C,[296] finally leading to abnormal anti-apoptotic effect, arrested cell cycle and improper cell growth. Additionally, increased DNA strands are broken and chromosomal damages involving aberration, sister chromatid exchange and aneuploidy also happen because of V oxide compounds.[297–299]

Metals, in addition to causing structural damage and inactivating functional biomolecules, can inhibit signaling networks. For instance, the elevation of Co can create a hypoxic environment, which can result in the regulation of the PI3K/AKT/mTOR pathway, leading to cell autophagy or proliferation.[244,245] Moreover, Co-generated ROS can decrease macrophage motility by downregulating the RhoA signaling pathway.[246] Cr can cause endoplasmic reticulum stress, mitochondrial dysfunction, and carcinogenicity via Ca^{2+}/CaMK, SRC/Ras, and AMPK/PGC-1α.[247–249] Mo can trigger DNA damage, the release of IL-6, and cell death through JNK, ERK, and AMPK signaling.[250,251]

Ti is responsible for PI3K/AKT/p38MAPK and NF-κB signaling, leading to cell autophagy or apoptosis.[252,253] NF-κB controlled by PKCε and ERK1/2 stimulated by Ti has a pro-inflammatory effect.[254] On the other hand, Ti can inhibit osteogenesis via several signaling, including GSK-3β/β-catenin, MAPK/JNK, and HIPPO/YAP.[255–257] Abnormal activation of JNK and Ca^{2+}/CaMK pathway in osteoblasts in the process of Al-associated cell apoptosis,[259,260] plus the inhibition of osteogenesis via Al interfering with Wnt/β-catenin pathway,[261] both enhance osteolysis. Furthermore, Al-associated dysfunctional mitochondria affect Ca^{2+}-ATPase, hindering the Ca^{2+} influx.[258,262] The obstacle on the Ca^{2+} channel triggers the altered Ca^{2+} signaling, leading to the generation of pro-apoptotic factors and cell death.[263] Besides, Al-associated ROS also affects the PI3K pathways, with downstream effects on cell growth and proliferation and a close relationship to tumor development.[264] In nerve tissue, Al induces inflammation and synaptic damage through DDX3X/N2RP3 and PHF8/H3K9me2/BDNF pathways.[265,266] V can promote inflammation by elevating arachidonic acid via calcium-dependent PLA2,[267] and on the other hand, by facilitating COX-2 synthesis through SRC or EGFR and the downstream PKC and MAPK.[267] Besides, ROS generated by V also influences NF-κB.[267]

Conclusion and Perspective

Metallic prostheses have been developed and perfected over nearly a century, and are now used in joint replacements. However, the release of metals from Co-Cr-Mo and Ti-Al-V prostheses cannot be overlooked. Several studies have found a significant link between these metals and long-term adverse consequences of the implanted prosthesis. Metals released from implants can distribute in multiple organs and accumulate in surrounding tissues. While blood metals can be presented in various ways, significantly elevated blood metals have been detected in patients undergoing TKA and THA. High levels of metals can have considerable toxic and destructive effects on distributed organs and surrounding tissues. This adverse effect is linked to the disturbance of the inflammatory cascade and the dysfunction of critical cells and biomolecules.

Factors such as unstable implantation or a mismatch of prosthetic components can lead to an increase in metal concentration. The clinical application of digital technology may help solve problems and improve the curative effect. Robot technology is currently the most advanced representative of digital technologies. Although the current use of robot-assisted artificial joint replacements has some limitations, it represents the future development trend in joint surgery and is an inevitable result of industry advancement. Current hip and knee replacement surgery robots provide doctors with visual 3D preoperative planning, which allows for more precise operations. Robotic assistance can reduce human error and help ensure the accurate placement of the prosthesis during the operation, which can reduce the risk of postoperative complications. The use of this technology can also help achieve better soft tissue balance in knee joint replacement. Joint replacement prostheses may become highly personalized in the future, with support from imaging technology, 3D printing, computer technology, and relevant laws and regulations.

Improved prosthetic implant materials are a promising direction of research. Four main design factors have been identified: reducing the elastic modulus to better match that of human bone (~30 GPa), improving the biocompatibility and corrosion resistance of metal alloys, using non-toxic alloy elements (avoiding toxic Al and V), and enhancing the tensile and fatigue strength of titanium alloys. Personalized design, particularly for children and young adults, can prevent damage during implant removal by designing new titanium alloys that do not grow well into bone. In the future, joint replacement prostheses may be highly personalized, but this will require support from imaging technology, 3D printing, computer technology, relevant laws, and regulations.

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Disclosure

The authors declare no competing interests in this work.

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