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## The Biological Response to Orthopaedic Implants for Joint Replacement: Part I: Metals

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### Abstract

Joint replacement is a commonly performed, highly successful orthopaedic procedure, for which surgeons have a large choice of different materials and implant designs. The materials used for joint replacement must be both biologically acceptable to minimize adverse local tissue reactions, and robust enough to support weight bearing during common activities of daily living. Modern joint replacements are made from metals and their alloys, polymers, ceramics, and composites. This review focuses on the biological response to the different biomaterials used for joint replacement. In general, modern materials for joint replacement are well tolerated by the body as long as they are in bulk (rather than in particulate or ionic) form, are mechanically stable and noninfected. If the latter conditions are not met, the prosthesis will be associated with an acute/chronic inflammatory reaction, peri-prosthetic osteolysis, loosening and failure. This article (Part 1 of 2) is dedicated to the use of metallic devices in orthopaedic surgery including the associated biological response to metallic byproducts is a review of the basic science literature regarding this topic.

### Keywords

orthopaedic implants; biological response; foreign body response; inflammation; biomaterials

### INTRODUCTION

The use of implanted devices in surgery has increased dramatically; when considering the field of orthopaedic surgery alone, the underlying industry is expected to grow to \$41.1 billion by 2016.<sup>1</sup> Briefly, the goals of total joint replacement (TJR) implants are to relieve pain and restore function, with limited impact on the surrounding tissues. Studies focusing on long-term outcomes of total knee replacement have shown survivorship after 15 years ranging from 81.7 to 98.14%.<sup>2–4</sup> Similarly, studies for total hip replacement showed

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survivorship after 15 years ranging above 90%.<sup>5,6</sup> Several materials are currently available for the surgeons and bioengineers when designing a TJR. As a support for artificial joints, metal implants are widely used in orthopaedic surgery. Metal implants can be monobloc (one piece), modular (different pieces put together) or articulate to each other. As implanted in a living body, metal implants may have adverse effect. Metal alloys are mainly used to replace the bone (e.g., femoral stem and acetabular shell), metal alloys or ceramics replace the articular surface on the femoral side, and polyethylene (PE) or ceramics replace the articular surface on the acetabular side. Polymethylmethacrylate (PMMA) can be used to cement the implants within the bone.

Historically, the use of metal alloys started in 1923 when Smith-Peterson introduced the cobalt–chromium alloy (Vitallium, Howmedica). Stainless steel was introduced in 1942 and titanium alloy in 1951. Animal experiments conducted in the early 1960s by Laing et al.<sup>7</sup> showed that the tissue reaction to various metallic implants can be classified according to the degree of severity of the reaction. In general, the degree of tissue reaction was proportionate to the amounts of constituent elements released by corrosion of a pure metal or an alloy. Discussing the electrochemical fundamentals of implant metal performance, Pourbaix<sup>8</sup> later pointed out that both electrochemical thermodynamics (determining corrosion tendencies) and electrochemical kinetics (determining corrosion rates) are important to consider in order to better understand and predict the corrosion behavior of metals and alloys in the presence of body fluids. This article identified 13 metals that may theoretically be considered for use as surgical implants and dental alloys. 8 of them (Au, Ir, Pt, Rh, Ru, Pd, Ag, and Os) are noble metals, which keep a pure metallic surface. The remaining 5 (Ti, Ta, Nb, Zr, and Cr) are passive metals, which are covered by a layer of protective oxide. Subsequent electrochemical tests by Zitter and Plenk<sup>9</sup> demonstrated that the use of passive metals is more preferable for surgical implants because of their protective surface layers of semi- or nonconductive oxides that prevent any exchange of electrons and thus any redox reaction at the surface. The electrochemical “inertness” ranking of the metal surfaces tested was increasing in the order of gold, stainless steel, the cobalt-based alloy, and the TiAlV alloy, with the pure metals Ti, Nb, and Ta being the most favorable. The authors concluded that this rating of metallic implant materials based on *in vitro* measurements of current densities was in good accordance with their biocompatibility rating reported from *in vivo* experiences. These electrochemical studies in the mid-1980s also pointed out that “more basic work remains to be done for studying thoroughly the conditions of crevice corrosion and fretting corrosion of metallic surgical implant materials”<sup>8</sup> and that “the effect of a redox reaction taking place without corrosion is same as that of a corrosion reaction: in both cases the most significant chemical changes are an increase in the pH value at the cathode and a decrease in this value at the anode.”<sup>9</sup> All these considerations became even more important in the following years when the use of modular implant devices increased significantly.<sup>10–12</sup> Therefore, the selection of metal to be used in a TJR is highly important for bioengineers who design the implant. The goal being to provide the patient a harmless long lasting implant.

This review of the basic science literature will focus on the mechanisms of metal ion and particle generation during TJR (e.g., modular junction corrosion and metal wear), most frequent use metals in TJR, as well as the effect of these metals on the surrounding cells and

tissues. Polymers, ceramics, and composites will be the subject of a second review (see Part II).

## MODULAR JUNCTION CORROSION IN TJRs

Corrosion of orthopaedic implants was first reported in 1956 after discovering that metal ions had harmful effects on the soft tissues.<sup>13</sup> Five different modes of corrosion are described: galvanic, fretting, crevice, pitting, and intergranular.<sup>14–18</sup> In an oxygen rich environment, the surface of metal implants is covered in a thin layer of a metal oxide that protects the underlying metal from further oxidative damage. This oxidized protective layer is the by-product of passivation (Figure 1). If this oxide layer is damaged, the surface of the metal implant re-oxidizes (re-passivates) to recreate the protective oxide layer. When the re-passivation process is disrupted, corrosion can occur.<sup>19</sup> Corrosion and subsequent production of metal ions or even implant fracture is seen at all modular junctions utilized in TJR: head–neck junction (i.e., trunnion), neck–stem junction (i.e., dual modular implants), and metaphyseal–diaphyseal junction. Studies show that modularity can lead to increased corrosion of all metal implants in a highly design-dependent fashion (Figure 2).<sup>20–24</sup> The emergence of mechanically assisted corrosion as a failure mechanism for the trunnion and dual modular junctions has forced manufacturers to re-evaluate their existing designs.

All modular junctions are susceptible to crevice corrosion. At modular junctions machined with tight tolerances, such as the head–neck junction, the space between the two surfaces is partially shielded from the aqueous chemical environment of the body fluid. This microisolation of the tiny gaps (or crevices) between the two surfaces of the implant is the source of crevice corrosion.<sup>25</sup> The imbalance of oxygen between the cathode (the surface of the implant outside the crevice) and the anode (inside the crevice) creates a current even if each part of the modular junction is made from the same metal (Figure 3). At the anode, oxygen is low, while the concentration of metal, hydrogen, and chloride ions are high. In this oxygen-poor environment, the surface of the implant cannot repassivate.<sup>26–28</sup> If the metal ion released is chromium, it reacts with phosphate to form a black or green, tarry, or glassy precipitate (i.e., chromium III phosphate and/or other metal oxides) near the crevice and on the surface of the implant.<sup>29–31</sup> Hence, the serum chromium level remains normal or only slightly elevated in patients with corrosion at modular junctions, whereas the serum cobalt level rises due to its increased solubility.<sup>20,29,30</sup> This fact can be used to distinguish a failed metal-on-metal articulation, which in general will have an equivalent rise in serum cobalt and chromium levels, from a failed modular junction, which in general will have a differential elevation of the serum cobalt level several fold above that of the serum chromium level.<sup>32,33</sup>

Modular junctions are susceptible to fretting corrosion. During fretting corrosion, surface pressure between contacting surfaces at modular articulations cause friction. Surface pressure is often initiated by micromotion at the interfaces during mechanical loading. This micromotion can physically disrupt the passivation layer, leading to metal particle release and facilitation of crevice corrosion.<sup>34</sup> Micromotion is not a result of a loose implant. Rather, when the joint is loaded, the various components of the modular implant flex (slip region) while remaining together (stick region, Figure 4).

## METAL WEAR DURING TJR

There are different modes for wear, including adhesive, abrasive, third body, fatigue, and corrosion. Metal wear occurs between metal-on-metal articulation and between metal-on-polymer (MOP) articulation as well. In the case of a metal-on-metal articulation, adhesive wear predominates, suboptimal implant positioning leads to additional wear.<sup>35</sup> After the initial placement of a metal-on-metal articulation (Figure 5), “bedding-in” occurs with high wear conditions and metal particle production. During this time one metal component wears into another until an “optimal contact area” develops and the wear rate is reduced, contact stress is decreased, and lubrication conditions improve (Figure 6).<sup>36</sup> The bedding-in period is followed by a much lower steady-state wear rate that continues for the life of the metal-on-metal articulation.<sup>37</sup> The transition from the bedding-in period to the steady-state phase represents a change in the mode of lubrication from high friction boundary lubrication to low friction fluid-film lubrication.<sup>38</sup>

Corrosion and wear act synergistically leading to even greater metal breakdown in the presence of proteinaceous solutions.<sup>27</sup> Tribocorrosion involves similar corrosive modes present in modular junction corrosion.<sup>39</sup> Tribocorrosion occurs during fluid film lubrication even when the metal components are not in contact. Tribocorrosion is the irreversible transformation of a material due to the simultaneous action of corrosion and wear taking place in a sliding tribological contact area.<sup>40</sup> In the case of metal-on-metal articulations, the two metal surfaces along with the synovial fluid react to form what is known as a tribomaterial. This material has an acidic nanocrystalline structure and consists of metallic and organic constituents, which are liberated within the surrounding soft tissues.<sup>41</sup> In the case of metal-on-polymer articulations, metal wear and tribocorrosion occur as well. Using hip stimulators, De Villiers et al.<sup>42</sup> showed an increased cobalt release in MOP arthroplasty with large femoral head, which was even worse with third body abrasives. Moreover, Savarino et al.<sup>43</sup> showed a significant increase of Co and Cr in serum of patients with MOP arthroplasty compared to subjects with no implant.

## METALS UTILIZED DURING TJR

The most common metal alloys used in TJR are cobalt–chromium–molybdenum (CoCr or CoCrMo) and titanium-6 aluminum- 4 vanadium (Ti6Al4V). Other metals or alloys include iron–chromium–nickel (stainless steel, AISI 316 L), commercially pure titanium (cpTi), titanium–aluminum–niobium (Ti6Al7Nb), and tantalum (Ta). The above alloys are generally named by the most representative elements forming their composition and as the percentage of the remaining elements (aluminum, vanadium, niobium, and so forth). These alloys exist in different compositions and structures. Currently, the chemical, mechanical, and metallurgical requirements for implant quality stainless steel are documented in F138-13a. Similarly, there are two representatives of CoCr based alloys: cast CoCrMo and the wrought MP35N, the main difference being the percentage of Cr and how the alloys are processed. Ti6Al4V alloy (ASTM F136) is the most common alloy of titanium in medical implants.<sup>44</sup> Furthermore, as shown by Rae et al.<sup>45,46</sup> there are differences in the biological responses to bulk and particulate metal, so each will be discussed separately.

## Titanium and titanium alloys

**Bulk**—The biological response to bulk cpTi, Ti6Al4V, and Ti6Al7Nb involves transient inflammation but little cytotoxicity. A cylinder of bulk cpTi placed in bone demonstrated hypocellular fibrous tissue surrounding the implant with little inflammation.<sup>47</sup> MC3T3-E1 preosteoblast cells do not exhibit cytotoxicity when cultured on cpTi unless a cathodic voltage is applied.<sup>48–50</sup> As bulk, the advantage of Ti-alloy as a stem is lower modulus of elasticity, and its disadvantage as a head is poor wear resistance.<sup>51,52</sup> Moreover, as shown by Tengvall et al.<sup>53</sup> the Fenton reaction (decomposition of H<sub>2</sub>O<sub>2</sub> by metal surfaces or metal ions leading to the production of harmful hydroxyl radicals) is diminished at a titanium surface making this metal highly biocompatible. Goldberg et al.<sup>54</sup> investigated, the issue of corrosion and self-passivation of Ti6Al4V alloy and CoCrMo alloy. They concluded that Ti6Al4V re-passivation takes slightly longer to occur and more electrons are released during this process. However, Ti6Al4V appears to be more resistant to corrosion if the oxide on the surface is not mechanically disturbed.

## Particulate titanium alloy

Particulate cpTi, Ti6Al4V, and Ti6Al4Nb stimulate inflammation and bone resorption. Clinically relevant particles of cpTi placed in bone were phagocytized by macrophages without an acute inflammatory response (i.e., no polymorphonuclear leukocytes (PMNs) or lymphocytes), fibrosis, or granuloma.<sup>55</sup> However, with increased concentration of Ti6Al4V particles, the cortical endosteal surfaces showed evidence of scalloping and resorption.<sup>56</sup> The macrophages responded to cpTi particles with increased release of prostaglandin E2 (PGE2), interleukin-1 $\beta$  (IL-1 $\beta$ ), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ).<sup>57,58</sup> The release of the cytokines was associated with an increase in tyrosine phosphorylation and mitogen-activated protein kinase (MAPK) activation.<sup>59</sup> Interestingly, inhibition of phagocytosis with antibodies to CD11b/CD18 receptors did not decrease the release of IL-6 and TNF- $\alpha$  indicating a phagocytosis-independent mechanism of macrophage activation by cpTi particles. This was also supported by data from co-culture of macrophages and lymphocytes, which demonstrated a dose-dependent release of IL-6 and TNF- $\alpha$ .<sup>59,60</sup> Osteoblasts exposed to cpTi particles respond with acute increase in nuclear factor (nuclear factor IL-6 (NF-IL-6) and nuclear factor-kappa B (NF $\kappa$ B)) translocation, IL-6 release, and type-1 collagen expression.<sup>61–63</sup> The addition of cpTi particles was not associated with increased cell death, nitric oxide production, and alkaline phosphatase (ALP) or osteocalcin production expression.<sup>62</sup> Fibroblasts cultured with cpTi particles release monocyte chemoattractant protein 1 (MCP-1) and increased expression of bone-resorbing metalloproteinase in a dose- and time-dependent manner, which coincided with the release of IL-6.<sup>64–66</sup> However, exposure of fibroblasts to cpTi particles did not induce MCP-2, monocyte inflammatory protein 1 alpha (MIP-1 $\alpha$ ), or RANTES (regulated on activation, normal T cell expressed and secreted, also known as CCL5). A murine model using a cpTi intramedullary femoral rod demonstrated that addition of cpTi particles resulted in release of MCP-1, macrophage colony stimulating factor (M-CSF), and IL-6 without evidence of cell necrosis.<sup>67</sup> However, cpTi particles downregulate the expression of toll-like receptor (TLR) proteins and decrease the number of TLR immunoreactive cells.<sup>68</sup> This unexpected result is possibly due to a positive feedback loop to inhibit excessive

inflammation. Titanium particles appear to induce pro-inflammatory cytokine production, including IL-6, TNF- $\alpha$ , and MCP-1, and induce a minor inflammatory reaction. This reaction is distinctly different from that seen with cobalt chrome based alloys in particulate form, which are associated with significant cell necrosis. Blocking titanium-induced osteoclastogenesis and titanium-induced release of TNF- $\alpha$  could potentially mitigate the adverse effects of titanium particles.<sup>69–71</sup>

### Cobalt–chromium alloy

**Bulk**—The biological response to bulk CoCr involves cytotoxicity and inflammation. Bulk CoCr placed in bone evoked a discontinuous fibrous tissue layer mainly composed of collagen fibers with decreased cellularity.<sup>47</sup> Bulk CoCr in different fluids (e.g., human serum, fetal bovine serum, synovial fluid, and water) showed that the thickest calcium deposit was obtained with human serum, but metal ions were trapped as hydroxides and phosphates.<sup>72</sup> Corrosion of bulk CoCr affects osteoprogenitor viability and adhesion at the cathodic edge of voltage through a time-lapse study.<sup>73,74</sup> The presence of CoCr corrosion contributes to increased local tissue inflammation.<sup>75</sup> Interestingly, Willert et al.<sup>76</sup> have shown that CoCr particles as well as bulk material undergo corrosion and repassivation, releasing metal ions. The same group also demonstrated that hypersensitivity reactions to metal ions “start immediately after implantation, accelerate or at least facilitate sensitization and the consequent immunological response.”<sup>77</sup>

**Particulates and ions**—Co and Cr are specifically toxic at high concentrations, and can affect tissue that is both local to the modular implant and remotely. Metal ions can travel via lymph and blood to various sites throughout the body including bone marrow, lymph nodes, spleen, liver, and heart.<sup>78–80</sup> Chromium ions have varying effects on the body depending on ionic valence. Hexavalent chromium is classified as a group 1 carcinogen and can cause pulmonary epithelial cancer, while trivalent chromium is less harmful.<sup>81</sup> Merritt and Brown<sup>82</sup> discovered that hexavalent chromium is the principal chromium ion that is released during the corrosion of stainless steel and CoCr implants. However, hexavalent chromium is quickly reduced to trivalent chromium in red blood cells, and thus the trivalent chromium ion is often detected in the cells surrounding TJR.<sup>83</sup> Co ions from MOM implants inhibit osteoblast function,<sup>84</sup> alter lymphocyte function and chemokine secretion,<sup>85,86</sup> as well as cause neurological, thyroid, and cardiac dysfunction.<sup>87,88</sup> CoCr implants pose three main threats to human cells: genotoxicity, cytotoxicity, and hypersensitivity.

**Genotoxicity**—Co and Cr are genotoxic, which means they can damage the genetic makeup of a cell and thus cause cancer, and there is some concern that this is possible even at concentrations that are considered “subtoxic.”<sup>89,90</sup> Co and Cr damage tissues and DNA by oxidative stress.<sup>91</sup> Cr specifically can release free radicals, which can cause breakage in DNA strands.<sup>92</sup> Both Co and Cr ions inhibit DNA repair pathways, which results in defective gene expression.<sup>93</sup> Co also inhibits topoisomerase II, which aids in DNA replication.<sup>94</sup> Some basic science studies suggest metal-on-metal articulations may put individuals at risk for developing cancer or other genetic defects. One study, found a decrease in DNA synthesis when cells were exposed to Co and Cr.<sup>95</sup> A similar study by Dunstan et al. found that individuals with modular THA implants had a greater number of



chromosomal aberrations compared to individuals who did not have implants.<sup>96</sup> In addition, individuals with implants exhibited a 2.5-fold greater risk of aneuploidy when compared to individuals without implants, as well as a 3.5-fold greater risk of chromosomal translocations.<sup>97</sup>

Lewis et al.<sup>98</sup> challenged primary human fibroblasts with CoCr particles that had been previously incubated with either human serum or minimal essential media. When particles were preincubated with human serum, they were phagocytosed less readily. They also found a significant increase in DNA damage when cells were exposed to CoCr particles compared to untreated cells. The size of the particles also plays a role on the damage to the surrounding cells. Papageorgiou et al. investigated the effect of CoCr particles on human fibroblasts of different ages.<sup>99</sup> They found that the level of DNA damage was similar in both groups but older cells experienced a greater loss of viability and demonstrated more complex aneuploidy. This was confirmed by Raghunathan et al.<sup>100</sup> and Behl et al.<sup>101</sup> who also found an increase in reactive oxygen species (ROS) production which was dose-dependent after 24 h of exposure. Finally, Posada et al.<sup>102</sup> found significantly higher cellular uptake of Co than Cr regardless of the concentration. They also showed an increase apoptosis after 48 h of exposure.

Despite the above reports, it is still unknown if genotoxicity from modular hip implants is a serious threat clinically. One study analyzed over 80 published papers to determine if there is a relationship between CoCr implants and an increase in cancer. They found that the Co and Cr ion concentration in the bodies of those with meal-on-metal articulations were far too small to substantially increase the risk of developing systemic cancer.<sup>103</sup> *In vitro* and *in vivo* assays showed that DNA defects would be very unlikely to occur due to the increase in Co or Cr ion concentration as a result of a MOM articulation.<sup>103</sup> Moreover, in 40 tumor bioassays where Co and Cr ion concentrations were significantly higher than those in hip implants, none reported a significant increase in systemic cancer.<sup>103</sup> A Finnish study also looked at 2,000 patients roughly 15 years after a first generation MOM articulation and found that there was no increase in the incidence of cancer. The authors concluded that factors other than the TJR surgery are responsible for the development of cancer in hip implant patients.<sup>104</sup> Similarly, studies of patients with more modern metal-on-metal articulations failed to suggest an increased risk of cancer.<sup>105</sup> Lastly, DNA damage as a result of modular implants is not necessarily predictive of cancer risk. Christian et al.<sup>103</sup> noted that DNA damage has been seen in patients with implants that were made of materials other than Co and Cr. They concluded that effects on DNA in the blood surrounding metal-on-metal articulations is not due to the metal ions that are released, but is instead due to local effects, such as inflammation, that are unrelated to the implant material.<sup>103</sup> Although there is concern that Co and Cr ions could cause cancer, thus far no definite conclusions can be drawn.

**Cytotoxicity**—Co and Cr ions are very cytotoxic, with the former being more toxic than the latter. Co ions, even at smaller concentrations, can result in greater macrophage and lymphocyte death than Cr ions.<sup>36,106,107</sup> Both ions stimulate TNF- $\alpha$  secretion and macrophage apoptosis.<sup>108</sup> Several *in vitro* studies suggest that Co and Cr ions lead to macrophage apoptosis even after being incubated for both 24 and 48 h. DNA laddering

indicates that DNA fragmentation declines after 48 h, which could be a sign of necrosis.<sup>36,107,108</sup> Co and Cr particles reduced the viability of histiocytes by 97% and fibroblasts by 95%.<sup>109</sup> CoCr alloy was shown to be much less toxic than Co or Ni alone in primary fibroblasts.<sup>110</sup> CoCr alloy particle injection within the knee joint resulted in large zones of necrosis with infiltrating macrophages and lymphocytes.<sup>111</sup> Haynes et al.<sup>112</sup> studied the effect of age of CoCr particles under physiological conditions with human monocytes. Their results showed that (1) Co particles were more significantly released than Cr particles, (2) this release decreased with time, (3) aged particles were less toxic than freshly produced particles, and (4) aged particles stimulated the release of IL-6 and PGE2. Kaufman et al.<sup>113</sup> demonstrated that CoCr particles were “mildly stimulatory” for cytokine release: when challenged with CoCr particles, macrophages released two- to five fold greater levels of IL-1a, IL-6, IL-10, and granulocyte–macrophage CSF (GM-CSF) compared to unchallenged cells. Papageorgiou et al.<sup>114</sup> used nano- and microparticles in an *in vitro* study with human fibroblasts. Nanoparticles were found to release significantly more free radicals and to induce more DNA damage than the microparticles. Unexpectedly, exposure to CoCr particles did not increase the release of IL-6, IL-10, TNF- $\alpha$ , or FGF-23, possibly due to cell death.

**Hypersensitivity**—Hypersensitivity refers to the immune system overreacting to an allergen and producing an undesired reaction. Metal allergies (or hypersensitivities) are characterized by contact allergies to Cr, Co, or Ni, and are found in roughly 10–15% of the general population.<sup>115,116</sup> Metal allergy can develop from extended exposure to items, such as jewelry, cell phones, and clothing fasteners.<sup>116–123</sup> This is of concern to orthopaedic surgeons because if a patient has a metal allergy, implanting a metal hip could potentially have negative consequences, such as hives, eczema, redness, and itching (in <1% joint replacement patients).<sup>124</sup> Ni is often found in the CoCr alloys that are used in orthopaedic implants, and has been shown to be the strongest immunological sensitizing metal when compared with Co and Cr. Metal ions cannot initiate an immune response by themselves. Instead, they bind to proteins and form haptens. It is the metal-bound denatured protein, such as albumin, that is large enough to elicit an immune response.<sup>125</sup> CoCr particles also have an effect on T-cells. As shown by Hallab et al.<sup>126</sup> metalloprotein complexes made from CoCr degradation byproducts are capable of inducing a lymphocyte proliferative response. This response was greatest with high molecular weight protein (180–250 kDa); a possible trigger of the response is a crosslinking reaction with lymphocyte receptors (BV17 or CDR1 T-cell receptor).

When individuals with a metal allergy are exposed to immunoreactive haptens that are made from Ni, Co, or Cr particles, a hypersensitivity reaction occurs. This is characterized by the activation of T-cell mediated delayed-type hypersensitivity lymphocytes by antigens, which leads to cytokine release and the activation of macrophages. A hypersensitivity reaction can either be an immediate humoral response or a delayed cell-mediated response, but hypersensitivity reactions as a result of orthopaedic implants are usually a cell-mediated type-IV delayed hypersensitivity response.<sup>127</sup> A hypersensitivity reaction is initiated when haptenic antigens activate T-cell mediated delayed-type hypersensitivity lymphocytes, which are a subtype of CD4<sup>+</sup> helper T-cell lymphocytes. These lymphocytes are presented with a



haptens, and interact with a major histocompatibility complex (MHC) class II molecule to release interferon-gamma. Interferon-gamma activates macrophages to secrete various cytokines, such as granulocyte-macrophage colony stimulating factors, tumor necrosis factors, monocyte chemotactic factors, and migration inhibitory factors. These cytokines recruit cytotoxic T-cells that are involved in the cell-mediated type IV-hypersensitivity reaction. The macrophages are also able to activate T-cell mediated delayed-type hypersensitivity lymphocytes, which will then activate more macrophages, and a vicious cycle develops. Thus, an immunologic overreaction occurs.<sup>128,129</sup> Patients who are sensitive to Ni often exhibit crossreactivity with Co and Cr.<sup>130</sup> This is because when patients react to a hapten, they actually are reacting to the denatured carrier. Ni, Co, and Cr all have similar mechanisms by which they denature carrier proteins, and thus cross-reactivity occurs.<sup>131,132</sup>

### Stainless Steel

**Bulk**—Stainless steel is mainly used in polished tapered cemented femoral stems.<sup>133</sup> The main components of stainless steel are iron (Fe), chromium (Cr), nickel (Ni), and Copper (Cu). The biological response to bulk stainless steel involves transient inflammation and lacks cytotoxicity. Macrophages demonstrated increased IL-1 $\beta$  release and late apoptosis when exposed to ingots of stainless steel.<sup>134</sup> Interestingly, Hierholzer et al.<sup>135</sup> have shown that the inflammatory reaction associated with infection causes an increased dissolution of the metal ions from stainless steel implants. Karov et al.<sup>28</sup> investigated corrosion and self-passivation under physiological conditions. Their results showed that self-passivation can take up to 10 s and continue to evolve thereafter. The authors stated that a fast repassivation rate is an important biocompatibility requirement for alloys used to manufacture dental and orthopaedic devices.

**Particulates and ions**—The rate of stainless steel ion release depends on several factors including alloy composition and surface finish. The ions release by stainless steel alloy and its pure constituents after immersion in a synthetic biological medium to mimic the reaction within the human body show Ni release in the first hour followed by Fe and Cr which increase for four hours prior to assuming a steady state concentration (with Fe being the highest).<sup>136</sup> When the surface was abraded the rate of ion release was 3- to 5-fold higher.

Stainless steel corrosion products affect osteoblast survival and stimulate macrophage-dependent inflammation. Osteoblasts exposed to stainless steel corrosion products have lower DNA content, decreased ALP activity, and failure to mineralize. The effect of 316 L stainless steel and nitro-generated stainless steel (NSS) alloys (both in particles and bulk shapes) found that 316 L stainless steel particles were more toxic than NSS particles to macrophages. However, both of the alloys induced significant increase in IL-1 $\beta$  and TNF- $\alpha$  expression.<sup>134</sup> Stainless steel particles cultured with osteoclasts increased IL-1 $\beta$ , IL-6, and TNF- $\alpha$  expression.<sup>137</sup> Osteoclasts induced the corrosion of stainless steel particles and led to a significant release of Cr, Ni, and Mn ions into the supernatant.<sup>138</sup> With regards to corrosion, Woodman et al.<sup>139</sup> have shown that the predominant form of the corrosion product of these metals is an organometallic complex with serum proteins.

## ADVERSE LOCAL TISSUE

Adverse local tissue reaction (ALTR) refers to untoward histological reactions (often associated with clinical manifestations) that occur when metal implants corrode to produce metallic byproducts including particles, complexes, and ions. ALTR is a contributing factor to TJA failure.<sup>140</sup> It is unknown what the relationship is between ALTR and genotoxicity, cytotoxicity, and metal hypersensitivity, but ALTR is often associated with pain in the groin, hip, thigh, and buttock.<sup>141</sup> There are three major types of ALTR: aseptic lymphocyte-dominated vasculitis-associated lesions (ALVaL), pseudotumors, and osteolysis.

ALVaL describes a periprosthetic inflammatory reaction that is similar to a type IV hypersensitivity response in the soft tissue surrounding metal-on-metal implants.<sup>142,143</sup> It is characterized by soft tissue necrosis, lymphocytic infiltration, and abnormal joint fluid. In TJR patients who needed revision surgery due to symptoms of implant failure, tissue samples showed perivascular infiltrates of T-cell and B-cell lymphocytes, as well as an accumulation of plasma cells and macrophages (Figure 7).<sup>144</sup>

Pseudotumors are large, cystic masses that are often seen in patients with ALTR (Figure 8). Pseudotumors result in symptoms similar to ALVaL, but the lymphocyte infiltration and necrosis is much broader and more extensive. Pseudotumors may be characterized by pain, nerve palsy, palpable mass, and spontaneous dislocation. Various studies have attempted to determine the prevalence of pseudotumors amongst hip implant patients, and thus far the results have varied widely. Pandit et al.<sup>145</sup> estimated that 1% of patients with metal-on-metal implants develop a pseudotumor within 5 years, while a study by Hart et al.<sup>146</sup> found that roughly 60% of patients with metal-on-metal implants develop a pseudotumor. Van der Weegen et al. reported a rate of 37% of asymptomatic pseudotumors in their cohort of metal-on-metal implants.<sup>147</sup>

Osteolysis is the destruction of bone, resulting from osteoclast resorption.<sup>148</sup> Cystic bone lesions and radiolucent regions near the femoral calcar and acetabular components are strong signs of osteolysis (Figure 9). Osteolysis can be asymptomatic, but can also be associated with pain if the bone loss affects the implant stability.<sup>148</sup> It is difficult to determine the prevalence of osteolysis, as it exists in many asymptomatic patients. However, in Sweden, osteolysis was the cause of revision surgery for 75% of patients with metal-on-metal articulation.<sup>149,150</sup>

## CONCLUSIONS

Due to their mechanical strength and durability, metal alloys are widely used in TJR. Titanium alloy, cobalt–chromium alloy, and stainless steel in bulk form all induce a mild inflammatory response. However, byproducts of these metal alloys can have increased harmful effects including various degrees of cytotoxicity, genotoxicity and induce adverse local tissue reactions. Future implants, bearing surfaces and modular junctions should be designed to minimize the generation of metallic byproducts and the potential resultant consequences.

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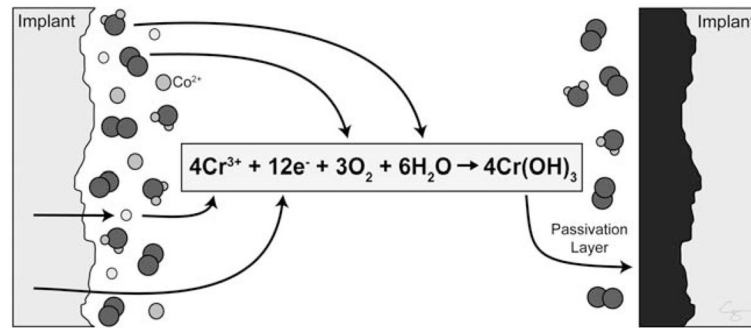


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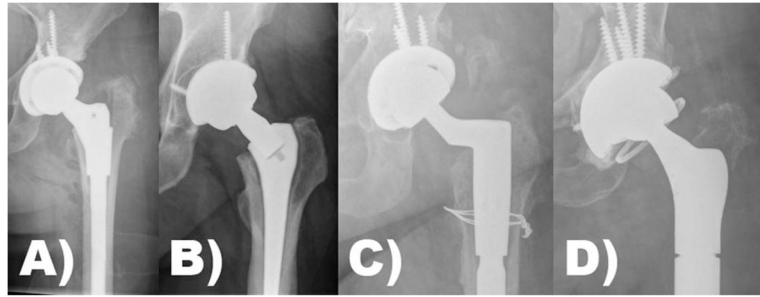
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**FIGURE 1.**

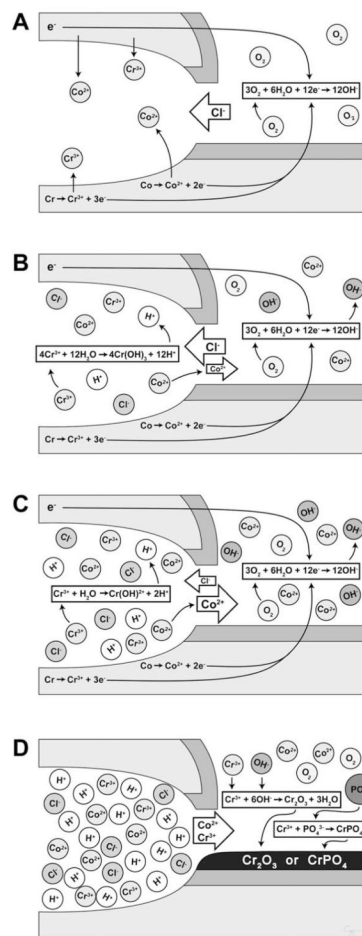
The passivation layer is an oxidized metal (black). The passivation layer prevents further degradation of the underlying alloy (Implant, gray). Metal implanted into the body has reacted with oxygen and is passivated. However, damage to the passivation layer results in exposure of the reactive alloy surface, which reacts oxygen ( $\text{O}_2$ ) and water ( $\text{H}_2\text{O}$ ) resulting in repassivation. Illustration created by Chrisoula Toupadakis Skouritakis, Ph.D.



**FIGURE 2.**

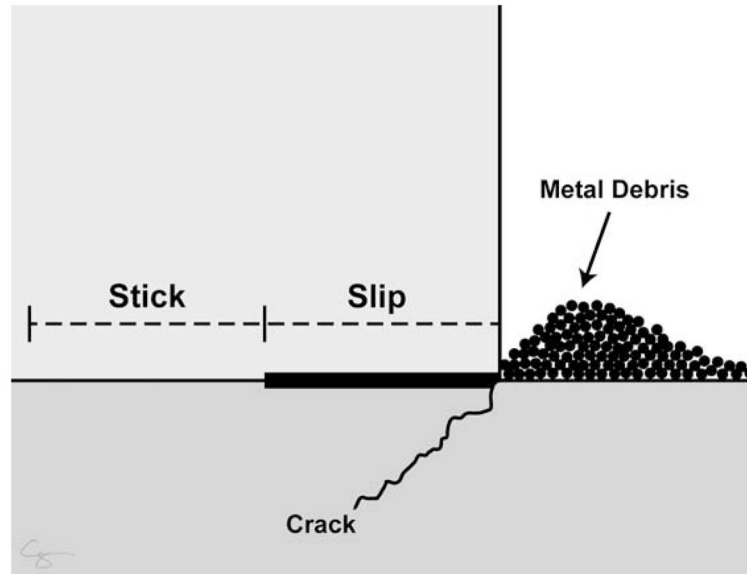
Examples of the types of modular junctions in total hip arthroplasty: (A) S-ROM illustrating proximal metaphyseal modularity, (B) dual modular design illustrating neck–stem modularity, (C) fluted tapered modular stem illustrating distal diaphyseal modularity, and (D) total femoral replacement illustrating modularity at its extreme. Note, examples A–D all illustrate head–neck modularity using the trunnion of the stem to accept a modular femoral head.





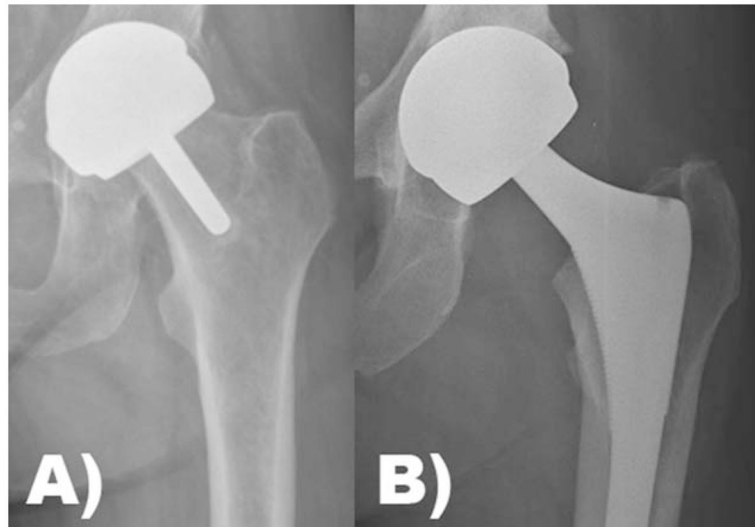
**FIGURE 3.**

The junction between the passivated femoral head and stem trunnion (dark gray) results in the microisolation of the corrosive environment that establishes an oxygen gradient between the interstitial fluid (“normoxic”) and the crevice fluid (“anoxic”). (A) The lack of oxygen inside the crevice leads to the separation of the anodic process (metal dissolution inside the crevice) and the cathodic process (oxygen reduction outside the crevice). The excess of positive ions in the crevice solution is balanced by an influx of negatively charged ions, primarily chloride ions ( $\text{Cl}^-$ ). The electrons generated by the anodic process is picked up by oxygen at the cathodic sites on the metal surface outside the crevice. (B) The hydrolysis of the chromium produces chromium ion ( $\text{Cr}^{3+}$ ) during the anodic process results in hydrogen ion ( $\text{H}^+$ ) generation inside the crevice, dropping the pH of the microenvironment and accelerating metal ion release. (C) As the crevice solution becomes more acidic, the hydrolysis of chromium becomes less and less complete, and the rate of acidification decreases. (D) As the critical pH is reached, the chromium ions are no longer hydrolyzed and crevice corrosion progresses at the rate of metal ion ( $\text{CO}_2^+$ ,  $\text{Cr}^{3+}$ , and so forth) diffusion. The metal ions then can react with organic and inorganic anions in the vicinity of the crevice opening, and—in the case of chromium ions—form insoluble precipitates containing chromium oxide ( $\text{Cr}_2\text{O}_3$ ) and chromium phosphate ( $\text{CrPO}_4$ ) on the metal surface. Illustration created by Chrisoula Toupadakis Skouritakis, Ph.D.



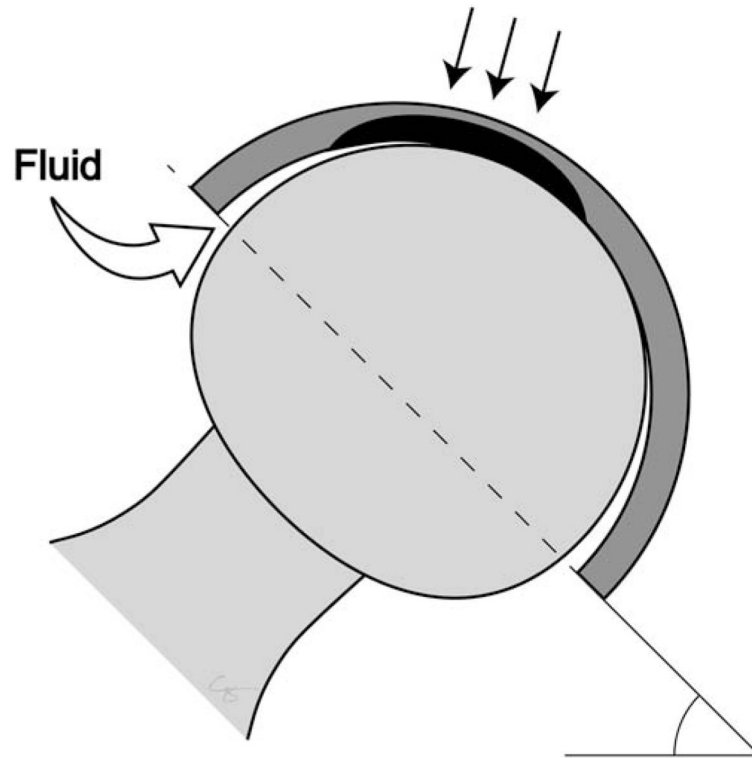
**FIGURE 4.**

When a modular junction is loaded, the implant flexes (slip region) while remaining together (stick region). This micromotion can physically disrupt the passivation layer, leading to metal wear or implant fracture. Micromotion does not equate to loosening. Illustration created by Chrisoula Toupadakis Skouritakis, Ph.D.

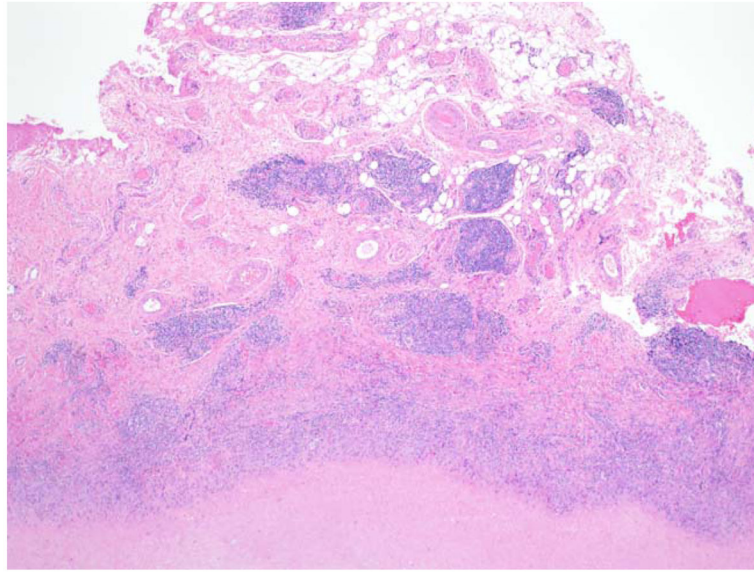


**FIGURE 5.**

(A) Hip resurfacing arthroplasty and (B) total hip arthroplasty with a metal head and metal acetabular liner are types of metal-on-metal articulations in total joint arthroplasty.

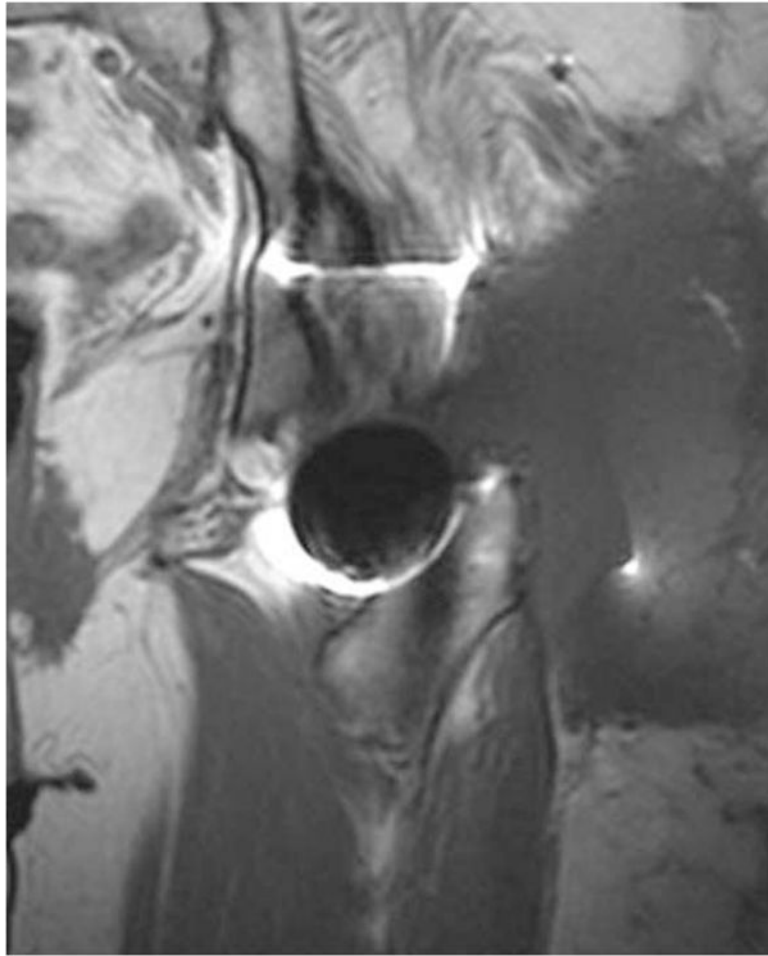


**FIGURE 6.** A polar bearing prosthesis leads to proper bedding-in and low steady-state wear as well as fluidfilm lubrication assuming proper implant positioning. Illustration created by Chrisoula Toupadakis Skouritakis, Ph.D.



**FIGURE 7.**

4× magnification of the diffuse perivascular infiltrates of T- and B-lymphocytes along with plasma cells as well as macrophages with or without metal debris that is characteristic of aseptic lymphocyte dominated vasculitis-associated lesions (ALVAL).



**FIGURE 8.** T1-weighted coronal section from a metal artifact reduction sequence (MARS) MRI demonstrating large pseudotumors involving the gluteus maximus muscle and lateral left hip.





**FIGURE 9.**  
Severe osteolysis of the calcar and failure of acetabular fixation.