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Metallic materials for biomedical applications: Laboratory and clinical studies*

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Abstract: Prolongation of the average life expectancy and an active lifestyle in old age are related to the constant increase in the number of joint diseases that eventually require a surgical procedure. The diseased joint is replaced with a joint prosthesis, the functionality of the joint is recovered, and pain is reduced. In the last decade, the number of joint replacement operations has increased several times over and is expected to increase further. In order to enable patients to have a painless and active lifestyle, it is necessary to develop materials that are long-lasting in vivo. Metallic biomaterials must exhibit high corrosion and wear resistance. In vitro research on materials under simulated physiological conditions is presented. These experiments are complemented by examples from clinical practice performed in collaboration with orthopedic surgeons. Morphological and chemical changes in the material during the course of in vivo performance are related to processes of wear and corrosion. The local and systemic consequences of these processes in the human body are presented.

Keywords: clinical performance; corrosion; in vitro; metallic biomaterials; orthopedic implants.

INTRODUCTION

Prolongation of the average life expectancy and an active lifestyle in old age have led to a constant increase in the number of various implants and devices, e.g., orthopedic, cardiovascular, and ophthalmological implants. The present paper deals with orthopedic implants, primarily total hip and knee replacements. According to the American Academy of Orthopedic Surgeons [1], there were more than 1 million hip and knee replacements in 2006 in the United States. In the future, this trend is expected to further increase. In addition, the number of hip prostheses implanted in patients aged 50 years or less is increasing [2]. Among the diseases of the joints that in most cases require a surgical orthopedic procedure, osteoarthritis is the most important, followed by osteonecrosis, osteoarthritis secondary to dysplasia, rheumatoid arthritis, post-traumatic osteoarthritis, etc. Osteoarthritis is the most common type of arthritis, affecting millions of people worldwide, usually middle-aged and older people. This is a non-inflammatory degenerative joint disease characterized by a breakdown of the joint's cartilage. The cartilage that "cushions" the bones of the hip starts to erode, eventually allowing the bones to grind or rub together and causing hip pain and stiffness (Fig. 1). The exact cause of osteoarthritis is unknown. The diseased hip joint is replaced with a hip prosthesis (Fig. 1), the functionality of the joint is recovered, and the pain is reduced. The total replacement of this joint has become one of the most success-

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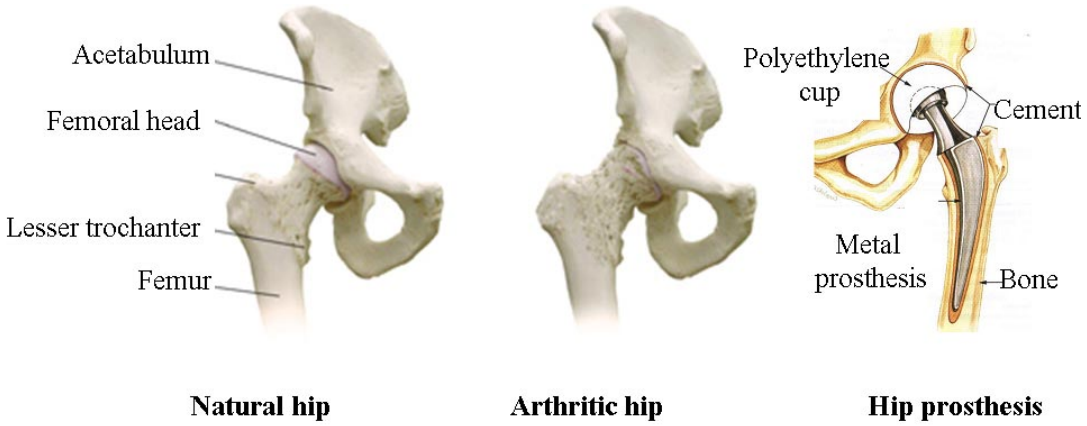

Fig. 1 A healthy and an arthritic hip joint (<www.zimmer.com>), schematic presentation of a total hip prosthesis.

ful elective surgical procedures in modern medicine. The long-term performance of hip replacements is largely determined by the process of aseptic loosening, this being the most common reason for revision surgery [2,3]. Problems with achieving successful long-term results may be understood by comparing the performance of an artificial and a healthy hip joint. Healthy joint cartilage enables bones within the joint to slide smoothly, with a low friction coefficient, in a broad range of loads, with millions of cycles during the average period of 70 years. This outstanding performance of a healthy joint still cannot be surpassed by an artificial joint, although the development of materials, designs, and surgical techniques has led to the prolongation of the expected lifetime of joint prostheses, which is currently about 20 years.

The long-term stability and performance of each biomedical implant is largely dependent on the type of materials used in its manufacture. In biological systems, both natural and synthetic materials are used. Natural materials are, for example, cellulose, sodium alginate, rubber, keratin, gelatin, etc., and materials of animal origin, e.g., animal heart valves, collagen, heparin, etc. Although natural materials are important in numerous applications, the use of synthetic materials (metals, alloys, polymers, ceramics, and composites) is indispensable in the manufacture of biomedical implants. In the first section below, the general characteristics of metallic biomaterials will be presented, followed by a short history of hip implants. In the second section, the biocompatibility and physical-chemical conditions of the biological environment will be presented and complemented by examples of in vitro studies of biomedical alloys in simulative physiological solutions. The third section is devoted to studies related to the performance of metallic biomaterials in vivo.

METALLIC BIOMATERIALS

A survey of the most important alloys

Metallic biomaterials are used in orthopedic applications for joint replacements and bone fixation devices, in dentistry, and in cardiovascular treatments. The most commonly used metallic biomaterials are stainless steel and Co- and Ti-based alloys.

Stainless steel

Stainless steel, 18Cr–8Ni with 2–4 wt % of Mo and low C content, was patented in 1926. The stainless steel that was initially used exhibited intergranular corrosion due to high C content (0.08 %) and pitting corrosion due to low Mo content. The stainless steel used today in biomedical applications has the denotation AISI 316L (*surgical or orthopedic stainless steel*), where the denotation L means that the con-

tent of the C is lower than 0.03 % (Table 1). It exhibits good mechanical properties, ductility, and relatively low price [3,4]. The corrosion resistance of stainless steel is based on the formation of a thin passivating layer mainly containing Cr(III) oxide, Cr_2O_3. Stainless steel has an austenitic microstructure with a face-centered cubic cell. A delta-ferritic structure exhibits worse corrosion resistance than an austenitic structure, and it is not used in biomedical applications. Furthermore, an austenitic structure is not ferromagnetic, and patients implanted with stainless steel prostheses can undergo diagnostics using magnetic resonance.

Table 1 Composition of various alloys used for the manufacture of implants.

Type of material	ISO Denotation*	Composition (wt %)
Stainless steel 316L	ISO 5832-1(D)	17.0–19.0 Cr; 13.0–15.0 Ni; 2.25–3.5 Mo; ≤ 0.030 C; ≤ 2.0 Mn; ≤ 0.10 N; ≤ 0.50 Cu; ≤ 0.025 P; ≤ 0.010 S, ≤ 1.0 Si; rest Fe
Co–28Cr–6Mo, cast	ISO 5832-4	26.5–30.0 Cr; 4.5–7.0 Mo; max 1.0 Ni, 1.0 Fe, and 1.0 Mn; rest Co
Co–28Cr–6Mo, wrought	ISO 5832-12	26.0–30.0 Cr; 5.0–7.0 Mo; max 1.0 Ni and Mn; max 0.75 Fe; rest Co
Commerically pure Ti	ISO 5832-2	Max 0.05 N; 0.10 C; 0.125 H; 0.50 Fe and 0.40 O; rest Ti
Ti–6Al–4V, wrought	ISO 5832-3	5.5–6.75 Al; 3.4–4.5 V; max 0.05 N, 0.08 C, 0.015 H, 0.30 Fe and 0.20 O; rest Ti
Ti–6Al–7Nb, wrought	ISO 5832-11	5.5–6.5 Al; 6.5–7.5 Nb; max 0.05 N, 0.08 C, 0.009 H; 0.25 Fe; 0.20 O and 0.50 Ta; rest Ti

*ISO: International Organization for Standardization

The density of stainless steel is 7.9 g/cm^3, almost twice that of Ti and its alloys (Table 2). For temporary bone fracture treatments, where today stainless steel is the leading material, this is not so important. However, for fixed larger implants such as joint replacements, this fact is important due to the possibility of stress shielding [4,5]. The stiffness of the material is inversely proportional to the elastic modulus, which for stainless steel is approximately 80 % greater than for Ti. This consequently means that for an implant of the same size, stainless steel implants are significantly stiffer than Ti implants.

Table 2 Mechanical properties of most common metallic biomaterials [4].

Material	ASTM	Elastic modulus (GPa)	Ultimate tensile strength (MPa)	Hardness HVN*	Density (g cm^{-3})
Stainless steel	F138	190	930	130–180	7.6
CoCr alloys	F75	210–253	655–1277	300–400	8.9
	F90	210	1896	300–400	
	F562	200–300	800–2068		
	F1537	200–230	1300		
Ti and Ti alloys	F67	110	760	120–300	4.5
	F136	116	965–1103	310	

*HVN: Vickers hardness number.

Co-based alloys

Co-based alloy can be described as non-magnetic, wear- and corrosion-resistant, and stable at elevated temperatures. Many properties stem from the crystallographic nature of Co, the formation of a solid solution with Cr and Mo, and consequent formation of extremely hard carbides [4,5]. The corrosion resistance of Co-based alloys is, similar to stainless steel, based on the formation of a thin passivating layer of Cr_2O_3.

E. Haynes developed a series of Co–Cr alloys named Stellites [6]. In 1913, Co–Cr–W alloys were patented. In the 1930s, the Co-based alloy Vitallium was patented and used for the manufacture of parts used in aircraft engines. In the original specification it contained 30 % Cr, 7 % W, and 0.5 % C; later, the tungsten was replaced by 5 % Mo. Mo is added to refine grain size, enhance solid solution strengthening, as well as to increase corrosion resistance. The composition of Co–Cr–Mo alloys has not changed significantly since. The largest change is related to the stricter control of the content of carbon and, consequently, the more homogeneous distribution of hard carbide grains and increased abrasion resistance of the alloy. There are six ISO 5832 standards for Co-based alloys, which correspond to various compositions and manufacturing processes [5]. Today, cast and wrought alloys are primarily used (Table 1). These two alloys have almost identical composition but differ in microstructure. Cast alloys have a Cr-rich matrix and larger grains. With hot isostatic pressing, the grain size can be reduced to 8 μm. Cast alloys exhibit an inhomogeneous, large-grained, cored microstructure. The dendritic regions are Co-rich, whereas the interdendritic regions can be a quaternary mixture consisting of various Co-rich, Cr-rich, and Cr- and Mo-rich phases [6]. Wrought alloys have a face-centered cubic structure which exhibits an austenitic microstructure with finely distributed small block carbides. Co alloys are very tough materials. A combination of high hardness and compression strength (Table 2) is the basis for their applications in joint replacements, but they are less important for fixation devices.

Ti and Ti-based alloys

It was only in the 20^{th} century that technology enabled the isolation of metallic Ti from its minerals. Thus, industrial production of Ti began relatively late, in 1946 [6]. Due to its low density and high corrosion resistance, Ti became indispensable in the aerospace industry. The use of Ti in biomedical applications dates from 1965. Commercially pure (CP) Ti and its alloy Ti–6Al–4V are the most commonly used Ti-based biomaterials. There are four compositions of CP Ti depending on the content of the trace elements. For biomedical purposes, the composition determined by the standard ISO 5832-2 is used (Table 1). Ti and its alloys do not provoke allergic reactions and are considered to be biocompatible. None of these materials is ferro-magnetic.

CP Ti does not yield sufficient hardness for load-bearing applications and is therefore mainly used in dental surgery, for the manufacture of acetabular shells, and in the form of coatings for joint replacements. The Ti alloys Ti–6Al–4V and Ti–6Al–7Nb exhibit an $\alpha + \beta$ structure and higher compression strength compared to Ti, consequently their range of applications in orthopedics is broader (Table 2).

Due to the very high stability of the TiO_2 passive film that forms spontaneously on the alloy surface, Ti and its alloys are the most corrosion-resistant of the alloys described. A specific property of these materials is their osseointegration capability, which is based on the formation of bone cells and mineralized bone matrix on the Ti surface. The effect of osseointegration can be increased by increasing surface roughness and consequently surface area. This can be achieved by means of various processes encouraging bone in-growth and providing enhanced fixation, such as surface roughening, a porous coating, using wire as fiber-metal coatings, employing a beaded surface or plasma-sprayed surface, etc.

Short history of hip implants

The first hip replacement dates to 1890 when Gluck published a description of carved ivory femoral head replacements using bone-cement-like materials such as pumice and plaster [4]. In 1923, M. Smith

Peterson created the first mold arthroplasty. A half-ball made of glass was fit between the femoral head and acetabular cup. Later this design was improved by replacing the glass with polymers. It was not until the late 1930s that the first metals, a Co alloy and stainless steel, were used in hip arthroplasty. In 1937, a short stem made of Vitallium was designed by Bohlman, later popularized by the Judet brothers in Paris in 1946. The Judet brothers used poly(methyl methacrylate) (PMMA) to manufacture short-stemmed prostheses (Fig. 2). PMMA was later replaced by Vitallium. Short-stemmed prostheses are again occasionally used nowadays. In 1938, Philip Wiles designed the first total hip arthroplasty made of stainless steel. A steel ball was secured to the femur with a bolt, and a stainless steel acetabular liner was secured with screws. This design was rather disappointing since the stainless steel used at the time was insufficiently corrosion-resistant.

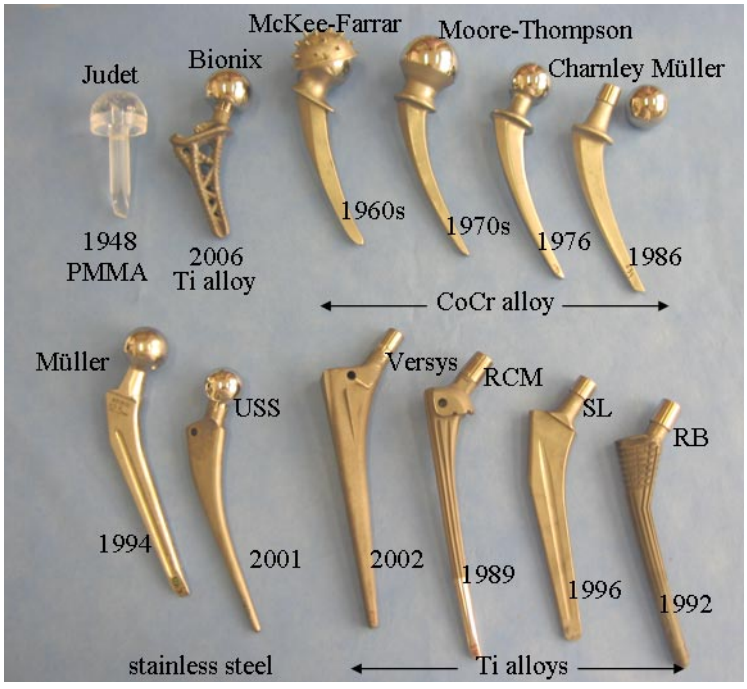

Fig. 2 Examples of older and recent types of hip prostheses made of PMMA, stainless steel, Co- and Ti-based alloys. For each prosthesis, the year of manufacture is denoted.

Long-stemmed prostheses appeared in the 1950s. The design of the Wiles' prosthesis was adopted in 1951 by G. K. McKee and J. Watson-Farrar, at first using stainless steel, and later a Co–Cr–Mo alloy (Fig. 2). This was a so-called metal-on-metal (MOM) combination comprising a metal femoral head articulating within a metal acetabular inlay. In the mid-1960s, PMMA cement was used for fixation in hip arthroplasty for the first time. The relatively high torque and frictional forces resulted in the generation of metallic debris and early loosening. In 1960, John Charnley developed a "low friction" arthroplasty using an acetabular shell made of polytetrafluoroethylene (PTFE, Teflon) (Fig. 2). Unfortunately, this resulted in early failures due to the poor wear resistance of PTFE. Charnley then replaced PTFE with high-density polyethylene, which was not as friction-free as PTFE but much more wear-resistant. The prototype of this prosthesis was developed in 1962 and still remains a gold standard of hip arthroplasty with metal-on-polyethylene articulation. This was the basic archetype that was followed by hundreds of different designs and modifications.

Ti alloys were introduced into hip arthroplasty in the 1960s and have been widely used since. Today the femoral components of hip replacements are usually made of Ti alloys, a CoCr alloy, or stainless steel (Fig. 2). They can be either press-fit or cemented, connected to modular metal or a ceramic femoral head that articulates on an ultra-high-molecular-weight polyethylene (UHMWPE) liner that is cemented or fitted into a Ti or CoCr cup screwed or press-fit into place. Not only new designs, but also new materials have been introduced into orthopedics, such as the Ti–6Al–7Nb alloy, stainless steel without Ni, Trabecular® tantalum and Ti, oxidized Zr, vitamin E-stabilized polyethylene, cross-linked polyethylene, etc. Furthermore, new manufacturing procedures have been developed, e.g., hot isostatic pressing and coating technologies such as sprayed Ti, porous Ti, hydroxyapatite, etc. Due to advances in the areas of materials technology, tribology, and biomedical engineering and other areas of sciences and medicine, orthopedic surgeons are daily faced with numerous decisions regarding the choice of material and type of prosthesis. Knowledge of these issues is therefore crucial.

IN VITRO STUDIES OF METALLIC BIOMATERIALS

Biocompatibility and the biological environment

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application [7]. An appropriate host response means that the material must not disturb the host or induce an undesired response. Based on the host response, biomaterials can be grouped as: *inert* (implantable materials that elicit little or no host response), *interactive* (implantable materials designed to elicit specific, beneficial responses, such as in-growth, adhesion, etc.), *viable* (implantable materials, incorporating or attracting live cells at implantation, which are treated by the host as normal tissue matrices and are actively resorbed or remodeled), and *replant* (implantable materials consisting of native tissue, cultured in vitro from cells obtained previously from the specific implant patient) [7].

The biocompatibility of a metallic implant that is to be placed into a human body is dependent not only on the corrosion resistance of the metal or alloy, which is again dependent on the metallurgical, microstructure, and composition variables, but also on the composition and physical-chemical conditions in the biological environment itself. As far as their inorganic salt composition is concerned, body fluids are essentially a dilute saline solution (Table 3). Chloride ions are the most important ion from the corrosion point of view due to their ability to disrupt passive films. Many different organic compounds are present in body fluids (Table 3), the most abundant among them being proteins, particularly albumin. Other substances like lipoproteins, fibrinogen, fatty acids, and glucose are also present. The total concentration of organics can exceed 80 g/l. Adsorption of proteins can have an important effect on the corrosion process. The physical-chemical conditions in the human body can differ substantially depending on the location (Table 4). Gastric juices, for example, can have a pH value as low as 1, while most body fluids are near-neutral, often tending to be slightly alkaline [3]. For example, the pH value of whole blood is between 7.03 and 7.78, of blood plasma between 7.38 and 7.42, and of synovial fluid between 7.29 and 7.7. Dissolved gases also have an important physiological role. CO_2 is an important regulator of body pH. Low pH values can significantly promote corrosion, therefore the acidity of the biological environment must be taken into account when predicting the in vivo behavior of metals.

Table 3 Concentrations of anions and cations in human serum [7].

Cations	mmol/l	Anions	mmol/l
Na^+	142	Cl^-	101
K^+	4	HCO_3^-	27
Ca^{2+}	5	HPO_4^{2-}	2
Mg^{2+}	2	SO_4^{2-}	1
Total	153	Total	131
		Organic acids	6
		Proteins	16

Table 4 Physical-chemical conditions in human body [7].

	Value	Location
pH	1.0	Gastric content
	4.5–6.0	Urine
	6.8	Intracellular
	7.15–7.35	Blood
pO_2 (mmHg)	40	Venous blood
	100	Arterial blood
	160	Atmospheric
	40	Alveolar
	2	Atmospheric
Temperature (°C)	37	Normal core
	20–42.5	Diseases

Simulated physiological solutions

Before implantation in a human body, materials must be tested in vitro. It is desirable to replicate as closely as possible the natural environment the metal will be exposed to after implantation. In general, four classes of exposure environments can be distinguished: (i) physiological (inorganic chemical and thermal conditions are controlled to normative mammalian values), (ii) biophysiological (the physiological conditions with the addition of various cell products, such as serum proteins, enzymes, etc.), (iii) biological (biophysiological conditions with the addition of viable, active cells), and (iv) pericellular (a special case of biological; the conditions in the immediate vicinity of viable, active cells) [7]. The compositions of the most commonly used simulated physiological and biophysiological solutions for in vitro investigation of metals and alloys are given in Table 5.

Table 5 Various simulated physiological solutions used for in vitro experiments.

Solution	Composition (%, g/l)
NaCl	0.9 % NaCl
Hank-simulating physiological solution	8 g NaCl, 0.40 g KCl, 0.35 g $NaHCO_3$, 0.25 g $NaH_2PO_4 \times 2H_2O$, 0.06 g $Na_2HPO_4 \times 2H_2O$, 0.19 g $CaCl_2 \times 2H_2O$, 0.41 g $MgCl_2 \times 6H_2O$, 0.06 g $MgSO_4 \times 7H_2O$ and 1 g/l glucose, pH = 7.4
Ringer-simulating physiological solution	8.60 g NaCl, 0.30 g KCl, 0.33 g/L $CaCl_2 \times 2H_2O$, pH = 7.4
Artificial saliva	0.40 g NaCl, 0.40 g KCl, 0.78 g $NaH_2PO_4 \times 2H_2O$, 0.795 g $CaCl_2 \times 2H_2O$, 0.005 g $Na_2S \times 5H_2O$ and 1 g/l urea, pH = 5.0
Artificial sweat	0.5 % NaCl, 0.1 % lactic acid, 0.1 % urea, pH = 6.5
Minimal essential medium (MEM)	Anorganic salts, vitamins, amino acids, Na-bicarbonate, dectrose

Electrochemical investigations and corrosion stability

The polarization curves for stainless steel AISI 316L, Co–28Cr–6Mo, Ti–6Al–4V, and Ti–6Al–7Nb alloys recorded in Hank-simulated (HS) physiological solution are presented in Fig. 3. All these alloys spontaneously form the passive oxide layer, as is evident from the absence of an active–passive transition following the Tafel region. Whereas the stainless steel and Co–28Cr–6Mo alloy show quite similar behavior, with the passive range extending up to the breakdown potential, E_b, at 0.2 and 0.4 V, respectively, the Ti alloys are stable to much more positive potentials, 3.5 and 6.0 V. The alloys were electrochemically oxidized at different oxidation potentials and then studied by X-ray photoelectron spectroscopy (XPS). The advantage of the XPS technique is the possibility to distinguish between various oxidation states of a particular element, e.g., Cr(III) in Cr_2O_3 and Cr(VI) in CrO_3, Fe(II) in FeO and Fe(III) in Fe_2O_3, etc.

The passive film formed on stainless steel in the physiological solution consists of two predominant oxides, i.e., Cr and Fe oxides [8]. Oxides of the alloying elements Ni and Mo are also detected in the film. In the lower potential range (up to 0.2 V) the layer is strongly enriched in Cr and Mo, and depleted in Fe and especially in Ni. As the potential becomes more positive, the layer becomes gradually depleted in Cr and slightly enriched in Fe, Ni, and Mo oxides. The domination of the Fe(III) species in the layer increases with increasing potential. At the same time, Cr(III) species are oxidized to Cr(VI). Ni is present as NiO, and Mo as MoO_3.

The Co–28Cr–6Mo orthopedic alloy passivates spontaneously in air, resulting in the formation of a thin oxide film containing mainly Cr_2O_3, which is a predominant oxide in the lower potential range, $E \leq 0.3$ V (Fig. 3) [9–11]. At higher potentials, both Co and Mo oxides enter the passive layer. Co is present mainly as CoO and Mo as MoO_3. The passive range is followed by the transpassive region in which Cr(VI) species were detected. The formation of Co_2O_3 and/or Co_3O_4 in the transpassive range cannot be excluded, but their identification is ambiguous due to the small chemical shift between Co(II) and Co(III) species and to the low Co content in the passive layer. The concentration of Cr- and Mo-oxides is higher in the outer part of the layer, whereas Co-oxides are present mainly in the inner part, closer to the oxide/metal interface [9].

The passive oxide layer formed on the Ti–6Al–4V alloy is predominantly TiO_2 [12]. It contains a small amount of the suboxides TiO and Ti_2O_3, which decreased with increasing potential due to the predominance of TiO_2. The oxide Al_2O_3 is incorporated in the TiO_2 matrix and is located mainly at the outer oxide/solution interface. A vanadium oxide was not identified by XPS. For the Ti–6Al–7Nb alloy,

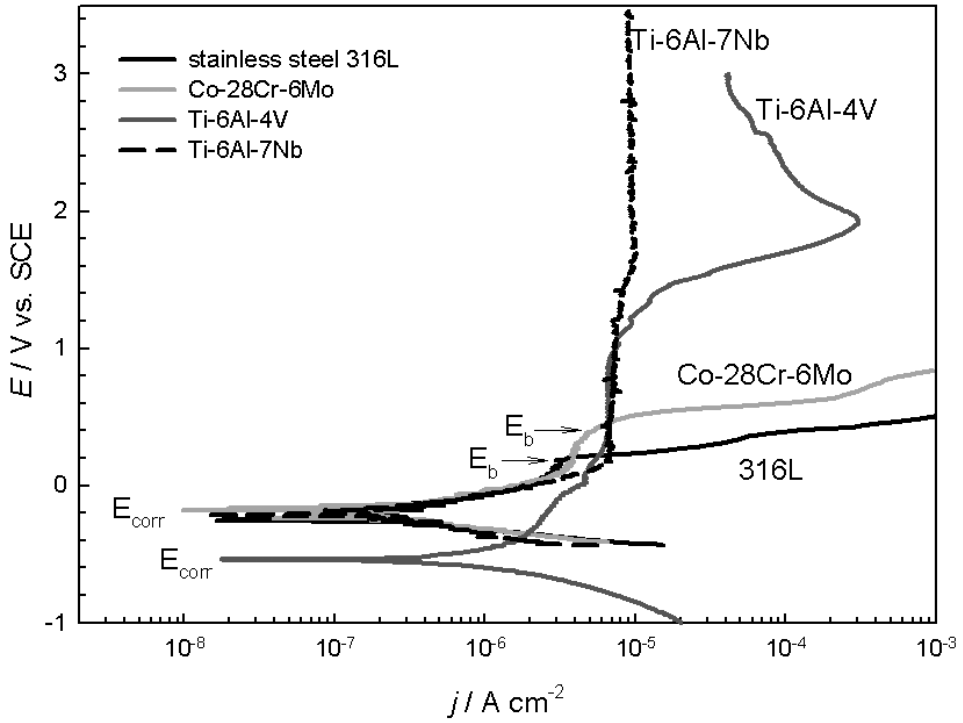

Fig. 3 Potentiodynamic polarization curves for stainless steel, Co–28Cr–6Mo, Ti–6Al–4V, and Ti–6Al–7Nb alloys recorded in HS physiological solution. dE/dt = 1 mV/s. Corrosion potential, E_{corr}, and breakdown potential, E_b, are denoted.

the formation of the suboxides TiO and Ti_2O_3 in the lower potential range is less pronounced than for the Ti–6Al–4V alloy [13]. At potentials more positive than 0.75 V vs. SCE, TiO_2 was the only Ti oxide formed. The passive range of Ti–6Al–7Nb alloy is broader than for Ti–6Al–4V and extends up to 6.0 V. The oxides Al_2O_3, Nb_2O_5, and NbO, and/or NbO_2 are incorporated in the passive layer and are located mainly at the outer oxide/solution interface of the TiO_2 matrix.

The addition of a complexing agent (citric acid and EDTA) significantly affects the passivation behavior of orthopedic alloys [14–16]. Dissolution at the surface of stainless steel is stimulated by the formation of soluble complexes, as evidenced by the increased current density of the anodic peaks and the shifting of the peak potential [14]. In this sense, organic molecules present in body fluids may be regarded as complexing agents and, in that sense, may affect the stability of metal implants. The presence of the proteins albumin, γ-globulin, transferrin, and fibrinogen in the physiological solution has a significant effect on the passivation behavior of stainless steel and its individual metals [15]. With the addition of proteins, the concentrations of metals, especially iron, dissolved into solution during potentiostatic oxidation increased. Similar to stainless steel, the addition of a complexing agent, Na-citrate, affects the passivation of the Co–28Cr–6Mo alloy. Co becomes strongly depleted in the passive layer, presumably due to the complexing of Co cations by the citrate and the consequent enhanced dissolution [9–11].

Proteins can thus stimulate the dissolution rate of a base metal and, consequently, suppress the formation of the protective oxide layer. The alloying of elements with small stability constants of the related complexes and/or slow rates of complex formation are essential requirements. When performing in vitro research on materials to be used in the human body, it should thus be taken into account that a pure saline solution does not entirely simulate the physiological situation.

CLINICALLY RELEVANT STUDIES OF METALLIC BIOMATERIALS

In vitro experiments performed in simulated physiological solutions are necessary in order to understand the behavior of a particular metal or alloy [8–18]; however, the results of these experiments are difficult to translate into in vivo clinical situations of total hip replacement for a number of reasons. Whereas the experimental conditions in the electrochemical cells in vitro are strictly controlled, the composition of the biological medium is different (due to the presence of various organic molecules, bone, blood, etc.), and the metal components are under stress, load, and wear. The prerequisite for an investigation of metals subjected to long-term functioning in the human body is the possibility of collaboration with orthopedic surgeons and access to a collection of prosthetic materials and tissue samples [19]. Following the example of the Scandinavian arthroplasty registries, the Arthroplasty Register of the Valdoltra Orthopaedic Hospital was established in 2002 in order to ensure the results of arthroplasty treatment and long-term follow-up of clinical results [20,21]. One specialty of our Register is that it includes an implant retrieval program for explanted prosthetic components and samples of periprosthetic tissue. The collected samples are the basis for various research analyses aimed at revealing the changes at the surface of the component and in the periprosthetic tissue induced during in vivo functioning of the prosthesis.

Analysis of retrieved prosthetic components: Types of corrosion in vivo

In many orthopedic applications, implant components are subjected to wear so that the in vivo corrosion process is often combined with the wear process. Special modes of corrosion regarding implant alloys that occur in vivo include pitting, crevice, fretting, and galvanic corrosion [22]. Pitting corrosion is a type of localized corrosion caused by local dissolution of the passive film and the formation of pits surrounded by an intact passive surface. Chloride ions abundantly present in the human body are the most common promoter of pitting corrosion. Stainless steel shows higher susceptibility than Co- and Ti-based alloys to pitting corrosion in halide solutions. Corrosion damage is frequently observed at screw holes after the removal of temporary stainless steel plates.

Crevice corrosion is a type of localized corrosion closely related to pitting corrosion. It occurs primarily in regions on the metal surface where mass transfer is limited, e.g., in narrow crevices or under deposits. At these occluded areas the concentration of aggressive chloride ions, a decrease in the pH value, and the depletion of oxygen can rapidly lead to the activation of the surface.

In total joint replacements, the combination of corrosion and wear processes often promotes both crevice and fretting corrosion. Fretting corrosion is a form of damage that occurs at the interface of two closely fitting surfaces when they are subjected to slight oscillatory slip and joint corrosion actions. An example given is a femoral neck made of Ti–6Al–4V alloy articulating inside a stainless steel head, revised after 12 years in situ due to aseptic loosening (Fig. 4). Careful inspection of the retrieved implant components revealed fretting corrosion of the femoral neck and crevice corrosion in the interior of the femoral head. Corrosion products containing Fe and Cr oxides were identified.

Galvanic corrosion may occur when dissimilar metals are in direct contact in a corrosive environment. Orthopedic alloys are very stable, and the combination of alloys such as Co- and Ti-based alloys theoretically should not lead to galvanic effects due to the presence of stable oxide layers on the alloy surfaces. In practice, however, galvanic corrosion is often observed, primarily due to the conjoint action of mechanical wear and corrosive attack on the material surface. This may lead to corrosion damage even for the combination of Ti–6Al–7Nb and Co–28Cr–6Mo alloys (Fig. 5), where abundant black corrosion product consisting of Cr- and Ti-oxides is formed.

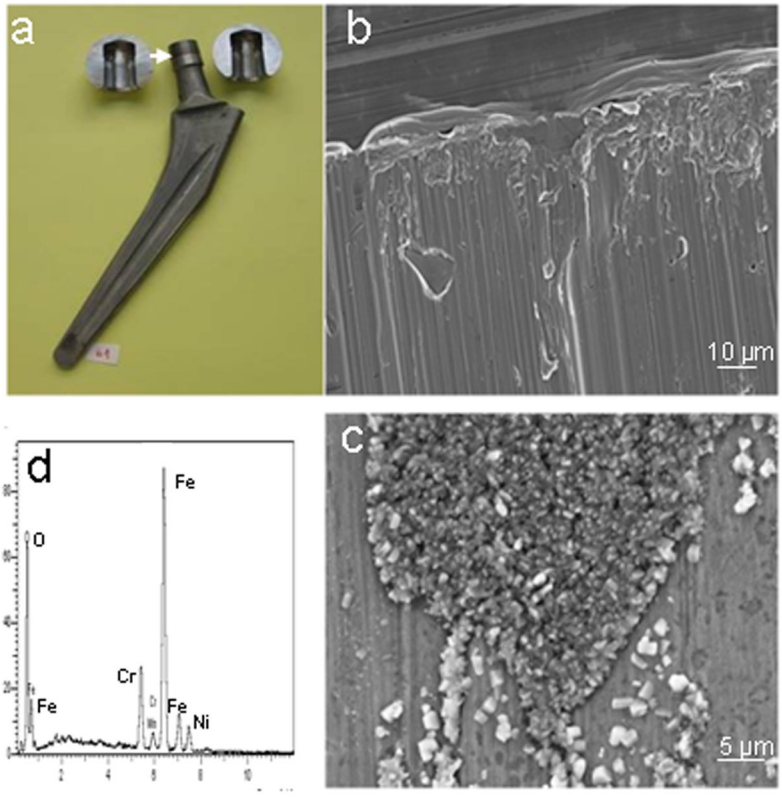

Fig. 4 Crevice and fretting corrosion in the interior between a femoral neck made of Ti–6Al–4V alloy and a femoral head made of stainless steel. The prosthesis was revised due to aseptic loosening after 12 years in situ. (a) The femoral stem and femoral head cut in half. Fretting scars at the neck are denoted by short arrow, (b) SEM image of fretting scars, (c) SEM image of corrosion product formed in the interior of the femoral head, and (d) an EDS spectrum of the corrosion product presented in (c).

Fig. 5 Crevice, fretting, and possibly galvanic corrosion between a femoral neck made of Ti–6Al–7Nb alloy and a femoral head made of Co–28Cr–6Mo alloy. Corrosion product is denoted by arrow. The prosthesis was revised due to aseptic loosening after 13 years in situ.

Analysis of periprosthetic tissue: The release of metal particles

In general, particulate debris in total hip replacements can be generated by corrosion and/or wear. The most common types of wear occurring on metallic components in total hip replacements are abrasive wear (a hard rough surface slides across a softer surface), third-body wear (hard particles stuck between two rubbing surfaces), and fretting wear (repeated cyclical rubbing between two surfaces). Some examples of wear damage identified on retrieved metal components are presented in Fig. 6. Wear processes result in the removal of metal particles from the surface and the release of particles into periprosthetic tissue. The presence of metal particles in the tissue changes its color to gray or black, a phenomenon usually referred to as metallosis. In our studies we isolate these particles from the tissue samples retrieved during a revision operation in order to study their size and composition. For this purpose, the tissue can be digested by strong alkali or acids, or by enzyme digestion. After isolation, the particles are transferred to filter paper, coated with C, and then analyzed using scanning electron microscopy (SEM) and/or transmission electron microscopy (TEM) [23].

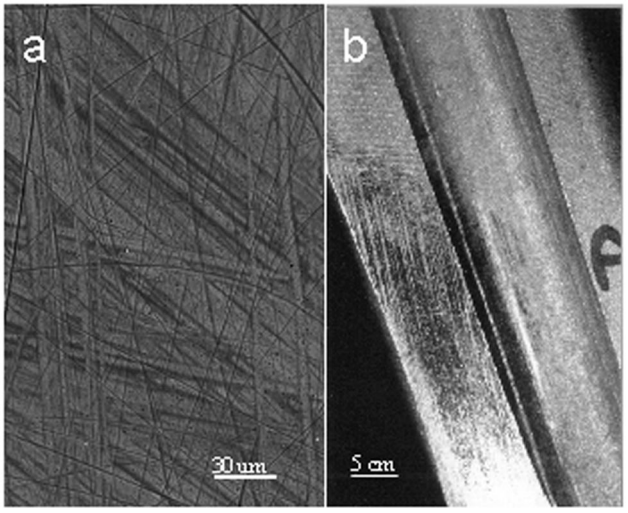

Fig. 6 A common surface morphology observed on retrieved metal components of a hip prosthesis due to (a) abrasive wear and (b) micromotion between the metal component and bone cement.

Metal particles released into the tissue range from the nanometer size to several micrometers. As an example, Ti-based particles isolated from periprosthetic tissue retrieved at the revision of a Ti alloy prosthesis are presented (Fig. 7). The image was recorded in back-scattered electron (BSE) mode, where metal particles are seen as white spots. The chemical composition of the particles was confirmed by energy-dispersive X-ray microanalysis (EDS). The particles are agglomerated in clusters. To study individual particles, clusters of particles were treated with ultrasound and then individual particles imaged at higher magnification by SEM and high-resolution TEM (Fig. 7). The size of the particles ranged from 60 nm (TEM image) to 300 nm (SEM image).

A precise characterization of the particulate wear debris generated in vivo is crucial for an understanding of their bioreactivity. The response of the biological environment to metal wear particles depends on their size, shape, and chemical composition [3,24,25]. Metal particles also have a cytotoxic effect and can cause cell death and apoptosis [24,26,27]. A decrease in lymphocyte count of peripheral blood has been found, and this can probably influence immunological response [28,29]. However, the clinical relevance of these changes has not been confirmed.

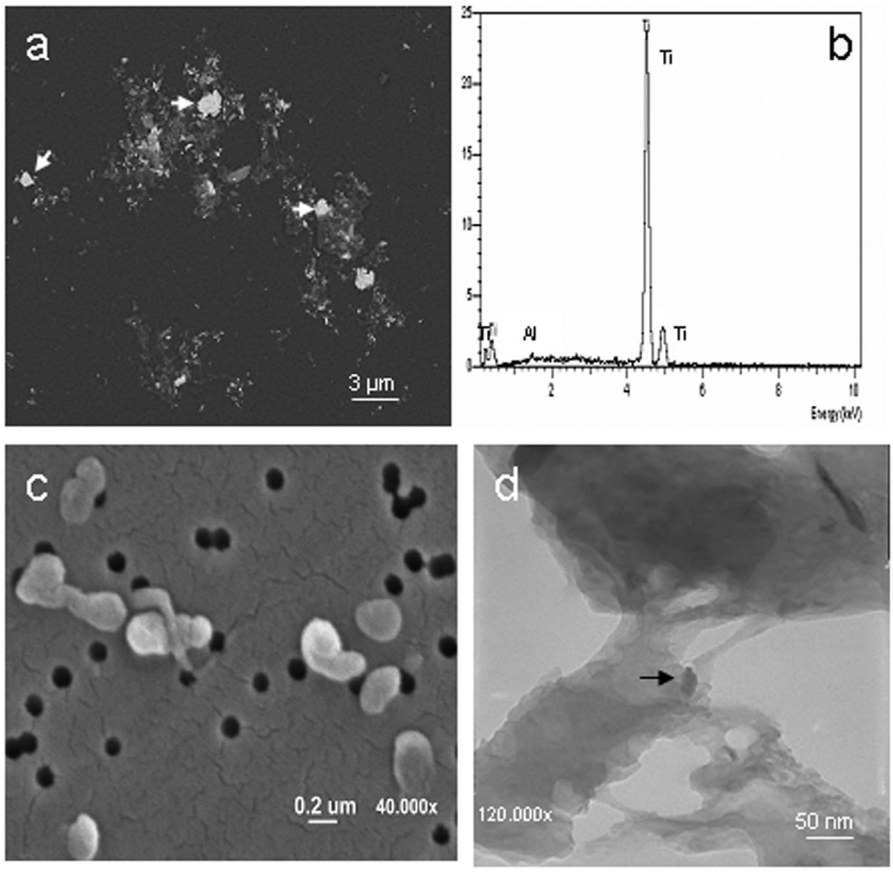

Fig. 7 Ti wear particles isolated from the periprosthetic tissue of a femoral stem made of Ti alloy: (a) SEM image of clustered particles recorded in BSE mode; Ti particles are denoted by arrows, (b) EDS spectra of the isolated particles, (c) SEM image of individual Ti particles (the holes in the filter paper are 200 nm in diameter), and (d) high-resolution TEM image of an individual Ti particle (arrow).

Local and systemic effects of the release of metallic products

When considering the consequences of the release of metallic products, i.e., particles or ions, from the implant surface, local and systemic effects should be distinguished. Metal particles released in periprosthetic tissue are not inert but are involved in biological processes such as phygocytosis, the process whereby macrophages engulf and digest a foreign body. These can be observed in histological images of the periprosthetic tissue. Metal particles appear as brown or black granules or flakes (Fig. 8). Smaller particles are stored intracellularly in macrophages, while larger particles and flakes are engulfed by foreign body multinucleate giant cells [3]. By engulfing foreign particles, these cells are activated and release pro-inflammatory factors and mediators that promote bone resorption in the periprosthetic area [3].

Once the particles are released in the artificial joint space, they can be carried away by the lymphatic and circulatory systems, and they have also been found to accumulate in the abdominal lymph nodes, liver, and spleen [30]. The process may well be dependent on the size and chemistry of the particles. Little is known about the systemic effects of various wear particles. A high concentration of metal ions may be derived directly from the implant itself where corrosion is present, or it may presumably originate from the numerous metal particles formed by the wear process [3]. Metal ions may bind to

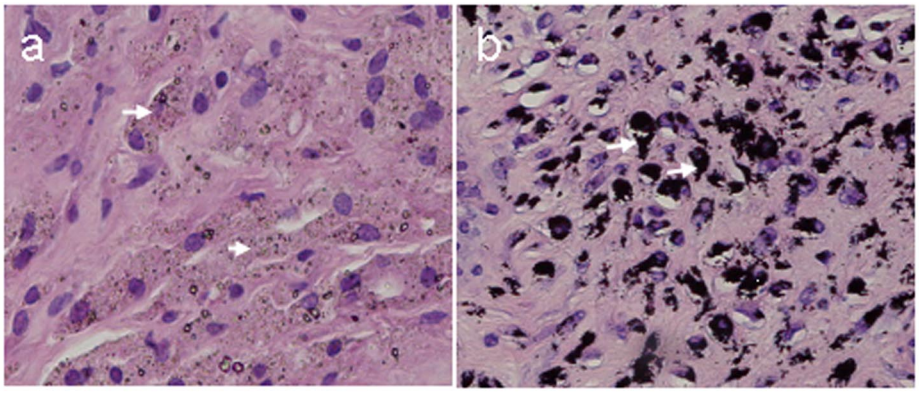

Fig. 8 Histological images of periprosthetic tissue containing metal particles: (a) tissue with a small amount of metal particles, seen as black granules within macrophages (arrow), and (b) tissue sample with a large amount of metal particles, seen as black flakes (arrow).

protein moieties that are then transported in the bloodstream and/or lymphatic vessels to remote organs [4]. The elevation of metal serum levels has been found in patients with well-functioning or loosened prostheses [4]. In the last decade, the measurement of elevated serum levels has been discussed especially in relation to the so-called MOM prostheses made of Co–28Cr–6Mo alloy. In our own study, we have measured Co and Cr serum levels for three groups of patients with MOM prostheses made of low-carbon Co–28Cr–6Mo alloy: a retrospective group, a prospective group, and a revision group [31,32]. The retrospective group of patients sampled at an average of five years postoperatively showed a three-fold increase in Co and a four-fold increase in Cr serum levels compared with the control group of healthy individuals without metal implants [32]. In the prospective group, the patients were sampled progressively after the implantation operation. Both Co and Cr serum levels increased over time and at an average of five months achieved a significant increase compared with preoperative values. The increase leveled off over time. In the revision group of patients, which was sampled progressively after a revision operation, we observed a decline of serum Co and Cr levels following the removal of MOM prostheses. A comparison of the results for the progressive and revision groups proved that the increase and decrease of serum Co and Cr levels are related to the presence and absence, respectively, of this particular type of prosthesis.

An increase in metal serum concentration is not specific for MOM patients, as it was proved that patients with other types of prostheses, e.g., metal-on-polyethylene, also had increased metal serum levels [32]. It should be pointed out that no reports in the literature considered the increase of metal levels in body fluids as a reason for revision but rather as a means for careful surveillance of the wear of the metal components, which is otherwise difficult while the implant is in situ. A close follow-up of these patients and further research concerning the dose-related toxicology of metal ions are needed in order to evaluate the possible risk of increased metal levels in body fluids. One of the possible responses is "metal allergy" or hypersensitivity to metallic biomaterials [4]. Released ions, although not sensitizers on their own, can activate the immune system by forming complexes with native proteins. Metal-protein complexes are considered to be candidate antigens (or allergens) in human clinical applications. The most commonly accepted senzitizers are Be, Ni, Co, and Cr.

CONCLUDING REMARKS

Biomedical implants have become an increasingly important issue due to the prolonged average life expectancy of the population. This paper was aimed at presenting interdisciplinary analyses devoted to the performance of metallic biomaterials. In vitro studies in simulated physiological solutions are

focused on the corrosion stability, composition, and electronic properties of the protective film, the effects of the physical-chemical conditions of physiological media, the types of possible corrosion processes, the dissolution of metal ions, etc. These studies, although important for a basic understanding of the behavior of metallic material in biological media, represent a first step toward the more realistic situation encountered in clinical situations. There, additional processes should be taken into account, such as wear and the motion of the components under load, the biological response to wear and corrosion products, long-term exposure, the effects of the physical-chemical conditions of the biological medium, etc.

Knowledge of the processes occurring in vivo should be substantially broadened since responses to orthopedic biomaterials are subtle and need to be studied further in more detail and from a long-term perspective. The importance of interdisciplinary research in evaluating the performance of orthopedic implants is crucial, even more so as new orthopedic implants and new materials are being developed and introduced with high expectations regarding their durability and long-term stability.

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