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(REVIEW ARTICLE)

Potentially toxic metallic wear nanoparticles and trace metal ions release from metal-on-metal orthopedic implants in the human biological specimens: An Overview of *in vivo* and *ex vivo* clinical studies

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Abstract

The use of metallic biomaterials in the medical implant devices has become increasingly prevalent over the past few decades. Patients find themselves being exposed to metals in a variety of ways, ranging from external exposure to instruments such as medical devices to internal exposure *via* surgical devices being implanted in their bodies. *In situ* generation of metallic wear nanoparticles, corrosion products and *in vivo* trace metal ions release from metal and metallic alloys implanted into the body in orthopedic surgery is becoming a major cause for concern regarding the health and safety of patients. The chemical form, particulate *vs.* ionic, of the metal species in the bodily fluids and tissues is a key to the local nanotoxicity effects arising in the body. Potential health risks are associated with metallic wear debris in the form of nanoparticles *in situ* generation and the release of *in vivo* trace metal ions into human biological specimen's circulation. This overview explores how migration of metallic wear nanoparticles and ultratrace metal ions in the area of metal-on-metal orthopedic implants influences the surrounding tissues and bodily fluids, and what the toxicological consequences of this process may be. Specifically, the present article is more informative of indicative multilevel *in situ/in vivo/ex vivo* analytical/clinical methodologies which will be helpful in a way to plan, understand and lead the analytical innovations in the area of nano-analysis to improve patient outcomes.

Keywords: Metal-on-metal orthopedic implants; Adverse local tissue reactions; Metallic nanoparticles; *In vivo* metal ion release; Biological fluids and tissues; *Ex vivo* quantifications

1. Introduction

Developing prosthetic implantology faces more and newer challenges and involves research in a wide variety of fields associated both with clinical and basic sciences. The development of research on materials used extensively in medical implantology reveals new data on the possible adverse side effects of metal release from metallic implant biomaterials (pure metals and metal alloys) into the human body. Increasing the number of people susceptible to allergic factors contained in the materials previously considered neutral allows for a better understanding of the phenomena, which an orthopedist may encounter at work. The corrosion of implant materials *in situ* is a type of material response to the host physiological environment. A major concern of modern implantology seems to be the possibility of release of toxic trace metal ions and nanoparticles through corrosion or wear processes of metallic orthopedic implants used in the production of implanted metal devices into the human body physiological environment.

This paper presents an overview of ongoing research regarding the potential related adverse biological effects associated with local nanotoxicity attributed to elevated trace metal ions and metal wear micro- and nanoparticles released from metal surgical implants, based on the available *in vivo* and *ex vivo* clinical studies. In accessible literature

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the majority of papers have established an *in vitro* approach which is not reliable to *in vivo* and/or *ex vivo* conditions; *in vivo* findings often do not correlate with *in vitro* results which may be very far from the chemical states of the *in vivo* degradation products generated from joint replacement implants. This may lessen the relevance of such toxicity studies. Thus, the development of *in vivo* metal ion analysis is critical to investigating the complex problems associated with the chemical nature that underlies metallic orthopedic implants function. However, recently, *in vivo/ex vivo* hip-simulator studies provided substantial evidence to prove that the debris generated using serum has similar characteristics to that of patient tissue samples [1]. Even so, *in vitro* testing of metallic implants with a combination of electrochemical and mechanical tribo-corrosion conditions for assessing the bio-corrosion properties of metals used in implanted metal appliances was not considered.

It should be noted that the reference list cannot represent the totality of Literature on the nature of metallosis of orthopedic metal implants, adverse reaction to metal debris, degradation products of metallic implants, and corrosion, but points to some of the more significant Literature that reflect the local nanotoxicity of metals related to orthopedic metal implants and to estimate tolerable human body intakes according to the recommendations of health agencies.

2. Metallic orthopedic implants

Locomotors system diseases are now one of the most serious threats to the health of the world's population. Osteoarthritis is third cause of disability in terms of incidence in the world's population. Due to the enormous technical progress in the recent decades, application of various kinds of implants in the treatment of orthopedic disorders has grown rapidly in bone surgery. A wide range of orthopedic devices are made from metal, but few implanted metallic orthopedic devices have attracted as much public and scientific interest as MoM joint prostheses. In particular, the growing application of metallic orthopedic implants which effectively take over the function of damaged bones and joints, allowing for the proper functioning of patients in their daily lives. In clinical practice within the field of orthopedics, metallic implants or more frequently alloyed metal implants are applied and mostly used to substitute, rebuild or replace hard tissues such as bones, due to the fact that their mechanical fatigue strength, hardness and fracture toughness, much higher than those of ceramics and polymers, allow to apply them as structural materials for the production of the most intraosseous implants [2-10]. At the same time, the decreased age of patients, who need a variety of orthopedic implants, puts high demands on implant biomaterials, which are placed for a long period of time in the body, should be of high biocompatibility [11-15]. As a result, around 80% of artificial hip and knee joints, bone plates and spinal fixation devices are currently produced from metal [16].

Metallic orthopedic implants, mostly composed of chromium, cobalt, molybdenum, nickel, titanium, tantalum, tungsten and zirconium alloys, are commonly used structural elements, which support the functions of the human body, in particular the skeletal system [7,8]. Metallic implant biomaterials: cobalt-based alloys (i.e. Co-Cr-Mo, Co-Cr, Co-Cr-W-Ni), pure titanium and titanium-based alloys (Ti-6Al-4V), and Nitinol shape memory alloy are the most commonly utilized metallic biomaterials used in various orthopedic implants. Co-based alloys are used more widely in longer-term permanent implants and those that require high wear resistance, such as artificial joints - hip and knee prostheses. Surgical medical grade stainless steel is known for its high strength and good ductility, but can be difficult to integrate with bone or soft tissue having poor wear resistance compared to other metallic implants. As a result, the only biocompatible stainless steel is commonly used in fracture fixation devices and/or temporary implants intended to be removed at a later time. Co-Cr-Mo alloys are categorized as bio-tolerant while titanium and its alloys are categorized as bio-inert. Therefore, titanium and its alloys are considered the most biocompatible and popular of all metallic biomaterials due to many fascinating properties, such as superior mechanical properties, strong corrosion resistance, and excellent biocompatibility [4,5]. Titanium alloys are further categorized according to their phase constitution as α-, (α + ß)-, and ß-type titanium alloys. ß-Ti alloys promise to face challenges because they have non-toxic elements and superior corrosion resistance. However, the application of Ti alloys for implant materials is impeded by their poor mechanical strength. Each of these metals and alloys has its own particular strength, rigidity and ductility properties. Their high resistance to corrosion has made them particularly suitable for use in the manufacture of orthopedic implants. However, prolonged contact of the body tissues with an implant causes a number of unwanted effects, which result in structural changes in the implant itself, reducing the lifetime and local and systemic toxicity.

Chemical compounds that compose a biomaterial, including a metallic orthopedic implant, are usually well tolerated by the body; however, they may be toxic [17,18], carcinogenic [19] or cause hypersensitivity [20,21] and allergic reactions [22]. As a result of the development of corrosion, metallic elements enter the tissue environment in the form of metal ions or corrosion products, causing a discoloration of tissue fluids and synovial fluid - the phenomenon of metallosis [23]. The physicochemical condition of the surface of an implanted material is changed as a result of the conduction of functional currents through an implant, corrosive processes and processes of friction and abrasion. An implant's surface is altered by surrounding tissues and bodily fluids in the oxidative processes. As a result of the corrosion of metal/metal

alloys, toxic active ions (Co, Cr, Mo, Ni) may enter the surrounding periprosthetic-implant tissue environment and thus can be transported *via* the vascular system to different parts of the body [24,25]. Besides electrochemical corrosion of implanted metallic biomaterials the effect of which is the release of soluble metals, other common forms of implant biodegradation are mechanical stresses and wear processes. These metal particles may dissolve in bodily fluids and are then distributed *via* the vascular system in the human organism.

3. Orthopedic metallosis

Metallosis, current issue in the field of orthopedics, is defined as a medical condition involving deposition and built up of metal debris in the periprosthetic soft tissues results from the surface deterioration of MoM bearings in orthopedic implants [26]. It occurs due to wear, corrosion particles and release of metallic nanoparticles and metal ions into the periprosthetic surrounding tissue of prosthese implant and was first seen in the setting of the fixation of fractures with metal implants [27]. Further, it has been an occasional but characteristic clinical finding in patients who have a MoM design of total hip replacement, such as the McKee-Farrar prosthesis [28]. The eventual outcome of this condition is local tissue damage and changes in tissue characteristics as a result of direct toxic effects and biologic reactions to metallic nanoparticles [29,30]. Lately, cases were diagnosed patients after total knee replacement [31-37], knee joint load absorber [38], and total hip replacement [39-44]. Although, metallosis is a well-established complication of MoM implants, emerging data reveal that it also may be a problem in non-MoM implants such as either metal-on-polyethylene (MoP) or ceramic-on-polyethylene (CoP) implants, perhaps related to modular corrosion [45,46].

Metallosis can occur in any orthopedic implant and is found during the revision surgery incidentally. This occurs because of the inconsistency of patient symptoms and the difficulty identifying this phenomenon through imaging techniques. The lack of clinical relevance could explain why this phenomenon is often used to describe the appearance of the tissue instead of a cause for implant failure leading to revision surgery.

4. *In situ* degradation of metallic orthopedic implants

Mechanisms involved in the degradation of implants are complex, as is evident from the range of clinical responses with some patients having no complications and others requiring revision of the implant. If the implant is placed in the harsh for metals, biological physiologic environment of the human body and interaction in place of contact of implant - soft tissue - bodily fluids often occurs. The degradation products of any metallic orthopedic implants and joint prostheses (e.g. hip, knee, shoulder, finger, elbow, ankle), and temporary implant applications such as bone plates, screws and prosthetic components in orthopedics are primarily generated by wear processes and corrosion, or by a combination of the two, of the metal alloy [47]. MoM prostheses generate metallic wear particles and corrosion debris, nanometer- to sub-micrometer metal particles, metal ions and metallo-protein complexes [48]. This section is focused on releasing of metallic nanoparticles and elevated ultratrace metal ions, from the surface of MoM bearings, to the human bodily fluids and tissues since metals have been focused to bear intense wear/corrosion and cause adverse local tissue reactions (ALTRs). The degradation products of ceramics, polymers and composites will not be considered, because these classes of materials generally are considered insoluble in physiologic environments.

Currently, there are no universally accepted thresholds for metals or specific elevated metal ion level leading to a reaction in the human body. However, for orthopedic implants, in the case of cobalt and chromium, values without clinical concern are at the moment less than 4 μg L^{-1} (normal steady-state values). Above a threshold of 7 μg L^{-1} (119 and 134 nmol L^{-1} for Co and Cr, respectively) metal ion levels, additional imaging and closer follow-up is recommended as it is considered as supportive evidence of adverse local soft tissue reactions and an increased risk of MoM-specific complications [49-52]. Therefore, in this overview, papers reported bodily fluid and tissue metal concentrations above exceeded, critically elevated 7 μg L^{-1} will be presented according to experimental analytical/clinical data.

4.1. Metallic wear nanoparticles

Metal implants induce the transfer of some metallic wear particles from any orthopedic implant to surrounding soft tissues [53]. Wear in joint arthroplasties can be defined as the net removal of material (metal or metal alloy) due to the mechanical activity [54] and is recognized as the most important limitations to long term stability of joint prosthetic devices. Wear debris is released from the articular surfaces after joint replacement as a result of friction between articulating implant components or between cement and implant [55]. There are four types of mechanical wear mechanisms: surface fatigue, abrasion, adhesion and erosion [56,57]. The generated metallic nanoparticles sizes are within the nanometer ranges between 25 and 50 nm diameters [58,59]. It was reported that metal wear CoCrMo particles from MoM implants were of smaller diameter compared to polyethylene wear particles from conventional implants and MoM bearings generated more particles than MoP and they have been found to be more biologically active

than MoP [60]. The linear wear rates for modern MoM bearing surfaces were reported in the range of 1 to 5 μm per year [61]. After a rapid wear rate for the first year after implantation, as a result of an initial conditioning phase, most MoM implants have a constant low wear rate [62]. Prosthesis-derived metal wear products can be extensively identified within the synovial and periprosthetic tissues and bodily fluids of arthroplasty patients [63].

4.1.1. Hip and knee implants

Particulate metal debris comprises a substantial portion of metal degradation products generated by joint replacement prostheses. Wear and corrosion are probably the major causes of release of metal into the tissues of MoM patients, and this poses a major concern regarding the use of MoM articulating devices [64].

Several studies have focused on the difference in cobalt and chromium ions concentration between MoM total hip arthroplasty (MoM THA) and MoM hip resurfacing arthroplasty (MoM HRA) [65,66).

In a prospective study, synovial fluid metal levels from stainless steel, cobalt-chromium, and titanium-alloy cemented total hip implants were measured [67]. Implant retrieval analysis showed severe burnishing and scratching in all titanium-alloy femoral heads and extensive burnishing and scratching in the majority of the femoral stems.

Keel and Kuster [68] reported on a case of massive wear because of an incompatible MoM combination, a cobalt-chromium (Co-Cr) alloy cup was paired with a stainless steel head. The resultant wear volume was increased by a factor of 18 for the head and 2 for the cup compared with normal MoM articulation.

To establish the types of wear particles around human prostheses the periprosthetic tissues around 50 hip arthroplasties were examined by light microscopy, transmission electron microscopy, and energy-dispersing X-ray microanalysis. The tissues around cementless metal-on-bone prostheses contained few or no prosthesis metal wear particles [69]. Buly et al. [70] reported studies on total hip arthroplasties and characterization of wear particles.

The chemical composition of wear particles embedded in soft tissue around failed hip and knee implants have been reported [71]. Polarized light and scanning electron microscopy were used to locate metal wear particles and energy-dispersive electron microprobe analysis was used for their elemental microanalysis (Co, Cr, Cu, Fe, Mo, Ti, Zr). From tissue collected at revision from patients showed mainly chromium oxide and very few CoCr particles.

Lohmann et al. [72] found that the type of tissue response to periprosthetic metal wear debris correlated with the concentration of metal (Co, Cr, Ni) in the tissue.

Oudadesse et al. [73] and Chassot et al. [74] study contamination induced by metallic element released by joint prostheses. Neutron activation analysis (NAA) and particles induced X-ray emission (PIXE) has been used to analyze some tissues near the femur in contact with metallic prostheses. It was shown a very heterogeneous contamination by metals (Co, Cr Fe, Ni) under particles which migrated through soft tissues. High-resolution transmission electron microscopy (TEM) and X-ray photoelectron spectroscopy (XPS), combined with chemical analysis, has been used to identify the morphology and composition of particles isolated from periprosthetic tissue of MoM hip bearing [75]. Two types of particles, CoCr and Cr-based, were identified as originating from the bearing and the majority of particles were CoCr, while some contained no cobalt. De Pasquale et al. [76] were focused on the correlation between metal nanoparticles often present in synovial fluid and circulating Co/Cr ions in whole blood as well as serum samples of patients. Co and Cr both in serum and whole blood represents a systemic representation of the particle release at local level and can be therefore used to confirm a diagnosis and monitoring of wear processes of MoM articular prostheses.

Ichinose et al. [77] examined the distribution of metal nano-sized particles which were released from the Co-Cr-Mo and Ti-Al-V alloys. These metallic wear particles, produced by the abrasion of both Co-Cr-Mo and Ti-Al-V alloys, are accumulated in the synovial fluid. As Co-Cr-Mo alloys disintegrate easily in the synovial fluid, Co dissolves from the peripheral areas of them, although Cr remains within the synovial fluid. In contrast Ti-Al-V alloys are very stable in the synovial fluid. From these findings they concluded that the Co-Cr-Mo alloys are hazardous to the body as the alloys release Co which enters the body. In contrast the Ti-Al-V alloys are very stable and are patiently safer.

In another report, Sidaginamale et al. [78] investigated the influence of metal debris exposure on the subsequent immune response and resulting soft tissue injury following MoM hip arthroplasty. The statistical modeling suggested that a greater source contribution of metal debris on Cr and Co concentrations from the taper junction was associated with smaller aggregated particle sizes in the local tissues and a relative reduction of Cr ion concentrations in the

corresponding synovial fluid and blood samples. Metal debris generated from taper junctions appears to be of a different morphology, composition and therefore, potentially, immunogenicity to that generated from bearing surfaces.

The results reported by Hahn et al. [79] emphasized the distinction between the effects of MoM and MoP implants. Studies of 13 undecalcified femoral heads which had undergone surface replacement showed increases in cobalt concentrations, up to 380 μg g^{-1}, compared to control specimens without an implant or with MoP implants.

Quantitation of metallic wear nanoparticles *in situ* isolated from human soft tissue adjacent to MoM orthopedic implants is presented in Table 1.

4.2. Elevated concentrations of trace metal ions in human bodily fluids

Metal-on-metal prostheses generate metallic wear nanoparticles, corrosion products and trace metal ions. Moreover, wear particles may undergo a corrosion process contributing to enhance the metal ion level [80]. Most *in vivo* studies that have been published in the literature are related to the effects induced by cobalt and chromium in human biological specimens. Other known potential toxic metal ions released by orthopedic implants are titanium, vanadium, aluminum, molybdenum and nickel [81,82].

In this section below, the information on the metal ion release from MoM implants into human bodily fluids (blood, serum, plasma, synovial fluid and urine) of patients and the local toxicity of released *in vivo* ultratrace metal ions is presented, according to the experimental analytical/clinical data.

4.2.1. Cobalt and chromium

Hip and knee implants

Most of the work relating to MoM orthopedic prostheses has concerned the concentrations of cobalt and chromium in human bodily fluids. The elevated metal ion levels observed in this overview were also comparable to those of the levels in patients with MoM total hip and knee replacements. The interest in metal ions level following MoM total hip arthroplasty were first reported more than four decades ago by Coleman et al. [83]. Elevated cobalt and chromium ion level have been documented in the blood and urine samples of the patients with Co-Cr McKee-Farrar implants (THAs) who have undergone hip replacement procedures using MoM articulations. Authors reported approximately 3-fold increases of Cr in whole blood, 11-fold elevations of Co in whole blood, and 15-fold elevations of Cr in urine in patients with Co-Cr MoM THAs in comparison with their preoperative values. None of these elevations were observed in patients with MoP THAs.

Since then, elevated concentrations of ultratrace cobalt and chromium have been reported in the blood of patients with failed total joint replacements [30,65,76,83-89,91-94,114-116], and in serum and plasma [40,76,90,85-103,105-112]. Elevated urine metal levels in patients with loosening implants were found to generate higher metal levels [83,93,94,103,112]. Metal alloy ion release in synovial fluid, less studied, has also been reported [40,66,95,104,113,117].

The elevated total concentrations of cobalt and chromium in the bodily fluids of patients following ion release from MoM orthopedic implants are presented in Table 2.

Table 1 Quantitation of metallic wear nanoparticles in situ isolated in soft tissue of patients adjacent to MoM orthopedic implants

Implant type	**Time *in situ***	**No. patients**	**No. particles**	**Particle size (nm)**	**Metal/ kind of wear particles**	**Metal/particle tissue content/concentration ($\mu g\ g^{-1}$)**	**Detection system**	**Wear nanoparticles morphology Clinical outcomes**	**Refs.**
Hip/THR	15-26 m	8	20 - 580	< 50 (6 – 834)	Co-Cr-Mo alloy	n/a	TEM	Oval or round Fewer local biological effects	[60]
Hip/THA	2 y	7			Co-Cr alloy Ti-6Al-4V alloy	45*(6 – 248) 4,470*(110 – 25,000)	GF-AAS	Pseudocapsules Loosing implants occurs	[67]
Hip/THA		71		< 200	Ti alloy/ CoCr	2,111* (60-11,823) mg g^{-1}	n/a	Spherical and needle-shaped wear debris Accelerate bone loss and loosing	[70]
Hip/THA		27			Co, Cr, Ni	222.2*(1.4 - 4604)	GF-AAS	Hypersensitivity reactions Suspected ALTR (pseudotumor)	[72]
Hip/THR	63 m	1		40 - 120	CoCr	n/a	TEM, XPS	Needle-shaped or round	[75]
Hip/THA	4.4 y	40	1 - 5		CoCr	n/a	SEM-EDX	Egg-shaped	[76]
Hip/THR	101-225 m	3	75 - 110	3 - 67	Co-Cr-Mo alloy/ Cr_2O_3	n/a	TEM	Round, oval and needle-shaped	[80]

Analytical techniques: TEM, transmission electron microscopy; GF-AAS, graphite furnace atomic absorption spectrometry; XPS, X-ray photoelectron spectroscopy; SEM-EDX, scanning electron microscopy-energy dispersion X-ray; ICP-MS, inductively coupled plasma mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometry; n/a - data not available; Results are reported as mean*/median** concentration, range (in parentheses); m-month; y-year

Table 2 *In vivo* times and Co and Cr elevated total concentration in bodily fluids of patients following ion release from MoM orthopedic implants

Implant type	Time *in vivo*	No. patients	Bodily fluid analyzed	Metal ion(s) measured	Concentration (μg L^{-1})		Median (μg L^{-1})	Analytical technique	Clinical outcomes	Refs.
					MoM	Control				
Hip/HRA	51 m	12	Blood	Co Cr	36.00 41.40	n/a		TEM, EDS	Increased failure rates due to adverse local tissue reactions (ALTRs)	[30]
Hip/THA	2.9 y	26	Serum Synovial fluid	Co Cr Co Cr		n/a	33.8 (4.3-94) 33.9 (5.3-93) 2185 (110-5120) 5136.5 (155-29 080)	ICP-MS	High concentration of metal ions are more likely to be associated with metallosis	[40]
Hip/THA	2 y	23	Synovial fluid	Co Cr	21(0.2-152) 19(0.8-238)	n/a		GF-AAS	Toxic local reactions	[67]
Hip/THA	4.4 y	17	Whole blood Serum	Co Cr Co Cr			23.8(0.05-109.6) 7.4(0.5-99.3) 18.5(0.8-131) 9.5(0.8-98.8)	ICP-MS	Local reaction cases	[76]
Hip/THR	1 y	25	Whole blood Urine	Co Cr Co Cr	6.5 3.9 24 6.0	0.6 1.4 0.5 0.4		NAA	The long-term effects of the accumulation of chromium in the body need to be studied further	[83]

Hip/THR	3 - 4 y	28	Whole blood	Co Cr	36.55 ng g^{-1} 48.04 ng g^{-1}	0.7 ng g^{-1} 0.21 ng g^{-1}		GF-AAS	There has been no significant epidemiological evidence	[84]
Hip/THR	4.3 y	35	Blood	Co Cr	277 nmol L^{-1} (2-1899) 226 nmol L^{-1} (12-1407)	n/a	58 nmol L^{-1} (12-1407) 73 nmol L^{-1} (2-353)	ICP-MS	Evidence of adverse reactions to metal debris (ARDM)	[85]
Hip/BHR	5.1-14.3 y	15	Blood	Co Cr		n/a	8.5-185.8 7.6-55.5	ICP-MS	Revision for adverse reactions to metal debris	[86]
Hip/ASR HR	1 y	38	Whole blood	Co Cr		n/a	12.6 3.4	ICP-MS	Annual measurement of blood metal ions is beneficial in patients with bilateral high risk THA, although changes in Cr were minor	[87]
Hip/BHR	12 y	16	Blood	Co Cr		n/a	125(59-181) nmol L^{-1} 105(52-125) nmol L^{-1}	ICP-MS	Annual blood Co and Cr have limited discriminating capacity in diagnosing the occurrence of metallosis	[88]
Hip/THR	4 y	94	Blood	Co Cr	22.83 14.42	n/a		n/a	Poor correlation between blood metal ions and development of ARDM	[89]
Hip/BHR	3.4 y	26	Serum	Co Cr	9.8(0.6-111.3) 9.7(0.6-94.6)	n/a		ICP-MS	A higher concentration of metal ions does not correlate with the level of activity	[90]
Hip/THR	27 m	25	Whole blood	Co Cr			10.6(2.6-72.1) 7.9(2.3-42.1)	ICP-MS	Painful MoM joints pre-revision surgery	[91]
Hip/THR	30-47 m	90	Whole blood	Co Cr	23(0-236) 9(0-86)	n/a		ICP-MS	Soft tissue damage	[92]
Knee/TKA	5 y	40	Whole blood	Co Cr	116.1 108.1	0.8 5.8		GF-AAS	Indication of the loosened prosthesis	[93]

			Urine	Co Cr	0.8 1.1	0.7 0.6				
Hip/ASR	4.5 y	72	Whole blood Urine	Co Cr Co Cr	29.1(0.56-231) 12.8(0.1-128) 966(0.56-767) µg g^{-1} 26.6(0.08-28) µg g^{-1}	n/a	6.29 2.27 26.55 5.45	GF-AAS	Symptom "pain" appear predictive of metal ion release in bodily fluids	[94]
Hip	134 8	20 Synovial fluid	Serum Co	Co Co	max. 175 56.9-22,400	n/a		ICP-MS	Not evaluated	[95]
Hip/THA	1 y	31	Serum	Co	14.1 (0.9-29.0)	n/a	13.0	AAS	Patients are clinically asymptomatic with a low rate of ALTR (7.5%) and no osteolysis observed at medium term	[96]
Hip/ HRA Unilateral HRA Bilateral HRA	4.3-5.0 y	16	 Serum Serum	 Co Cr Co Cr	 6.6 (0.5-125) 8.5 (0.7-95.6) 7.3 (0.5-146) 10.7 (2.0-104.7)	n/a	2.1 4.2 2.5 6.1	ICP-MS	Moderately elevated levels; additional investigations advocated	[97]

Hip/ASR	1 y	25	Serum	Co Cr	56.3 (7.2-220) 20.5 (1.9-61)	n/a		ICP-MS	In patients with normal renal function, these metal ion levels would decline at a reproducible rate and return to low levels	[98]
Hip/THR	45	57	Serum	Co Cr	14.5 (0.7-60.6) 10.8 (0.3-47.2)	n/a		ICP-MS	Soft tissue reactions, MoM implants are at risk for failure	[99]
Hip/HRA	7.2 y	12	Serum	Co Cr		n/a	9.0 (0.3-175.3) 14.7 (0.3-88.7)	ICP-MS	Patients were identified having ALTRs	[100]
Hip/THA	n/a	26	Serum	Co Cr	1.35-85.64 0.56-61.59	n/a		n/a	Alpha-defensin testing is prone to false-positive results in the setting of ALTR	[101]
Hip/THA	7 y	9	Serum	Co Cr		n/a	18.97 19.37	ICP-MS	Regular laboratory analysis should be considered	[102]
Hip/ASR	6 y	11	Serum Urine	Co Cr Co Cr	25.81 (0.50-110.00) 23.08 (0.6-101) 205.62 (1.40-810.20) 42.83 (3.90-163.70)	n/a		ICP-MS	Patients required revision surgery due to metallosis	[103]
Hip/THA	36 m	29	Synovial fluid	Co Cr		n/a	1014 (1-12444) 1512	ICP-MS	Defined cause of failure. Unexplained pain	[104]

							(0-263298)			
Hip/THR	6.7 y	9	Serum	Co Cr	6.9(1.2-14.9) 4.4(1.1-7.6)	n/a		ICP-MS	Hips revised for ARDM	[105]
Hip/ASR THA	2.2-9.1 y	21	Serum	Co Cr	6.88 (1.24-38.05) 22.35 (3.67-136.2)	n/a		n/a	Pseudotumor Increased risk of ARDM	[106]
Hip/THA	1 y	20	Serum	Co Cr			7.5(3.6-10.2) 4.4(1.4-6.3)	Co (ICP-MS) Cr (AAS)	Persistent pain significantly associated with higher metal ion levels, with a probable cobalt cut-off about 8 μg L^{-1}	[107]
Hip/ HRA	2 y	8	Serum	Co Cr			24.0-140.0 5.3-60.0	ICP-MS	Not assessed	[108]
Hip/HRA	1.9 y	209	Plasma	Co Cr			8.5 (0.5-153.3) 5.9 (0.2-66.9)	ICP-MS	Cobalt and chromium levels have moderate sensitivity and specificity in the diagnosis of ARMD in symptomatic patients	[109]
Hip/BHR	3-24 m	60	Serum	Co Cr Mo			4.28 5.12 2.11	GF-AAS	Not evaluated	[110]
Hip/THA	n/a	5 15	Serum	Co Cr	5-27 1.2-4.4	n/a		ICP-MS	Not evaluated	[111]
Hip/THA	15.3 m	14	Serum Urine	Co Cr Co	14.0 (3.70-43.2) 2.88 (0.45-4.98) 5.46	3.46 (1.42-6.30) 1.47 (0.31-1.97)		ICP-MS	No assessment has been made to establish a safe level for body fluids in patients with prostheses	[112]

				Cr	(0.24-11.7) 2.00 (0.25-4.56)	0.27 (0.06-0.83) 0.82 (0.04-4.35)				
Hip/THA	18 y	32	Synovial fluid	Co Cr		n/a	113.4(3.9-176) 54.0(1.5-334)	GF-AAS	Consideration for evaluation of wear and adverse tissue reactions in MoM THA	[113]
Hip/THA	37 y	1	Whole blood	Co Cr	22.92 19.43	n/a		ICP-MS	Not evaluated	[114]
Hip/BHR+THA	4.3 y	1	Whole blood	Co Cr		n/a	138 39	ICP-MS	Persisting pain	[115]
Hip/BHR	9 y	16	Whole blood	Co Cr	43 22	n/a		ICP-MS	Association with pain and joint effusions	[116]
Hip/THA	2 y	17	Joint fluid Whole blood Serum	Co Cr Co Cr Co Cr			~5000 (4000-7000) ~9000 (1000-38000) 69(7.82-99.1) 29.3(3.89-41.8) 29.7(4.95-96.6) 33.6(3.84-67.5)	ICP-MS	Joint failure association with groin pain ARMD	[117]

Analytical techniques: NAA, neutron activation analysis; GF-AAS, graphite furnace atomic absorption spectrometry; AAS, atomic absorption spectrometry; ICP-MS, inductively coupled plasma mass spectrometry; TEM EDS, transmission electron microscopy element mapping; Results are reported as "mean/median, concentration, range (in parentheses)"; n/a - data not available; m-month; y-year

4.2.2. Titanium

In vivo monitoring of titanium release was usually based on the determination of the metal level in blood or serum [118,119]. A number of investigations have reported blood/serum titanium levels associated with different types of well-functioning and malfunctioning hip and knee prostheses. Although most have focused on the toxicity of cobalt and chromium, other studies have also reported issues concerning titanium release from implants [120].

Hip implants

Agins et al. [121] was one of the first to recognize that titanium release from joint hip implants might lead to adverse local tissue responses. They noted that titanium prostheses (Ti-6Al-4V) liberated potentially toxic local concentrations (average, 1047 μg g^{-1}) of metal debris into the surrounding tissues, which was enhanced if loosening was present. In line with these results, elevated Ti ion concentrations in human bodily fluids (blood, serum and synovial fluid) [122-125] have all been reported. The whole blood levels of Ti were grossly elevated by a factor of 50 times in patients with loose MoM articulations when compared with the control group. On the other hand, the urinary Ti concentration was not elevated in patients with MoM proximal femoral replacements [122]. Vendittoli et al. [123,124] reported a 3-5-fold increase trend in whole blood Ti ion levels in patients with MoM large-diameter head total hip arthroplasty after 1 year. Lavigne et al. [125] compared the amount of Ti ion release from four different types of MoM prostheses. This investigation revealed that Ti ion release differs greatly between various THA implants with large-diameter femoral heads.

In a series of papers, Sanz-Medel research group [126-128] reported an analytical methodology for the determination of trace Ti at the μg L^{-1} level in blood/serum samples, in order to monitor metallic implant function in humans. Since titanium is relatively slowly transported in the body, a modest increase in concentration likely reflects a significant release of titanium into the local joint space, and can potentially serve as a marker for wear or corrosion. More recent investigations [129-132] have reported blood/serum titanium levels associated with different types of well-functioning and malfunctioning prostheses.

Elevated Ti ion concentrations in serum/plasma have continue been reported, because the higher titanium levels are easier to detect and quantify. In addition, the Ti ions could also be used to *in vivo* monitor MoM implant performance (serum titanium level, 15 μg L^{-1}) [133]. Loosening implants gave rise to even higher titanium levels in the serum [134] and in the synovial fluid [66]. Savarino et al. [135,136] have measured and compared serum titanium in patients with well-fixed implants.

Engh et al. [137] compared 2-year post-operative Ti ion levels for 28-mm and 36-mm MoM bearings. They reported a 3 to 4-fold serum titanium increase with well-functioning implants. These results are similar to those described in the study by Vendittoli at al. [138] showed that the whole blood Ti concentrations rapidly increased after 1 year. Gofton et al. [139] reported that titanium was released from modular femoral necks after 1 year, and the difference between the preoperative and postoperative serum Ti levels was almost 10-fold. More recently, Zijlstra et al. [140] set up a randomized clinical trial to evaluate periprosthetic acetabular bone density and serum Ti ion levels in MoM THA, compared to MoP THA. Contrary to their hypothesis, acetabular bone density was retained with large head MoM THA, compared to 28 mm MoP THA at one year postoperatively.

Knee implants

A number of investigations have been carried out over the years to determine potential titanium release into blood, serum and urine in patients with total knee arthroplasties (TKA), but data on Ti ion levels after knee arthroplasty are sparse.
In knee replacement patients, failed titanium patellas were shown to lead to particularly large increase in serum titanium. Serum levels of the titanium cases with MoM contact were over 10 times higher than those in cases without MoM contact [141]. Savarino at el. [142] ascertained significant Ti serum elevation in a patient group with painful TKA compared to healthy subjects. Lons and co-workers [143], who monitored blood titanium levels in patients, up to one-year post knee implantation, reported significant blood elevation of Ti levels one year after implantation exceeding the normal values.
Several authors have reported an analytical methodology for the determination of trace Ti at the μg L^{-1} level in bodily fluids, in order to monitor metallic knee implant function in humans [93,127,144].

The elevated total concentrations of titanium in the bodily fluids of patients following ion release from MoM orthopedic implants are presented in Table 3.

Table 3 *In vivo* times and Ti total concentration in bodily fluids of patients following ion release from MoM orthopedic implants

Implant type	Time *in vivo*	No. patients	Bodily fluid analyzed	Metal ion(s) measured	Concentration (μg L^{-1})		Median (μg L^{-1})	Analytical technique	Most important observations	Refs.
					MoM	Control				
Hip/THA	2 y	8	Synovial fluid	Ti	109 (13-194)			GF-AAS	Pseudo capsules loosening implant occurs	[67]
Knee/TKA	5 y	4	Whole blood Urine	Ti	319.6 10.1	9.3 5.2		GF-AAS	Loosening of a titanium component	[93]
Hip/THR	24-38 y	3	Whole blood Urine	Ti V Ti V	1.47 (1.4-1.5) ng g^{-1} 0.71 (0.62-0.8) ng g^{-1} 0.79 (0.55-0.89) ng g^{-1} 1.67 (1.0-1.22) ng g^{-1}			(HR) ICP-MS	Loosening of a titanium component. Changes in blood Ti level (compared with control group): 165% (MoM radio logically loosening)	[122]
Hip/THA	3 m	34	Whole blood Erythrocytes	Ti Ti	3.74 (1.40-8.80) 0.80	0.57 (0.10-1.50)		(HR) ICP-MS	No difference in Ti ion levels in small or large-head MoM bearings	[123]
Hip/THA	6-12 m	29	Whole blood	Ti	2.77 (0.90-5.60)			(HR) ICP-MS	No pathologic metal ion threshold level has been determined	[124]
Hip/THA	2 y	144	Whole blood	Ti	3.34		3.10 (0.60-7.11)	(HR) ICP-MS	Titanium levels significantly increasing in the six-month to twelve-month follow-up period	[125]
Hip/ CrCo alloy	2 y	7	Blood	Ti Ni Mo	0.316-1.770 0.451-0.957			(HR) ICP-MS	Possible observed metal toxicity pathologies	[126]

					0.280-0.790					
Hip/Knee/ Ti-6Al-4V Co-Cr-Mo alloys	13-108 m	11	Whole blood	Ti Ni Mo	0.590-2.306 0.505-1.12 0.407-1.426	0.300-0.890 0.300-0.770 0.300-1.500		(HR) ICP-MS	Blood Ti concentration in patients with failed stems	[127]
Hip/Ti stem and cup	n/a	15	Blood	Ti	2.1-3.5	0.5		(DF) ICP-MS	Significant differences have been found for Ti, both in blood and in urine samples	[128]
Hip/ Ti-6Al-4V alloy	4 y	4	Serum	Ti	5.50	0.80		ICP-MS/MS	The method permits the accurate monitoring of 5 different Ti isotopes at the μg L^{-1} level	[130]
Hip	12-24 m	101	Whole blood	Ti	0.27 (0.47-6,30)			(HR) ICP-SFMS	Change in blood Ti level between pairs of reference and reserve samples: 130%	[131]
Hip/THR		16 169 66	Whole blood Serum Hip fluid	Ti Ti Ti	15.3 10.5 58.4		2.3 (0.8-184) 2.4 (0.4-795) 5.1 (0.8-1275)	ICP-OES	Serum is recommended for monitoring Ti in patients	[132]
Hip/THR	26-60 m	21	Serum	Ti Al V	8.08 (2.11-17.2) 2.16 1.30 (<0.81-1.60)			GF-AAS	The implants were either subject to loosening or accelerated wear due to abrasion	[134]
Hip/THR	30-66 m	42	Serum	Ti	3.66 (2.91-11.60)		2.91	GF-AAS	Metal hyper-sensitivity-induced osteolysis	[135]

Hip/THA	106-136 m	16	Serum	Ti	3.43 (2.91-7.28)		2.91	GF-AAS	Metal hyper-sensitivity-induced osteolysis	[136]
Hip/THA	2 y	32	Serum Erythrocyte	Ti Ti	0.85 (0.72-1.09) 0.90 (0.70-1.70)	0.20 0.25		(HR) ICP-MS	Serum Ti increase with well-functioning implants	[137]
Hip/THR,HR	6.6-9.3 y		Whole blood	Ti	2.43 (0.90-5.10)		2.30	(HR) ICP-MS	Osteolysis in 37.4% of THR patients and in 2.4% of HR patients	[138]
Hip/THA	1-2 y	23	Serum	Ti			2.70 (2.11-3.25)	(HR) ICP-MS	Titanium levels have not been implicated in adverse tissue reactions	[139]
Hip/THA	1 y	14	Serum	Ti			5.74 (3.35-13.4)	ICP-MS	Titanium levels increased from pre to postoperatively in prosthetic groups	[140]
Knee/TKA		6	Serum	Ti	280 (70-425)			(Q) ICP-MS	Patellar component failure	[141]
Knee/TKR	8-108 m	35	Serum	Ti	3.05 (2.91-6.43)			GF-AAS	No significant differences in serum Ti level between all of the group (patients with implants and controls)	[142]
Knee/TKR	1 y	16	Whole Blood	Ti	4.08 (1.95-6.51)	2.94		ICP-MS	No correlation between Ti ions release and clinical scores or metallic volume were noticed	[143]
Knee/metallic implants			Urine	Ti Mo	650 100			HR-CS GF- AAS	The method permits the simultaneous determination of Ti and Mo	[144]

Analytical techniques: (HR) ICP-MS, high-resolution inductively coupled plasma mass spectrometry; (DF) ICP-MS, double focusing inductively coupled plasma mass spectrometry; ICP-MS/MS, inductively coupled plasma-mass spectrometry/mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometry; GF-AAS, graphite furnace atomic absorption spectrometry; (Q) ICP-MS, quadrupole inductively coupled plasma-mass spectrometry; HR-CS GF-AAS, high-resolution continuum source graphite furnace atomic absorption spectrometry; Results are reported as "mean/median, (range)"; m - month; y - year

4.3. Chemical metal speciation

It has been well established that all metallic and alloy implants corrode to some extent *in vivo* and release of trace metals (Al, Co, Cr, Fe, Mn, Mo, Ni, Ti, V, Zn) as well as other trace metal ions into the surrounding tissue and bodily fluids. Although total content analysis of trace metals is important, their speciation analyses are just as necessary. The problem of the trace metal analysis of biological fluids is complicated by the fact that the toxicity of a particular metal depends on, not only, its concentration in the human body but also its speciation and intake mode. Therefore, identifying the chemical states of released metals from metal and metal alloy implants in human tissues and fluids is essential. Trace metal species exist in different oxidation states when in the form of free ions and metal nanoparticles, or as inorganic and metallo-organic compounds, each of which may exert different toxic or carcinogenic effects. There is insufficient interest, however, in identifying the chemical valency state and in measuring the trace metal incorporated into the matrix of human body tissues and fluids released from metallic joint implants. Metal ions of different valencies are released from Co-Cr alloys and their effects vary with the type of oxide compound they form. Co(II) and Cr(III) ions predominate under physiological conditions because these ions are the most stable at neutral pH. However, no stable Co oxide exists and thus formation of soluble Co ions instead of solid Co oxides is favored. On the other hand, Cr(III) oxides are stable under physiological conditions. For example, chromium from metallic implant may be incorporated into organometallic complexes as Cr(III)) or Cr(VI)) [145,146]. Information about the speciation of trace metals released from metallic joint implants is scarce; however, some procedures for speciation have been reported.

Merritt and Brown [147] discovered that hexavalent chromium Cr(VI)) is the principal chromium ion that is released *in vivo* during wear and corrosion of stainless steel and Co–Cr alloy implants in the red blood cells (RBCs) of patients undergoing total joint revisions (hip implants). Thus, corrosion of implants can lead to the release of biologically active hexavalent chromium into the body, which is rapidly reduced to trivalent chromium Cr(III)) in the RBCs. It was also concluded that the ratio of serum to RBC levels of Cr could be used to measure the proportion of the Cr ion that is in the hexavalent form. Although, the authors provided no details, nor any citation to any details, regarding the methods of serum and RBC sample preparation or analysis. Afolaranmi et al. [148] provided information on the distribution of Cr(VI) in the blood fractions. Chromium Cr(VI) is predominantly partitioned into RBCs compared with plasma; the data have been cross-validated using radioactively labeled ^{51}Cr ($Na_2{}^{51}CrO_4$).

Ektessabi et al. [149] measured the distribution and chemical states of the trace metal elements (Cr, Fe, Ni) incorporated into a matrix of human tissues around a failed total hip replacement prosthesis that had been inserted in a patient's body for more than 5 years. The implant was made of stainless steel (SUS316L) and titanium alloy (Ti-6Al-4V). The analysis showed that chromium and iron from the stainless steel that was diffused in the tissues had undergone chemical changes.

A study on the possible association of the released trace metals (Cr, Co) to human serum proteins from patients carrying MoM (based on Co-Cr alloys) total hip prosthesis have been conducted [128]. This work relates to patient samples where concentration in the blood of Cr and Co was low (≤ 3 μg L^{-1}) for a hip implant patient. Analysis of the association of Cr with serum proteins was not possible in the patient samples due to the low concentrations present, but Cr spiking showed it was associated with transferrin (Tf). Walter et al. [150] found that normally functioning MoM Birmingham Hip Resurfacing (BHR) hips indicated that only very minor amounts of Cr and Co were associated with RBCs, with most being associated with serum/plasma. Their work indirectly supported the concept that Cr found in these patients is in the trivalent Cr(III) chemical form.

Loeschner et al. [151] developed a measurement procedure for the characterization of hip patient samples as it gave information on the binding of released trace metals (Cr, Co) to important serum transport proteins, such as albumin (Alb) and Tf, and also provided information on particle size and elemental composition of wear metal particles present in the hip fluid. Finley et al. [152] determined the valency state of chromium in the blood of individuals with Cr-containing metal hip implants. The study deals with the chromium fractionation in blood samples (serum and red blood cells fractionation). The analysis showed that Cr released from hip implants is preferentially distributed in serum and not RBC, indicating that the form of Cr present in blood of hip implant patients was in the form of non-toxic Cr (III) and do not appear to pose any adverse health risk to the patient.

One of the most recent studies deals with the differentiate between Cr(III) and Cr(VI) and determination of the chromium species (Cr(III) and Cr(VI)) released from metal implants into blood and joint. The results show that the majority of chromium is present in the trivalent form and bound to proteins [153].

Goode et al. [154] using spectromicroscopy of *ex vivo* peri-implant tissue surrounding failed Co-Cr MoM hip replacements detected corroded nano-scale debris (mean diameter of particles, 30 nm) in periprosthetic tissue in two

chemical states, with concomitant mitochondrial damage. The majority of debris contained Cr(III), with trace amounts of oxidized cobalt. A minority phase containing a core of metallic chromium (oxide, hydroxide, and phosphate) was also observed.

The toxicity of an element is closely related to the chemical state of the element that has been incorporated in the tissues surrounding the implant. Although the oxidation state of released Cr *in vivo* is still controversial whether Cr is released as Cr(VI) in patients with MoM implants, with some reports supporting this idea [147,148] and others disapproving (150,152-154). Analysis of the speciation of chromium is fraught with difficulty due to the instability of Cr (VI), which tends to reduce to Cr(III) very rapidly. It is nonetheless a general consensus, however, that Cr(III) is elevated in the biological fluids of all patients with MoM-type implants (39,155).

Very little is known about titanium toxicity regarding the identity of the species (TiO_2 nanoparticles or Ti(IV) ions) and their concentrations from metallic orthopedic implants. Nuevo-Ordóñez et al. [156] developed and conducted *ex vivo* a quantitative Ti speciation method to address the concentration of Ti bound to different human serum biomolecules. It has been observed that Ti is uniquely bound (99.8%) to human serum Tf. Their studies corroborate their initial findings that Ti is uniquely associated to serum Tf in human serum at physiological levels in implanted individuals [157].

Conventional X-ray absorption near edge structure (XANES) has been used to identify different metallic species within tissues, surrounding MoM hips, exposed to THR systems [158]. It was recognized that particles released from MoM implants were generally in the sub-micron to nano-size range and contained mostly Cr with little Co, in a metallic form as well as a Co(II) structure, to no Co. In all MoM hips they found mainly Cr(III) phosphate. There was no evidence of Cr(VI) in the tissues. In areas of high Cr abundance there was cobalt in metallic state, Co(II), and Mo(VI) in the tissue. These metal ions may have arisen from corrosion, wear, or a combination of the two. These results are similar to those described in the study by Morrell at el. [159]. As a result, in the context of THRs, they demonstrated much greater variation in Cr chemistry within *ex vivo* tissues compared with previous report on similar metallic form [157] included Cr(III) complexes: phosphate ($CrPO_4$), hydroxide ($Cr(OH)_3$), oxide (Cr_2O_3), metallic-CoCr particles and organic complexes, which correlated with Co and Mo distribution.

In view of drawbacks related to the sample preparation step, the direct analysis of solids (tissues) has been proposed as an alternative for metal determination in bodily fluids [154,158]. However, their application in routine analysis is hampered in view of problems related to the lack of sample homogeneity and the calibration step, since in many cases it is necessary to use Certified Reference Materials (CRMs) due to matrix effects, which may impair the analysis due to lack of CRMs of tissues or with a similar matrix.

4.4. *In vivo* corrosion of metallic orthopedic implants

Corrosion is the deterioration of a metal due to electrochemical oxidation-reduction reactions with its complex *in situ* environment of the body fluids [160-162]. All metallic implants corrode [163] and no metal or metal alloy is completely inert *in vivo* [164]. The biologic effect of corrosion is a public health concern for the community of patients who have an orthopedic prosthesis, since these prostheses remain inside the body over long periods of time. Corrosion of metallic implants presents two main risks: release of trace metal ions and micro- and nano-particles into surrounding tissues, which may cause adverse tissue responses at the site of the implant and deterioration of the mechanical properties of implants which may contribute to fracture. For metal devices, local changes in tissues surrounding an implant are the most commonly reported issues. Significant increase of concentrations of heavy metal ions could alter the local tissue environment leading to up-regulation of inflammatory mediators.

The lack of available data to correlate *in vitro* and *in vivo* corrosion and metal ion release represents one of the main challenges in understanding the biological responses to metal implants and for future product design considerations. *In vivo/ex vivo* corrosion clinical studies, while limited, have been reported; however, existing corrosion testing methods, *in vitro* performance, do not adequately simulate *in vivo* conditions where cells, proteins, mechanical loading, and other factors can impact ion release. General corrosion/metal ion release is the uniform release of metal ions over an exposed surface. For metals with surface oxides, it has been shown that the amount of metal ions released from the implant is dependent on the composition and structure of its passive oxide layer [81]. In a static environment of the body, this layer provides great resistance. However in a dynamic state, as is the case *in vivo*, wear leads to destruction of this passive layer resulting in an increase of corrosion. Typically, the release of metal ions is the greatest immediately after implantation and the release rate reduces over time. However, in cases where the implant's oxide layer is not protective, release of metal ions may continue for longer durations and exhibit dramatic increases in release rate after implantation. The *in vitro* test methods are typically conducted under idealized and/or hyperphysiological conditions, which enables comparisons between devices that does not reproduce the *in vivo* physiological environment. Therefore, in this section,

papers reported clinical studies that have characterized *in vivo* corrosion of orthopedic implants from the point of view of release of trace metal ions and micro- and nanoparticles into tissue and bodily fluid will be presented.

For local exposure, studies have shown blood and serum levels of 0.58 to 190 μg L^{-1} of chromium and 0.38 to 228 μg L^{-1} of cobalt [165]. For hips, there is a correlation between metal ion levels and prosthetic size and positioning. The mean values for Co and Cr were 9.8 μg L^{-1} and 9.7 μg L^{-1}, respectively [90]. Other clinical studies have shown on increasing trend in metal (Co, Cr) ion levels, before and after surgery, in blood over time [117,166].

Local corrosion by-products from MoM modular hip have also been investigated. The results suggest that the bulk of corrosion products found are due to chromium ions precipitating out of synovial fluid, with more soluble cobalt ions free to spread further. Analysis of local tissue has shown a wide variation in the amount of metal and that there can be greater than 500 ng g^{-1} of cobalt, titanium, and iron present with lesser amounts of chromium and nickel [167]. The same work also illustrated that the metal content was highest in the capsule and the bursa. Other analysis showed much higher maxima of metals in the local periprosthetic tissue [71]. More recent investigation [123] has reported metal ions in the blood of patients with MoM THA, when compared with healthy individuals. Apart from wear of bearing surfaces, passive corrosion of exposed metallic surfaces is a factor which influences metal ion concentrations.

Corrosion at the modular neck-body junction in dual-tapered stems with a modular Co-Cr alloy femoral neck leads to release of metal ions resulting in local soft tissue destruction. Serum metal levels demonstrated greater elevation of cobalt (mean, 6.0 μg L^{-1}) than chromium (mean, 0.6 μg L^{-1}) or titanium (mean, 3.4 μg L^{-1}). All hips showed large soft tissue masses and surrounding tissue damage with visible corrosion at the modular neck-body junction [168]. Systemic arthroprostetic cobaltism, a recently described syndrome that results from wear or corrosion by Co-Cr hip implants has been reported. Significantly high blood cobalt concentrations were observed in patients with Cr-Co implants (mean 324 μg L^{-1}) but not in blood chromium (mean 57 μg L^{-1}) [169].

4.5. Cobalt toxicity related to metallic orthopedic implants

Toxic effects in response to metallic orthopedic implants are frequently described, in the literature, to cobalt and are referred to as cobaltism [170]. They reviewed at least 18 published case reports where cobalt metal ion toxicity has been attributed to the use of Co-Cr alloys in hip arthroplasty. Of these cases, the great majority reported more pronounced toxicity at serum Co levels exceeding 100 μg L^{-1}. From these reports, it seems evident that CoCr nanoparticles and metal cobalt ions released from MoM THA implants have toxic effects *in vivo* and may pose a health risk to patients [171-174]. Van Der Straeten et al. [175] collected questionnaires, validated to detect cobaltism in occupationally exposed individuals, in a MoM hip implant population. They found a significant correlation between increasing Co levels and the prevalence of several toxicity symptoms, and concluded that patients with repeated high blood or serum Co concentrations exceeding 20 μg L^{-1} are at risk for systemic toxicity, as an indication for revision surgery to alternative bearing surfaces. Devlin et al. [176] reviewed 10 cases of suspected prosthetic hip-associated cobalt toxicity and reported that these patients had findings consistent with cobalt toxicity. In another study performed by De Smet et al. [40] serum levels have been used to estimate the MoM HAs wear at the bearing surfaces over time, based on the positive correlation that exists between the wear measurements and the serum Co ion level measurements. Patients with metallosis had significantly higher serum cobalt-ion concentrations (>19 μg L^{-1}) and significantly greater amounts of femoral component wear.

Metal ions can be generated not only at the junction between the femoral head and socket, but also at the junction of the head and stem of the femoral component [177]. Use of large-head MoM bearing surfaces in THA has created new and unique modes of failure for this type of articulation; that of the wear at the trunnion of the prosthesis. The excessive Co debris has been linked to "trunnionosis" [178,179], i.e. the phenomenon whereby wear particles are produced due to corrosion at the head-neck junction (trunnion) in modular hip replacements [180].

The majority of patients with well-functioning MoM hip implants have cobalt blood concentrations ranging between 0.2 and 10 μg L^{-1} [40,181]. Different organizations attempted to define threshold values for the identification of patients with adverse local tissue reactions that require clinical follow-up or intervention. According to the European multidisciplinary consensus statement on the use and monitoring of MoM bearings, while Co values < 2 μg L^{-1} are probably devoid of clinical concern, the range of 2-7 μg L^{-1} represents the threshold value for clinical concerns in unilateral MoM hip replacements [49]. The Mayo Clinic stated that Co serum levels above 10 μg L^{-1} indicate significant implant wear, whereas values between 4 and 10 μg L^{-1} reflect good condition of the MoM implant device [182]. The Medicines and Healthcare products Regulatory Agency identified the value of blood Co level as the threshold of 7 μg L^{-1} for toxicity related to prosthesized patients [183].

5. Clinical response to metallic orthopedic implants

The clinical response to metal implants is complicated and no simple explanation for the wide variety of reported local adverse responses is available. A patient's overall response to a metal implant consists of responses both at the implant location as well as systemically. Specific local tissue responses depend on the device or biomaterial and peri-implant tissue type as well as patient-related characteristics. The entire spectrum of local findings related to metal implants is incorporated into the term "adverse local tissue reactions" (ALTRs) to metal debris into the bodily fluids [184]. The term ALTRs refers specifically to local periprosthetic tissue changes and is one of the main causes of total joint arthroplasty (TJA) or total joint replacement (TJR) failures. Metal wear debris from implants, in the form of trace metal ions and micro- and nanoparticles, has various effects. The nano- and micron-sized particles generated by wear may further release metal ions when exposed to bodily fluids. Metal debris may damage cells and may activate specific immune and inflammatory pathways, sometimes leading to patient sensitization. Metallic wear particles are taken up by macrophages, which can lead to inflammatory [185] and tissue-destructive reactions of various degrees. The cellular uptake of particles by macrophages can also lead to additional metal ion release, causing a positive feedback loop. More frequent ALTRs include local responses such as pain, skin rash, tissue destruction including bone loss (osteolysis) [186], escape of fluid from the joint, and solid and cystic masses called pseudotumors [187]. Quantitative analysis of the metal in the human biological specimens particularly played an important role in identifying the source of metal debris. The increase in the blood levels of metal ions, the description of delayed metal allergy/hypersensitivity reactions [188], as well as the demonstration of pseudotumors has become almost obsession topics; locally, metal particles and ions are toxic [189]. Based on follow-up studies, a threshold value for clinical concern is expected to be within the range of 2-7 $\mu g\ L^{-1}$; however, exact levels have still to be determined within this range [49]. Some have advised that a blood ion level $>7\ \mu g\ L^{-1}$ indicates potential for ALTRs [190]. Although, metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) is the most sensitive and specific tool for evaluating ALTR in MoM hip implants [191,192].

5.1. Metal allergy

Metal allergy has been an identified problem in orthopedics for nearly half a century [193]. Metal allergy is much more common in patients who undergo joint replacement than in the general population of those without a metallic implants. This percentage is even higher in patients with a poorly functioning, painful MoM articulation [194]. However, metal allergy, as a potential cause for painful, to orthopedic implants is a rare phenomenon.

Metal allergy may develop following internal exposure to metal-releasing implants and it is especially linked to chromium, cobalt and nickel allergy. In a study of 22 patients undergoing primary total joint replacement who had no known prior metal allergies, 32% developed a positive leukocyte migration inhibition test to titanium, cobalt, chromium, or nickel ion solutions 3 months - 1 year after surgery. One patient developed a severe reaction [195]. In a retrospective series of 165 patients who had undergone primary cementless total hip replacement with a contemporary MoM hip design, patch tests for metal allergy were performed on 9 subjects with an osteolytic lesion localized to the greater trochanter and on 9 randomly selected controls without osteolytic change. The patients with early osteolysis had a significantly higher rate of patch test positivity for cobalt (8 of 9 patients) than controls (2 of 9 patients) [196]. Further support for the concept that MoM joint can cause allergy comes from a series of 200 patients who received MoM hip replacements, in which there were 5 cases of joint loosening with prosthetic failure; of these, 3 were metal-allergic on patch testing [197]. Krecisz et al. [198] assessed contact allergy to metals in 14 patients suffering from poor implant tolerance. In some of them, recurrent skin eruptions generalized or nearby implants, have occurred and in 3 patients skin fistula was observed. These complain appeared one year after surgery. The patients underwent patch tests with allergens, including Ni, Cr, Co, Pd, Cu, and Al. Of the 14 patients, 8 persons were sensitized to at least one metal, mostly nickel (7/14) and chromium (6/14). Of the 8 sensitized patients, 3 were reoperated. A more recent study, evaluation of the allergenic properties of the metal knee or hip joint implants 24 months post surgery and assessment of the relation between allergy to metals and metallic implants failure, supported the notion that chromium and cobalt in particular may result in metal allergy following implantation, as the prevalence of chromium allergy increased after TKA or THA from 5% to 8% and the prevalence of cobalt allergy increased from 10% to 17% [199]. MoM implants for hand joint replacement have also been associated with metal (Co, Ni) allergy [200].

Several authors have assessed the association between metal allergy and revision surgery of total joint replacements [201-202]. Milavec-Puretić et al. [201] have found a higher rate of metal allergy in patients undergoing revision surgery for failed hip prosthesis, at 9 of 40 (23%). Nine patients were positive for Co, Cr, and Ni, metal rust or endoprosthesis scrapings, or combinations of these allergens. Other authors have found that orthopedic patients (TKA, THA) with numerous allergies of any type are at increased risk of revision [202, 203].

Recent studies, however, have shown that true metal allergy based on patch testing, has little to do with the failure of orthopedic implants in general [204-210]. Granchi et al. [211] noted that there was insufficient data to determine that a positive patch test represented a true metal allergy in patients who have had a total joint replacement, and was unable to discriminate between stable and failed arthroplasty.

5.2. Metal hypersensitivity

The *in vivo* effects of metal hypersensitivity has been a topic of interest in orthopedics with the focus to characterize the failure effects seen in some patients with orthopedic implants, especially in total joint arthroplasties (hip, knee, shoulder). Numerous review papers can be found in which the general aspects, unpredictable and poorly understood phenomenon of hypersensitivity reactions from orthopedic metallic implants are discussed in detail [212-219].

Specific types of implants with a greater propensity to release metal *in vivo* may be more prone to induce metal sensitivity. Total joint arthroplasty procedures are increasing, as such, the number of complications, including aseptic loosening, pain of unknown etiology and possible metal hypersensitivity, are also expected to increase. Support for the theory of joint implant loosening caused by hypersensitivity reactions to metallic implant components was first presented in the mid-1970s [220,221]. Studies were undertaken in response to clinical evidence of hypersensitivity reactions in patients after hip arthroplasty with MoM implants.

In recent decades, attention in the literature review has been drawn to metal hypersensitivity as another possible cause of TJA failure [222]. In a 2012 review of all available literature, Cousen and Gawkrodger [193] established that first-generation MoM implants could cause sensitization of patients to the implant metals. They also reported an association between metal sensitization and implant failure but did not establish a causal relationship [286]. Hallab et al. [223] revealed that the prevalence of metal (Co, Cr, Ni) allergy was ~25% among patients with a well-functioning hip arthroplasties and 60% among patients with a failed or poorly functioning implants. In fact, the prevalence of metal hypersensitivity in the latter group was nearly 4-fold greater than in the general population [216]. This phenomenon may be caused by the fact that the hypersensitivity reaction is elicited by continuous contact with metal ions; therefore, a loosening prosthesis could release more ions than an intact implant, thus inducing an allergic reaction [224]. In a prospective study, the incidence of sensitization to metals in orthopedic implants increased by 6.5% following hip and knee arthroplasty [225]. One study examined rates of metal sensitization in patients who had undergone total knee arthroplasty (TKA) and found a sensitization rate of 20% in the control group with no implant, 48.1% in the group with the stable implant, and 59.6% in the group with an unstable implant group [226]. Mihalko et al. [227] performed an analysis of available prospective and retrospective studies regarding hypersensitivity reactions after total joint arthroplasty. The available evidence indicates a correlation between metallic orthopedic implants, the development of metal hypersensitivity, and implant loosening. Another study by Bravo et al. [228] showed that in 161 Total Knee Replacements (TKRs) with preoperative positive patch tests, subjects had no increase in complication, reoperations, or revisions compared with matched controls with a negative patch test.

While much is known about the dermal response to metal allergens, determining metal hypersensitivity prior to the implant procedure or implant failure due to metal hypersensitivity has proven to be a challenge in clinical settings. Evidence is not conclusive as to whether metal joint implants increase metal sensitivity or whether pre-existing metal hypersensitivity leads to prosthesis failure [229].

One of the major difficulties in understanding the clinical implications of hypersensitivity to the implant components is the lack of universally accepted testing methods. With respect to standard laboratory examinations, testing for delayed-type hypersensitivity has been conducted *in vivo* by skin testing, that is, so-called patch testing and *in vitro* by lymphocyte transformation testing (LTT) and leukocyte migration inhibition testing (termed LIF or MIF testing). None of the tests have been universally accepted and applied. Currently, there is no consensus about the optimal testing for the detection of metal sensitivity. Patch testing is still the most widely used method for determining potential metal hypersensitivity reactions, both before and after implantation, however, there are no standardized commercial panels specific for total joint replacements available currently [230]. However, Schalock et al. [231-233] recommended a protocol for patch testing using a baseline series and an adjunctive metal series based on implant type [216].

Over the long term, patch testing alone (as well as any single assay: PT and LTT) may be an inadequate detector of delayed-type hypersensitivity. Yang et al. [234] in a review of the clinical relevance of the LTT provided a retrospective review of 27 well-fixed aseptic TKRs revised due to persistent pain and suspected metal allergy. They noted that "*LTT results alone were insufficient for the diagnosis of TKA failure due to an immune reaction. A positive LTT may not indicate that an immune reaction is the cause of pain and stiffness post-TKA*". Both PT and LTT have been suggested as screening tools for potential metal hypersensitivity in total joint arthroplasty [218]. The authors summarized the use of these two

tests by stating "*The ability of these tests to diagnose disease and predict outcomes has not yet been demonstrated*". While other tests to achieve an improvement in clinical practice, a PT confirmed by LTT could be introduced as standard procedure [235]. This would allow the identification of subjects who are likely to develop implant-related hypersensitive reactions. At the same time, it would avoid the development of allergies from joint implantation, and reveal any reactions due to implant compounds.

5.3. Pseudotumors

Pseudotumors were frequently reported metal-related local adverse reaction, referred to as ALTRs, after the introduction of MoM implants and increased modularity. The release of metal particles and ions around the prosthesis can result in tissue changes such as solid and cystic masses, termed pseudotumors [190]. It should be stressed, that the term pseudotumor is not related, in any way, to a cancerous tumor.

The term "pseudotumor", in reference to MoM orthopedic implants, was first used by Pandit et al. [187] who described it as neither infective nor neoplastic soft tissue masses present in patients with hip resurfacing. They estimated that 1% of patients with different types of resurfacing develop a pseudotumor, in 20 cases, within 5 years, while a study by Hart et al. [236] report similar pseudotumor frequency in Magnetic Resonance Imaging (MRI) screening of asymptomatic patients and found that roughly 60% of patients with MoM implants develop a pseudotumor. As suggested by the evidence of asymptomatic pseudotumors in patients with well-functioning prostheses (MoM THA and MoM HRA) [236,237], the true incidence of these tissue changes could be higher than estimated by incidental findings. Pseudotumors have been reported in as many as 32% of asymptomatic MoM hips and 25% of MoM resurfacing hips [237] and 68.6% developed pseudotumor with 60.9% of the asymptomatic group developing pseudotumor [238]. Further confusing this issue is the documentation of regression and spontaneous remission of pseudotumors with time. In five revised patients, pseudotumors completely disappeared in four patients. Although, pseudotumors have been reported in 32% of asymptomatic MoM hips. All revision 15 patients had a reduction of chromium (40.42 μg L^{-1} to 2.69 μg L^{-1}) and cobalt ions (54.19 μg L^{-1} to 0.64 μg L^{-1}) [239]. Pseudotumors around implants have also been reported with modular total knee replacement [240,241]. Pseudotumors causing severe symptoms have been found to be locally destructive, requiring revision surgery in a high proportion of patients; 13 of the 20 hips have required revision to a conventional hip replacement. It was estimated that approximately 1% of patients who have a MoM resurfacing develop a pseudotumor within five years [185].

Pseudotumors in patients with MoM implants is a manifestation of the biological response to excessive metal wear debris generated at the MoM articulation, as higher wear is positively correlated with the elevation of metal ion concentrations *in vivo* [242]. However, lymphocyte reactivity to Co, Cr, and Ni did not significantly differ in MoM hip resurfacing cases with pseudotumors compared to those without pseudotumors, further suggesting that type IV hypersensitivity can be hardly considered the dominant immune response driving development of pseudotumors [243]. However, the prevalence of pseudotumor formation was positively correlated with higher serum Co (5.6; 9.2 μg L^{-1}) and Cr (7.2; 12.0 μg L^{-1}) ion concentrations [243,244]. Moreover, the serum Co and Cr ion levels after MoM hip resurfacing arthroplasty were significantly elevated in the pseudotumor group in comparison to both the non-pseudotumor group and control group. Patients with a pseudotumor had up to a 6-fold elevation of median serum levels of Co and up to a 7-fold elevation of median serum levels of Cr ions in comparison to patients without pseudotumors [245].

Pseudotumors are a common complication of MoM arthroplasties, and elevated metal ion levels in patient blood/serum likewise are a common finding after such procedures. Moreover, elevated metal ion levels have been associated with increased wear [86,90]. Measurement of blood metal ion levels, specifically cobalt and chromium levels, are useful in diagnosis and treating ALTR. An association between cobalt and/or chromium concentrations, ranges from 2.5-10.0 μg L^{-1} in different cohorts and the development of pseudotumors has been suggested [246-251]. Although, the evidence that patients with pseudotumors have significantly greater metal ion levels, ranges from 2.2-11.0 μg L^{-1} in different cohorts, is not strong and remains controversial [252-258]. Moreover, the results do not, however, demonstrate whether Co and Cr have a causal role in the generation of pseudotumors.

6. *Ex vivo* human body specimen evaluation

6.1. Sample collection and preparation of specimens

One of the major technical challenges of human biological specimen metal ion testing is the risk for contamination from needles, collection tubes and containers and thus rigorous protocols and controls are advocated for every step of the process [259,260].

External contamination must be prevented by the appropriate choice of sampling biofluids. It is preferable to use a non-metal needle but a metal needle can also be used, provided the first 5 mL of i.e. blood are discarded in order to eliminate the metal ions from the needle [261]. The use of specific trace element tubes for metal analysis, with a certificate indicating that they are "metals free", is mandatory. Thus, rigorous tube validation protocols for venous-derived serum, plasma and whole blood specimens should be performed when selecting blood collection tubes (BCTs) [262].

Changes in the trace element concentrations of blood during storage are usually due to the effects of time and temperature on the stability of elements [263]. In this way, the following trace metal stability, specifically proposed for human whole blood were chosen: storage temperature of -20 ^{o}C and 4 ^{o}C are equivalent to -70 ^{o}C for stability of metals in human whole blood for at least 36 months when blood is stored in sealed polypropylene vials. Blood samples stored in polypropylene cryovials lose volume over time and develop clots at higher temperature conditions (e.g. 23 ^{o}C and 37 ^{o}C), making them unacceptable for metal testing after 2 months. However, the Monoject Royal Blue Stoper Tube is the only US Food and Drug Administration (FDA) approved evacuated blood tube suitable for Co and Cr analysis.

Whole blood collection is a routine clinical process which is largely standardized, although some variations in collection protocols can occur. For blood/plasma collected by venipuncture, differing anticoagulants, including heparin and EDTA, are used in order to prevent blood clotting. However, venipuncture can be painful, poses risks of needle sticks even to the trained clinicians, and requires a trip to a clinical site. Importantly, the total amount of blood (>5 mL) drawn per patient in a study also poses ethical concerns. As clinical study protocols are becoming more complex, a solution is needed to reduce patient burden without sacrificing the quantity or quality of the clinical data. Minimally invasive and patient microsampling procedures, intend to facilitate patient recruitment, improve retention, and support implementation of simplified trial design and conduct. Microsampling (microliter- and nanoliter-sized samples) technologies can also lower trial budget by improving enrollment efficiency and retention rate [264,265]. However, there is still need to develop microsampling technique that can reliably determine metals at the low levels at which they are present in controls (below μg L^{-1} level) and patients with metallic prosthesis [144]. This work explores the direct, simultaneous determination of Mo and Ti in urine, after its deposition (500 μL) onto clinical filter paper by means of solid-sampling high-resolution continuum source graphite furnace atomic absorption spectrometry (HR-CS-GFAAS) giving rise to a dried urine spot (DUS). The method could be relevant in the context of monitoring the functioning of metallic implants in humans.

Despite the current importance the use of dry sampling methods, such as the collection of dried matrix spots (DMS) [262], dried blood spots (DBS) [263], dried urine spots (DUS) [144], and, more recently, volumetric absorptive microsampling (VAMS) [266] as a biological specimen microsampling techniques sounds interesting in this field. Although, the implementation of VAMS devices introduces contamination problems for Al, Cr, and Ni, VAMS followed by ICP-MS analysis shows potential for future real-life routine applications when assessing levels of Co, Cr, Ti, and/or V. This type of sample is still underutilized when aiming at obtaining clinical elemental information. It is, however, that this situation is changing, and that the arrival of new microsampling devices and methodological approaches make it easier to obtain reliable information on clinical, in orthopedic area, metal contents.

6.2. Detection techniques

A more recent development in the clinical measurement of trace/ultratrace metals relates to the orthopedic area and the increasing use of metals and their alloys containing Co, Cr, Mo and Ti as the components of MoM joint metal implant replacements, as a result of complications with the use of such implants and the potential for failure requiring revision surgery. Analysis of ultratrace metals in bodily fluids and tissues serves several purposes, including determination of the concentration and distribution of trace metals in disease conditions, detection and allocation of potential toxic metals, and diagnosis of trace metal related diseases [112].

The main analytical problem is determining these ultratrace metals (Co, Cr, Mo, Nb, Ni, V, Ti and other metals) in bodily fluids and tissues as they are present at extremely low (sub-μg/ng L^{-1}) concentrations in a very complicated matrices. Atomic absorption and plasma-based analytical techniques have been used in the context of total metal detection in human biological specimens for a number of years. The four most commonly used techniques are flame atomic absorption spectrometry (FAAS), electrothermal atomic absorption spectrometry (ET-AAS), also known as graphite furnace atomic absorption spectrometry (GF-AAS), inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS) [267].

GF-AAS is the technique of choice for determination of trace and ultratrace metals in the μg/ng L^{-1} concentration range and has been used successfully for such analyses [23,82]. Its main analytical advantage is low detection limits (<0.01 - 10 μg L^{-1}), which are about 10 to 100 times lower than the ICP-OES, and extremely tolerance to complex matrices. Owing

to its power of detection, GF-AAS is becoming imported for speciation work. Although, conventionally, GF-AAS has been a single element technique, the appearance of commercial multi-element, ET-AAS capable of analyzing simultaneously several elements may offer new possibilities [268-271]. Furthermore, a system with a continuum light source has been developed, eliminating the need for a number of different lamps, and allowing better background correction [272]. These techniques [268-272] are an attractive alternative to other commonly used techniques, GF-AAS or ICP-MS, due to low detection limit and short measuring time. Recent developments in the availability of commercial continuum radiation source AAS, high-resolution continuum source graphite furnace atomic absorption spectrometry (HR-CS-GFAAS) instrumentation provide an interesting opportunity to see whether this capability will find an application in routine clinical laboratories [273]. HR-CS-GFAAS provides some possibilities for simultaneous multi-element analysis. This aspect was explored for true simultaneous determination of Mo and Ti in the urine of patients with metallic prostheses, after its deposition onto clinical filter papers, giving rise to a dried urine spot (DUS) [144]. Finally, the mature technique such as ET/GF-AAS will continue to be used in situation where it provides adequate results, and where the technique is a "fit-for-purpose".

Atomic absorption spectrometry (GF/ET-AAS) is still the dominant analytical technique used for ultratrace metal analysis in clinical laboratories. Although GF/ET-AAS allows direct sample analysis, most of the works reported in the literature perform specimen's analysis after the digestion of the sample. However, more and more clinical laboratories are transitioning away from graphite furnace AAS techniques toward those based on ICP-MS, which is a form of inorganic MS measuring metal ions rather than molecular ions [274].

ICP-MS is the method of choice for potentially toxic trace and ultratrace metal determination, in clinical specimens analysis, due to its extremely low limits of detection for most elements (<0.001-10 μg L^{-1}), which are about 1 - 3 orders of magnitude lower than GF/ET-AAS, very high multi-element coverage, outstanding accuracy, an extremely wide linear dynamic range of up to 12 orders of magnitude in the same run and also provides isotopic information, making high accuracy calibration *via* isotope dilution mass spectrometry available [275]. ICP-MS has become increasingly applied to clinical samples [276]. It can be used for specialist applications such as speciation analysis, where it is used as chromatographic detector for high-performance liquid chromatography (HPLC), capillary electrophoresis (CE) or gel electrophoresis (GE) separation [277].

Human soft tissue, surrounding metal implants, analyses for ultratrace metals are a promising area for development, but specimen collection is highly invasive. In this respect, the application of non-invasive techniques based on laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS), a well-established tool for trace and ultratrace elemental analysis has been shown to be particularly valuable in clinical studies, since *ex vivo* measurements are feasible [278,279]. LA-ICP-MS method allow to *ex vivo* quantitatively analyze the soft biological tissue in bulk and/or thin sections and present the results in the form of the two-dimensional (2D) maps of content and bio-imaging metal ion distributions in the specimen samples [280,281]. The only work that discusses application of laser ablation sector-field inductively coupled plasma mass spectrometry (LA-SF-ICP-MS) for *in situ* determination and spatial elemental profiling of nickel concentrations in tissues that have been exposed to nickel wire is the research paper by Ghazi et al. [282]. This study examines the diffusion of nickel with time and the spatial distribution of nickel around nickel-containing implants *in situ*. The concentration of nickel reached values as high as 60 μg g^{-1} near the implants, falling exponentially to undetectable levels 3-4 mm from the implants. This study demonstrates that LA-ICP-MS is excellent technique for macro- or micro-analyses of surrounding soft tissues, during implant degradation, in human body, both for quantification and imaging.

6.3. Quality control

Trace element analysis in complex matrices such as human clinical specimens is used to evaluate toxicity due to internal exposure to metal ions and metallic nanoparticles in patients with surgical devices, especially orthopedic prostheses. The measurement of trace and ultratrace metal concentrations for each matrix/metal combination presents its own set of methodological issues. Before sample analysis could begin, clinical laboratory medicine for trace element analysis have to develop or apply a validation of an analytical procedure that will reliably and reproducibly measure ultratrace level of metal in bodily fluids and tissues [283].

For method validation measurements and characterization of the analytical data, clinical reference materials: certified reference materials (CRMs), standard reference materials (SRMs) or reference materials (RMs) with certified or information values for numerous metals are available, which provide a list of human biological specimens [82,274,284]. Reference material is a general term that describes materials that can be used for purposes of calibration, method validation, and for quality control (QC), *etc*; the CRMs analysis demonstrates the trueness of the analytical method and also the traceability of the analytical measurements. Therefore, the purpose of the validation is not to achieve optimum

performance of the analytical method, but to demonstrate the determined values of the parameters in order to confirm that the evaluated analytical method is appropriate for the intended purpose which is the determination of the metals in the analyzed human biological specimens using the given procedure and the analytical technique.

"*Although use of CRMs, SRMs or RMs is recommended to verify accuracy, they are usually treated (e.g., lyophilized) for long-term conservation, and therefore may behave differently from real patients samples. Reference materials are always "idealized" matrices and as such relatively easy to handle. Thus, the analyst should be cautious in interpreting CRM/SRM/RM results and reporting of clinical studies*" [82]. In addition, the reference materials that exist are either: (1) not certified; (2) provide values at elevated concentrations; or (3) provide only a certified value for a single element of interest; e.g. Co in NIST 2670a Toxic metals in urine.

Determination of trace metal species in clinical samples is gradually becoming more widely accepted for toxicological purposes. There are several important aspects of the concept of speciation that are relevant to human health, such as identification of those specific forms of a chemical elements that exhibit more serious toxic effects. Since a trace metal, at very low level, can be present in biological human specimens as more than one species, including different oxidation states, it might be important to use well characterized multi-element certified reference materials. In the case of speciation analysis in clinical, human biological specimens, the main problem with determination of trueness is a lack of CRMs with certified values of analyzed metal species. Unfortunately, such specimens (blood, serum, urine) reference materials with certified concentrations of Co, Cr, and Ni at the required, very low concentration levels are not commercially available. Therefore, there is still an urgent need for clinical certified human biological specimen that contain endogenously bound trace metals certified at clinically relevant concentrations, in order to validate analytical speciation methods.

6.3.1. Analytical quality specifications

Analytical quality specifications represent a major issue and play a key role in assuring and continuously improving high-quality analytical/clinical laboratory services. The development of accuracy and sensitive analytical methods for the determination of ultratrace metals in human bodily fluids and tissues has been the subject of many studies over the years, not only in terms of trace analysis, but also in terms of clinical specimen sample collection, sample conservation, and sample preparation. Progress in this area seems to be significant, although medical orthopedics diagnoses are most often late in time. The apparent paradox between very effective medical diagnostics and relatively "good" chemical analysis is that specimen samples are analyzed after a long time from sampling. Therefore, the clinicians were questioning whether their long term monitoring would be effective as there was no indication the analytical methods used were stable enough over the follow-up period, e.g. every 3, 6, or 12 months.

Before clinical sample analysis could begin, clinical laboratory has to develop an analytical method that could accurately quantify trace metals in specimens. Analysis of clinical specimens by plasma based spectroscopy allows determining the content and distribution of trace metals in the bodily fluid and tissue sample. In order to obtain reliable results, the developed procedure should be based not only on the properly prepared sample and performed calibration. It is also necessary to carry out all phases of the procedure in accordance with the principles of chemical metrology whose main pillars are the use of validated analytical methods, establishing the traceability of the measurement results and the estimation of the uncertainty. The analytical procedure is characterized by the parameters that are assessed in the validation process: working range, linearity, limit of detection and quantification, trueness, and precision. The above parameters are determined on the basis of a series of measurements of CRMs, standards, and blank samples with a specified number of repetitions and time intervals [285].

Recent years have seen significant improvements in our perception of the importance of patients' safety and the need to reduce analytical errors. As they are part of the overall healthcare system, clinical laboratories are prone to analytical errors [286,287]. Further recent data underline the importance of analytical accuracy. The National Institute of Standards and Technology (NIST) report on "*The impact of calibration error in medical decision making*" demonstrates that calibration error, leading to analytical bias, is a key parameter affecting the number of patients passing decision thresholds in practice guidelines [288]. In laboratory practice, many strategies are used to reduce errors, including internal quality control procedures, external quality assurance programs, certification of education programs, licensing of laboratory professionals, accreditation of laboratories, and regulation of laboratory services. While the number of studies available on laboratory errors is small, it is clear that in the last four decades there has been a significant decrease in error rates, particularly in the case of analytical errors [287].

6.3.2. Reliability of metal ion testing

Trace metal analysis is commonly used to evaluate toxicity due to internal exposure to metal ions in patients with orthopedic prostheses, such as MoM bearings. These ions may serve as indicators of the *in vivo/ex vivo* performance of MoM bearing surfaces. Although the toxicological significance of ALTR elevations in ultratrace metal ions has not been definitively established, diagnostic testing of whole blood or serum metal ion levels has become an important part of assessing the risks of MoM hip implants in patients with metallic implants and monitoring the performance of MoM bearings, both in hip resurfacing arthroplasty and total hip replacement [177].

There is limited information available regarding how well measurements of ultratrace metal ions in clinical specimen samples agree within and between two (1,2) laboratories found the average concentrations of Co and Cr in whole blood, collected in 46 patients with MoM hip arthroplasty, in the first (1) laboratory was significantly higher than in a second (2) laboratory [389]. There was a clinically significant absolute difference between the two (1) and (2) laboratories, above the predetermined threshold, 35% of Cr samples and 38% of Co samples. Even though variations are not major, authors found that they are significant enough in more than 1/3 of the cases to risk misinterpretation in borderline cases. Therefore, decision to revise a MoM hip arthroplasty should not rely on a simple metal ion measurement and should include patient symptoms and radiographic evidences of implant dysfunction. The findings in this study [290] and in another [291] underscore that small differences in laboratories' protocols may lead to significant differences in test results. In an effort to determine the accuracy of testing, Saini et al. [390] performed an audit comparing the results of a new laboratory (B) tasked with testing clinical specimens with those of a recognized laboratory (A). Whole blood and serum samples from patients who had undergone MoM resurfacing of total hip arthroplasty were tested for cobalt and chromium concentrations at both laboratory (A) and laboratory (B). Laboratory (A) performed Co and Cr testing on whole blood and laboratory (B) performed cobalt testing on whole blood and Cr testing on serum. Samples from 104 patients were tested. Laboratory (B) reported lower whole blood cobalt levels than laboratory (A). Furthermore, laboratory (A) reported that all patients had elevated whole blood cobalt ion levels compared to the normal reference values for the laboratory, whereas laboratory (B) reported that 46 patients (44.2%) had whole blood cobalt ion levels within the normal reference range for the laboratory. This comparative study highlights the importance of using a single laboratory for metal ion testing, as values generated from different laboratories may not be directly comparable. The authors emphasized that, whenever possible, patient test samples should be tested in the same laboratory or metal ion measurements should be repeated to avoid the risk of misinterpreting inter-laboratory variations [87].

The ability of a laboratory to reliably repeat a sample value (e.g. within-laboratory value agreement) has been evaluated in a few studies. Barry et al. [129] assessed the reliability of Co, Cr, and Ti measurements using HR-ICP-MS by testing sets of paired samples from 78 patients undergoing total hip MoM arthroplasty. They found the mean concentrations from the first tube were significantly higher than the mean concentrations of the second tube. They were unable to identify why there were significantly different measurements of metal ions obtained from two blood samples that were collected from the same patient at the same time and treated the same way. However, many of the samples were at or close to the limits of detection where the method may have a high imprecision. Therefore, it is important to ensure that serial tests are performed by the same laboratory group to minimize variability in the test results.

In contrast to these studies, bodily fluid samples (whole blood, serum), ICP-MS and related methods themselves have been shown to be reproducible within individual laboratories. For example, Pei et al. [291] and Choi et al. [292] have demonstrated high reproducibility and repeatability (Co, Cr) with their octopule reaction system inductively coupled plasma mass spectrometry (ORS-ICP-MS) methods, with their imprecision below 6% CV (in the range of 6% to 15% coefficient of variation (CV)) in developing their analytical methodologies.

Internal quality control and external quality assurance are important prerequisites for measuring trace elements and making appropriate diagnosis or treatment decisions. A good example of this is the routine annual follow-up of patients with MoM joint replacements, where clinicians need to make sure that their decisions are based on well controlled analytical measurements. How, for instance, can a clinician decide if an increase in concentration of Co and/or Cr results from a change in the particular joint and does not arise from a change in the analytical laboratories measurement performance? Harrington [293] looked at data from the UK National External Quality Assessment Scheme for trace elements (TEQAS). This supplies whole blood specimens which are spiked with known amounts of a number of trace elements including Co and Cr. The mean recovery over the samples measured in the 2011-2012 scheme year was 96.4% (SD 2.23, CV 2.3%) for Co and 96.1% (SD 3.19, CV 3.3%) for Cr. The excellent agreement between the amounts in the specimens and the mean value indicates the results are accurate, and agreement between the pools distributed on different occasions shows they are reproducible over time. This should provide the necessary confidence to the clinical decision maker that the laboratories providing the Co and Cr results are competent and the results are suitable accurate.

Including information on the reliability of results in the analytical and/or clinical laboratories report may lead to a more careful evaluation of their effective value for diagnosing and monitoring diseases. Clinical laboratory professionals must consider the need to communicate analytical laboratory data and information more effectively to clinicians with a view in particular to assuring better clinical outcomes for patients.

6.4. Clinical value of specimen metal ion measurement

Clinical specimen samples serve as a final example to illustrate the diversity of applications in which multi-elemental analyses at ultratrace levels play a key role. To evaluate potential negative health effects from metals released from implants, accurate determination of many metals at sub-μg L^{-1} or even sub-ng L^{-1} levels in bodily fluid specimens is necessary. Considering general tendencies in the trace metal analysis of bodily fluids, two general analytical methodological approaches should be noted to the development of procedures for the quantitative ultratrace metal analysis of bodily fluids [294]. First, this is the development of adequate conditions for performing the analysis by commonly used highly sensitive techniques with special sample preparation. Second, this is the development of specialized methods of analysis, which minimize matrix influences and make it possible to perform direct analysis without sample digestion with only sample dilution of specimens. The direct analysis of bodily fluids without sample digestion is more attractive; it excludes contamination, minimizes losses, and shortens the time of analysis. Among the procedures based on the principles of GF/ET-AAS with the Zeeman Effect background correction (BC) and procedures based on HR-ICP-MS are the most widely used methods, and they make it possible to determine a wide range of metals; primarily, toxic ones: Co, Cr, Ni with detection limits at a level of background concentrations. Metal ion measurements must be performed under the rules of internal/external quality control (GF/ET-AAS and ICP-MS are considered as valid). The procedures developed based on these techniques should be recommended for laboratory diagnostic and screening studies.

Trace metal ions generated from joint replacements are a cause for concern. Evaluation of metal ion concentrations is often used as a surrogate of the status of the metal implant. However, no consensus has emerged regarding what kind of specimen sample is most appropriate; serum, plasma, and whole blood measurements are used in clinical practice. The blood levels of metal ions represent a balance between ion production from the implant and renal excretion, and these levels can be affected by changes in activity levels as well as renal function. Although, blood analysis that includes cells (whole blood or erythrocytes) tends to be more difficult due to complexity of the matrix components.

The use of blood metal level as surrogate markers of *in vivo* metal (Co, Cr) release from implants is a well-established method, as an indicator for wear to increase surveillance for at risk MoM joint implant patients, and is now recommended as a screening tool for the *ex vivo* performance of MoM joint implants replacement [40,86,87,94,154,245,289,295]. While there is a consensus that the measurement of blood levels may be useful, there is no consensus on the interpretation of blood metal levels has likely contributed toward the variable nature of MoM patient management and revision surgery decisions [92,296,297].

Local metal debris is also associated with increased serum metal ion levels. These levels may become grossly elevated with progressive implant loosening. Therefore, it has been suggested that serum metal levels are also surrogate markers of metal release from implants [106,141,298-300]. While there is a consensus that the measurement of serum levels may be useful, there is poor correlation between serum metal ions and development of ALTR and outcome following revision surgery [99,109,301-304]. Measurements of paired samples drawn at the same time but processed as different sample matrices suggest that serum, plasma, and whole blood concentrations cannot be used interchangeably for testing chromium and cobalt ions. Concentrations of chromium and cobalt are significantly different between blood and serum [305], and between whole blood, serum, and plasma [306,307]. Lohmann et al. [72] found that metal (Co, Cr, Ni) ion content of periprosthetic tissue but not serum would be predictive of the type of tissue response to metal wear debris. There may be superiority of serum over whole blood measurements, but whether these metal levels can be correlated is not fully understood. Unfortunately there is growing evidence that metal ion measurements alone are not sufficient method to detect failing or failed implants [49].

Synovial fluid metal ion concentrations may also be informative when whole blood or serum ion concentrations are not conclusive. However, since synovial fluid requires an ultrasound-guided needle biopsy and since most physicians performing such biopsies are not aware of the potential to contaminate the specimen sample, whole blood or serum is the preferred specimens for evaluation.

6.5. Consensus statement of the metal ion levels in metal-on-metal implants

It has long been understood that metal concentrations above base level are often measured in the human biological specimens of patients with MoM implants. Metals may be generated *in situ* as a result of the degradation of an implanted

prosthesis. The generation of metal products might lead to severe ALTRs. Although, it is accepted that grossly elevated metal ion levels raise concern for ALTR, controversy exists in determining the optimal cut-off levels. The interpretation of metal ion concentrations and their role in clinical management of patients with MoM implants is still controversial. Therefore, metal ion measurements and knowledge of their interpretation have thus become important. Many studies have attempted to correlate concentrations of metals in specimens with a biological response.

Metal ion measurements, prevalently cobalt and chromium, in blood or serum allow the early detection of increased wear before extensive tissue destruction has occurred with a better outcome of revisions. Unfortunately, there is growing evidence that grossly elevated metal ion measurements alone are not sufficient method to detect failing or failed implants [304], and controversy exists in determining the optimal cut-off levels.

Government agencies worldwide and international orthopedic implant registries have published recommendations on the surveillance and work-up of patients with MoM hip implants.

The United Kingdom's Medicines and Healthcare Regulatory Agency (Medicines and Healthcare Regulatory Agency 2012 (MHRA)) issued a safety "Medical Device Alert" for all types of unilateral MoM hip implant system regarding significant local tissue reactions and elevated revision rates of cobalt and chromium. The recommendation is to consider early revision if blood Co or Cr ion levels are >7 μg L^{-1}, suggest potential for soft tissue reaction, to worn clinicians of poorly functioning implants, and rising on repeating test at three months after first blood metal ion level test, and/or if imaging study reveals soft tissue adverse reactions, fluid collections or tissue mass, although it is unclear what this figure is based on or how it was derived [308]. It is worth noting that the 7 μg L^{-1} threshold is a means of understanding how well the hip is performing *in vivo*, and revision is only considered if imaging is abnormal and/or blood metal ion levels raise [295]. If imaging is done, then the preferred modalities are either ultrasound or metal artifact reduction sequence (MARS) magnetic resonance imaging. Whereas there are already action limits for these metals (Co, Cr) relating to occupational exposure, the concentration of 7 μg L^{-1} was chosen after consultation with orthopedic clinicians, not by medical toxicologists, and using information from the National Joint Registry for England and Wales [309], as a level at which the joint was not showing optimum performance. It was not set as an indication of toxicity but rather as an indicator of joint performance and is thus interpreted with this in mind.

The European Commission's Scientific Committee on Emerging Newly Identified Health Risks (European Commision Scientific Committee on Emerging Newly Identified Health Risks 2014) [49] and European Federation of National Associations of Orthopaedics and Traumatology (EFORT) [310] recommends the regular use of metal ion measurement; the threshold value for clinical concern is expected to be within the range of 2-7 μg L^{-1} were of clinical concern for potential implant failure. The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) decided to adopt the strategy as outlined in the European Consensus Statement [49], which includes recommendations on technical issues determination of critical threshold ranges (e.g. for Co a range of 2 to 7 μg L^{-1} Co whole blood) and systematic follow-up for all patients and all implants due to the risks of MoM bearings. The American Association of Hip and Knee Surgeons, the American Academy of Orthopedic Surgeons, and The Hip Society recommended lower cut-offs (< 3-5 μg L^{-1}) for more accurate risk stratification. Health Canada (Health Canada 2012) [311] and the Australian Orthopedic Association (AOA), National Joint Registry (NJR) [312] recommended a revision in patients with imaging abnormalities, especially if progressing, and rising blood metal ions. The United States' Food and Drug Administration (FDA), on the other hand, does not recommend routine measurement of metal ion levels in the blood. Although, noting that rising blood metal levels may indicate potential for soft tissue reaction. However, the FDA is recommending that asymptomatic patients with MoM hip implants continue to follow-up with their orthopedic surgeon every 1 to 2 years to monitor for early signs of change in hip status [313]. In addition, the FDA recommends the testing of metal ion levels in symptomatic patients with MoM hip implants [176]; it seems that this guideline is not universally used at the site of other joint implants. The recommended work-up of symptomatic patients by each of these organizations includes blood metal ion assessment. As noted by others, ion level cut-offs are arbitrary and not supported by scientific data [197,314].

In 2014, the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, and the US Hip Society published a consensus statement that outlined criteria for stratifying MoM hip patients into groups with low, medium, and high risk of failure [315]. The algorithm proposed a 10 μg L^{-1} Co (blood or serum) threshold for identification of patients with a high risk of failure. However, that recommendation acknowledged that metal ion levels were confounded by having more than one cobalt and chromium implant, and that lack of evidence was a limitation for assessment of the risk of metal ion levels in bilateral patients.

Interpretation of blood metal ions in patients with bilateral MoM hip replacements is challenging and scarce. Several authors' have provided surveillance algorithms for MoM implants [92,97,99,106,109,316-322].

Griffin et al. [92] assessed whether cobalt and chromium concentrations can predict soft tissue damage in a cohort of patients who underwent revision surgery. Whole blood cobalt and chromium concentrations were measured preoperatively and the presence of metallosis and/or soft tissue damage was noted during revision surgery. Using the MHRA cut-off of 7 μg L^{-1}, whole blood chromium predicted soft tissue damage with a sensitivity of 29% and a specificity of 75%, whereas whole blood cobalt had a sensitivity of 65% and a specificity of 56%. Based on these results, the authors concluded that metal ion concentrations are not reliable predictors of soft tissue damage, and therefore should not be used in isolation as a trigger for surgical intervention. Limitations of this study should be noted. Cobalt and chromium concentrations were measured by several different laboratories, so the results may have been affected by laboratory specific biases. Macnair et al. [199] also used a threshold of 7 μg L^{-1} and could show that the cobalt as well as the chromium levels in a significant proportion of their patients with MRI-documented ARMD was below this cut-off. The utility of cobalt and chromium concentrations in predicting soft tissue damage were only assessed independently of one another. Curiously, the mean whole blood cobalt concentration of the 23 patients without metallosis was 17.4 μg L^{-1}.

Van Der Straeten el al. [97] proposed safe upper limits (SUL) of Cr and Co ion levels of 7.4 μg L^{-1} and 5.0 μg L^{-1}, respectively for bilateral hips, and 4.6 μg L^{-1} and 4.0 μg L^{-1}, respectively, for unilaterally resurfaced hips (MoM HRAs). The authors concluded that these levels were lower than the 7 μg L^{-1} level proposed by MHRA but indicated that their study had a very low tolerance for what was considered a poorly functioning hip [96]. Serum Co and Cr concentrations from patients with a MoM HRA can be subdivided into 4 categories. Concentrations <4 μg L^{-1} are normal steady-state values. In the absence of clinical and radiographic symptoms, a routine follow-up regimen should be followed. Concentrations between 4 and 10 μg L^{-1} are moderately increased, and additional investigations, including cross-sectional imaging, are advocated. If no abnormalities are found and the patient is asymptomatic, a close clinical follow-up and re-measurement of metal ion concentrations are advisable. Concentrations between 10 and 20 μg L^{-1} are a definite sign of increased wear. Thorough diagnostic investigations including cross-sectional imaging are advocated and must be repeated even when no abnormalities are found. Metal ion measurements should be repeated even when no abnormalities are found. Concentrations >20 μg L^{-1} are concerning, because they are a sign of high wear, even in the absence of clinical and radiographic symptoms around the hip, and warrant additional investigations. The correct interpretation of metal ion concentrations implies the exclusion of other sources of metal ions. Revision must be considered even in the absence of clinical problems.

Macnair et al. [97] measured serum cobalt and chromium concentrations in patients with hip resurfacing or total hip replacements, and performed MARS MRI to detect soft tissue reactions. Using the MHRA cut-off of 7 μg L^{-1}, serum chromium detected soft tissue reactions with a sensitivity of 56% and a specificity of 83%, whereas serum cobalt had a sensitivity of 56% and a specificity of 76%. The authors concluded that cobalt and chromium concentrations are not sufficient as a screening tool for the detection of soft tissue reactions, and advocated for MARS MRI imaging in all patients. Metal ion assays should be taken in conjunction with clinical imaging, symptoms, and examination findings and not considered in isolation. Since this study assessed the concentration of cobalt and chromium in serum, it is likely that the MHRA cut-off of 7 μg L^{-1} is intended for whole blood specimens, regarding that the MHRA cut-off of 7 μg L^{-1} is intended for whole blood specimens. This is particularly the case for chromium, whose concentrations are significantly higher in serum compared to whole blood [303].

Carlson et al. [106] assessed the utility of metal (Co, Cr) ion levels in patients with articular surface replacement total hip arthroplasty (ASR THA). Seventy-one percent of patients who were revised and had multiple serum ion measurements demonstrated increasing cobalt ion levels or elevated ion levels over time. There was a trend toward an elevated risk of revision for increasing cobalt and chromium levels starting at 12 and 4 μg L^{-1}, respectively; this was significant for chromium levels above 7 μg L^{-1}. Similarly, there was a trend toward an elevated risk of pseudotumor formation for increasing cobalt and chromium levels starting at 5 and 2.5 μg L^{-1}, respectively; this was significant for cobalt levels above 7 μg L^{-1}. It was concluded that cobalt and chromium levels above 5 and 2.5 μg L^{-1} started to demonstrate an increased risk of ARMD, and should be considered as a lower cut-off for discussion with patients about the potential for future revision. Although, the authors provided no details, nor any citation to any details, regarding the methods of serum sample preparation or analytical procedure of cobalt and chromium analysis; how measurements are gathered, analyzed and reported, thus makes comparisons between studies difficult?

Malek et al. [109] recommended the use of a 3.5 μg L^{-1} cut-off (albeit at the sacrifice of a specificity of 27% and a sensitivity of 87%) in their study which compared metal ion level ARMD identified on MARS MRI. They also measured plasma cobalt and chromium concentrations in a cohort of symptomatic patients with unilateral MoM hip prostheses, and performed MARS MRI to identify ARMD. Plasma cobalt and chromium a cut-off of 7 μg L^{-1} identified ARMD with a sensitivity of 57% and a specificity of 65%. A lowered threshold of >3.5 μg L^{-1} for Co and Cr ion levels improved the sensitivity of 86%, but at the expense of specificity (27%). Once again, the authors emphasized that metal ion

concentrations should not be used as the only screening test for ARMD, but should be considered in combination with symptoms and imaging results.

Hart et al. [316] initially defined a cobalt and chromium cut-off level of >7 μg L^{-1} which was subsequently adopted by the MHRA, Health Canada, and the Hip Society algorithm for MoM arthroplasty surveillance [303,305]. However, there is concern that a cut-off of 7 μg L^{-1} results in a high specificity but low sensitivity. In a separate study, Hart et al. [155] determined a specificity of 89% and a sensitivity of 52% when the cut-off level was set at 7 μg L^{-1}. Although, this threshold is not based on soft tissue damage; levels of greater than 7 μg L^{-1} are associated with significant soft tissue reactions and failed MoM hips. The authors subsequently recommended to lower the cut-off levels for the maximum cobalt or chromium level associated with unexplained failures of MoM hips to be 4.97 μg L^{-1} (84.5 nmol L^{-1} cobalt or 95.5 nmol L^{-1} chromium), with a resulting specificity of 86% and sensitivity of 63% to predict failure, including, presumably, from ALTR, although this was not specifically studied. Unfortunately, absolute level of serum ion concentration which might indicate a patient at risk of adverse reaction is unclear. Of note, from analytical point of view, the significant figures in the optimal cut-off level 4.97 μg L^{-1} should be corrected to 5.0 μg L^{-1}.

A recent informational statement published on the American Academy of Orthopedic Surgeons' web site (AAOS) agreed with this suggested cut-off level of ~5 μg L^{-1} [317]. Sidaginamale et al. [318] found similar threshold in their analysis of implant retrievals. They observed that patients with abnormal wear patterns had metal ion levels above 4.5 μg L^{-1} when compared with those with normal wear patterns. The authors reported a high sensitivity (94%) and specificity (95%) of 4.5 μg L^{-1} as a potential threshold to indicate abnormal wear patterns which theoretically may lead to adverse reactions. The authors coveted, however, that these results apply only to hip resurfacings.

As illustrated in Bolognesi and Ledford [319] the cut-off level of 7 μg L^{-1} for Co and Cr has been generally recommended to guide treatment, mostly due to a large burden of false-positive results. However, many recommend that asymptomatic patients can be followed with annual exams that do not necessarily involve metal ion evaluation. Symptomatic patients should have metal ion levels evaluated and have either ultrasound or special MRI techniques for use around metal implants such as MARS MRI scans performed, taking into account that elevated metal ion levels do not necessarily correlate with development of ARMD [256].

In view of the large number of surgical revisions occasioned by failed MoM arthroplasties, Lainiala et al. [320] investigated whether the procedure led to reduction of blood Co and Cr concentrations and an improvement in joint functionality. One hundred and ninety eight patients were tested 2 and 12 months after revision surgery, and thereafter at 2 year intervals. Blood Co concentrations fell to below 7 μg L^{-1} in all subjects but Cr concentrations remained high in 4% of those who had a unilateral hip replacement and 12% of those with unilateral hip resurfacing. Joint functionality improved in most, but not all, patients. Those who had bilateral replacements, where one number MoM prosthesis was still *in situ*, continued to have increased blood metal ion concentrations. It was concluded that the initial failure does not compromise implant in-growth after revision surgery.

Chang et al. [321] reported that at a threshold of 5 μg L^{-1}, no association was identified between abnormal plasma metal (Co, Cr) ion levels and patients (eighty asymptomatic and seventy-six symptomatic patients) symptoms, prosthetic femoral head size, or acetabular cup inclination for MoM THA. In addition, the authors stated that abnormal plasma cobalt ions, above 5 μg L^{-1}, were associated with larger sizes of pseudotumors when present, but were not predictive of patient symptoms.

Hussey et al. [322] compared unilateral patients and bilateral patients with either an Articular Surface Replacement (ASR) hip resurfacing (HR) or an ASR XL total hip replacement (THR) and investigated whether cobalt or chromium was associated with a broad spectrum of patient outcomes. Regarding assessment of blood metal ion levels in female patients with MoM hip replacement, chromium ion levels >7 μg L^{-1} appear to be associated with reduced functional outcomes in both unilateral and bilateral patients. These associations were not observed in men.

Taunton [323] performed a prospective study of aseptic hip arthroplasty revisions with ALTR matched with revisions without ALTR. Author obtained metal levels in whole blood and synovial fluid of 29 hip arthroplasties with ALTR and 29 without ALTR before aseptic revision THA. In their study, whole blood Co levels in the ALTR hips were almost 50 times higher in the ALTR group, Cr 10 times; the threshold for ALTR was 36.5 μg L^{-1}, a sensitivity of 80%, and a specificity of 77%. In addition, when their separated out the different hip arthroplasty constructs in hips with ALTR, they found large variations in whole blood metal ions level: cobalt 2.5 μg L^{-1} for HRA, 29 μg L^{-1} for MoM THA, and 11.7 μg L^{-1} for dual-modular femoral necks in THA. The HRAs was considered "low risk" in the consensus statement. The study outlined the limitations of decision-making on whole blood metal ion levels alone. These limitations of whole blood cobalt levels outline where synovial fluid metal ion levels can be helpful. The study found that cobalt levels were

over 150 times higher in the synovial fluid of ALTR hips; the chromium levels were over 300 times higher. The synovial fluid cobalt had the highest correlation with ALTR compared to the other tests, with a threshold of 19.75 μg L^{-1} - a lower value than in whole blood, with a superior sensitivity of 92% and a specificity of 89%. Their studies reveal high risk of the synovial fluid cobalt is greater than 19 μg L^{-1} in a MoM hip, or in THA with metal junctions.

Both metal reactivity and metal sensitivity can cause periprosthetic bone resorption and can be associated with septic or aseptic loosening. Levels of metal ion in serum or whole blood greater than 10 μg L^{-1} can be an indication of increasing wear damage that could prelude an increased risk of adverse tissue reactions [40].

However, the overall utility of metal ion levels is controversial in itself, with one systematic review and meta-analysis concluding they are not useful tests for determining ARMD in asymptomatic patients [296]. While increased cobalt and chromium in isolation may not reliable in detecting ARMD, it is a useful adjunct in the evaluation of a patient with a MoM arthroplasty, and analytical methods may allow blood or serum metal levels to be used as a realistic biomarker of *in vivo* wear rate of MoM hips, in addition to the absence of clear criteria for relevant serum metal ion levels. Of note, blood, serum, and plasma metal ion levels are similar but are not interchangeable [109,150,297,300].

7. Overview

In the early-1990s, we have remarked on the interest and concern relating to metal-on-metal orthopedic implants and biomaterials, the possible localized adverse tissue reaction effects of excessive generation of metallic wear particles and trace metal ions release from such implants and how measuring concentrations of metals in human biological specimen samples, such as whole blood, serum, urine, synovial fluid and tissue may be used to investigate these issues. Much of the work has involved MoM arthroplasty systems where the incidence of failure of the implant increased among patients with newer designs of prostheses.

Despite the clinical success of prostheses joint replacements, this overview has summarized some of the work addressing the still present concern regarding the potential toxicity of metallic wear micro/nanoparticles and ultratrace metal ions produced at the articulation site of a MoM orthopedic implant and clinical response to metallic orthopedic implants. The potential dangers to patient health risks from metal alloy metallic wear nanoparticles generation and the release of *in vivo* trace metal ions into human biological specimen's circulation have been recognized [65].

From this overview, it seems evident that CoCr-based micro- and nanoparticles and ultratrace metal ions of different valences released from MoM implants have toxic effect *in situ* and may pose a health risk to patients, regardless of whether their implant is well-functioning or failing. It is still unclear if the toxicity of CoCr nanoparticles is due to the nanoparticles themselves or mediated by trace metal ions in bodily fluids. This toxicity helps explain the higher prevalence of adverse reactions to metal debris when compared to polyethylene or ceramic particles. The long-term effects of the exposure to these particles and metal ions remain a concern. To fully understand the implications of an exposure, the local chemistry of the metals directly involved in the biological interactions must be known. Adverse health effects caused by accumulated metal (ions and nanoparticles) in the periprosthetic soft tissues include metallosis, pseudotumors, metal hypersensitivity, metal allergy, and pain.

The physical and chemical form of the metal released from a metallic implant can have a significant impact on the toxicity of the compound. Consequently, it is important to take this factor into account when assessing the risk posed by patient exposure to trace metals released from metallic implants. Metals can be released from a device in particulate form or as metal ions, each of which may exert different toxic effects. When the different valence forms of a metal exhibit different toxic effects or potencies, it is important from a risk assessment perspective to understand which valence of the compound is being released from the device. At present, our knowledge about the risk of metallic micro- and nanoparticles is incomplete [324]. However, it is known that toxicity of nanoparticles depends on their size, shape, crystal structure, surface morphology, surface area, concentration and solubility (the possibility of dissolution into ionic forms). The presence of soluble trace metals at the nanoparticle surface are particularly efficient at generating reactive oxygen species (ROS), which generally accounts for the increased toxicity of soluble metal compounds when compared to metallic or insoluble metal nanoparticles [24]. Of particular importance is the need to understand the relationship between the physico-chemical and structural properties of nanoparticles and their cellular reactivity and interaction within soft tissue. Therefore, it is necessary to use several complementary analytical techniques to fully characterize the nanoparticles.

The clinical response to metal implants is complicated and no simple explanation for the wide variety of reported adverse responses is available. Recent issues with MoM orthopedic implants highlighted concerns about the potential safety of certain types of metal implants. A broad spectrum of clinical responses has been reported and often more than

one response can arise in the same patient. The entire spectrum of local findings related to metal implants is incorporated into the term ALTRs. More frequent ALTRs include local responses such as pain, skin rash, tissue destruction including osteolysis, escape of fluid from the joint, and solid and cystic masses called pseudotumors.

Diagnostic testing, such as soft tissue advanced *in vivo* imaging technologies and metal ion testing, may provide important clinical information for assessing the risk of MoM joint prosthesis of the hip and knee metal implants in patients. While the results of these diagnostic tests can be indicative of adverse tissue reactions, they cannot be relied upon as the only sign that a joint prosthesis of the hip or knee implant is failing.

Good diagnostic or screening tools to evaluate the full spectrum of a patient's responses to his or her metal implant are currently lacking, in part due to the failure of currently available testing methods, such as skin patch or metal ion levels, to definitively identify the patients at high risk for implant failure. It is unclear which biomarkers can reliably predict a potential toxicity response to the implants. There are a few diagnostic tests that evaluate the response but there is no clear consensus of how these tests should be used in the clinical setting. The best developed tests we have available include standard tests that measure metal ion blood levels (Co is recommended) or skin patch tests for metal allergies, correlates poorly with adverse responses. In some cases, patients with adverse diagnostic findings present no symptoms. For this reason, management of patients with metal implants is divided into proactive monitoring for asymptomatic patients and more aggressive diagnostic and therapeutic approaches for patients with clinical symptoms. A persistent rise in trace metal ion concentrations, irrespective of symptoms, should be investigated further with appropriate imaging.

There has been considerable recent interest in evaluating the soft tissue surrounding implant *in situ* using specialized imaging modalities techniques like ultrasound (US) and MARS MRI in a non-invasive manner. MARS MRI scans or US scans should carry more weight in decision-making than isolated blood metal levels alone noting that rising blood metal levels may indicate potential for soft tissue reaction. Conventional MRI sequences have not produced adequate images around metal implants; however, specialized MARS reduce the artifacts generated by metal in the adjacent tissue. In symptomatic patients or those who are asymptomatic but have raised blood metal ion concentrations, advanced *in vivo* imaging techniques (e.g. US, computed tomography scan and/or MARS MRI), and conventional radiographs should be considered to determine the presence of local adverse soft tissue reactions (e.g. bodily fluid accumulation of metallic products and pseudotumors). Unfortunately, serum biomarkers do not yet have the sensitivity or specificity to predict when a patient is developing an ALTR. At this time, MRI can tell us which patients are developing ALTR and can provide guidance as to when it may be appropriate to intervene [325].

With regards to monitoring patients for metal related toxicity, the prospects are even more distant. At this juncture there is no established toxicity threshold for the degradation products of metal alloy implants. Identifying the trace metal ions released from the implant and nanoparticles *in vivo* may help to predict potential toxicity from orthopedic metal implants, although this is inherently difficult. However, it is generally accepted that low ion concentrations (Co <2 μg L^{-1}) are rarely associated with significant local tissue damage and that significantly elevated ion concentrations (Co >7 μg L^{-1}) may indicate a problem with the articulation arthroplasties; additional imaging, e.g. ultrasound, CT-scan, and/or MARS-MRI, is recommended. At present, little has been done to standardize the methodology, the way patients are monitored and there is not enough evidence to support the routine need for checking metal ion levels in the blood or soft tissue imaging if patients with MoM joint implants have none of the signs or symptoms descibed above and the orthopedic surgeon feels the orthopedics joint metal implants is functioning properly. In the absence of toxicity threshold, monitoring serum or blood metal content would not be useful clinically. Standard operating procedures could be introduced to ensure that when studies are undertaken, the specimens that are collected, the time of collection, and the analytical techniques used to analyze them are identical. This type of standardization could allow several studies to be evaluated collectively without the error associated with comparing metal concentrations in different biological compartments, e.g. blood Co levels with serum Co levels. Precise determination of threshold values for good versus poor implant function, including their relevance for decision-making regarding revision surgery, necessitates further investigations. As a research tool, however, this can be helpful in establishing potential correlations between chronic disease and metal content.

Measurements of specimen trace metal ion levels, specifically cobalt and chromium, but can also include other metals such as molybdenum, nickel and titanium, are useful in diagnosing and treating ALTR. Monitoring of metal (Co, Cr, Mo, Ni, Ti) ions should be performed at the time of regular follow-up in asymptomatic patients. In all symptomatic patients, additional monitoring is recommended between regular follow-up investigations. Metal ion determination of body specimens can be performed in blood, serum, urine, periprosthetic fluid, and periprosthetic tissue. However, at present measurement of whole blood/serum remains the primary clinical specimen of interest and is most practible. Many of the analytical/clinical studies to date have been proof of concept, however, there have been little concerted, systematic

optimization of experimental analysis conditions. Specimen metal ion measurement must be performed under the rules of internal/external quality control and using a validated method. HR ICP-MS, ICP-MS/MS and GF/ET-AAS provide a standardized scientific approach and are considered as valid. The method should accurately and precisely measure concentrations as low as 1 μg L^{-1} Co/Cr. In terms of normal values, the mean normal for non-exposed subject's ±3 SDs (Standard Deviations), not ±2 SDs, should be referenced, as well as the biological exposure index (BEI) of the toxic concentrations of chemical elements in biological media.

In view of drawbacks related to the specimen sample preparation step, the direct analysis of solids should be proposed as an alternative for trace metal ions determination in biological tissue samples. Among them, LA-ICP-MS and Laser-induced breakdown spectroscopy (LIBS) have been used. These methods have been used to measure the content and distribution of elements *in situ* in clinical samples and visualizing them in the form of the two-dimensional (2D) maps; they illustrate the distribution of the elements in the neighboring bony tissues during implant degradation. LA-ICP-MS has been described as a novel approach for trace element quantification imaging of biological tissues [326]. In this work, the use of dried-droplets deposited on precut filter paper disks have been used for quantification strategy for LA-ICP-MS imaging experiments, giving the possibility of reliable and easy multi-elemental quantification. Only one work was found using LIBS mapping of nanoparticles and trace metallic elements in biological tissue [327]. The results demonstrate that LIBS offers a simple and robust method to study the distribution of metal-based nanoparticles in biological tissue, present in low concentration, without any labeling of the nanoparticles. However, their application in routine analysis is hampered in view of problems related to the lack of sample homogeneity and the calibration step, since in many cases it is necessary to use CRMs due to matrix effects, which may impair the analysis due to lack of CRMs of biological tissues or with a similar matrix.

Finally, this overview article has outlined the potential toxicity of steadily release ultratrace metal ions, particularly Co and Cr, into the surrounding soft tissues, and circulation based on the available literature information, and that elevated trace metal ion levels and implant retrieval are useful to the understanding the present status of the local biological response. To develop an accurate risk assessment of metals in implanted patients, experimental models should be developed using wear debris, cells, culture media and host physiological human environment which more closely simulate *in vivo* conditions.

In future, it is advisable to reach a consensus on the strategies for surveillance, and this will be mandatory especially for the introduction of newly marketed joint implants. Thus, analytical methodologies can play a role in the most time-critical decision-making processes; laser ablation, mass spectrometry and spectroscopy-based laser ablation intraoperative diagnostics can provide immediate feedback to surgeons during soft tissue resection. In addition, specialized methods with improved analytical sensitivity can allow ultratrace metal analysis in highly complex matrices such as human biological specimens: blood, serum, plasma, synovial fluid, urine and soft tissue. Undoubtedly, analytical innovations in the area of nano-analysis will improve patient outcomes. One could argue that the enthusiasm for new approaches indicates just how much uncertainty still exists in the clinical decision-making process. Our goal is to have a full set of effective tools that will predict adverse effects before implantation, for quantifying and visualizing adverse effects, or can quickly identify problems before they are clinically significant. There is a very real possibility that we are only at the beginning of personalized diagnostics based on multilevel *in situ/in vivo/ex vivo* analytical/clinical methodologies.

8. Addendum

We would be remiss not to acknowledge that, the number of publications referring to joint implants has decreased considerably as the use of MoM implant joints is no longer popular, due to a loss of confidence in certain devices. This has led to a cessation of MoM bearing surfaces for THA and a significant decrease in the number of hip resurfacings performed annually, due to serious complications encountered at the primary articulation [328]. Concerns about MoM implants have been raised since 2004 when metal ions were found in the blood and urine of patients with MoM implants [329]. Recent prospective study documenting increased cobalt and chromium ion levels in blood in patients with MoM THA at long-term follow-up (five-year time point), but ion levels were lowest in the metal on polyethylene group which revealed metal ion levels unchanged from pre-operative levels [330]. Evaluation of some national database registries that showed significantly worse failure and revision rates of certain MoM implants compared to contemporary non-MoM bearing surfaces, either MoP or ceramic on ceramic (CoC), certainly contributed towards this shift in MoM THA use. It was noted that the Australian National Joint Replacement Registry showed a "*failure rate of total hip arthroplasty (THA) with MoM bearings to be 2-3-fold higher than contemporary THA with nonmetal-on-metal bearings*" [331]. In 2017, the UK National Joint Registry reported <0.1% of all hip replacements utilized MoM bearing surfaces. It also reported a decreasing percentage of implanted hip resurfacings (0.6%) compared to all primary hip arthroplasty [332].

A design of hip prosthesis favored for patients with a high risk of dislocation, dual mobility cups, which have a cup formed of 19% Cr and 13-15% Ni, a ceramic head, and a titanium alloy stem, has not previously been studied for possible release of metal ions. Marie-Hardy et al. [333] investigated 16 patients two years after hip arthroplasty. Clinically, there were no complications of Cr and Ni were less than 1 μg L^{-1} and 0.2 μg L^{-1}, respectively. Two years later, the concentrtions of Cr were 0.4-0.7 μg L^{-1} and were 0.2-5.6 μg L^{-1} for Ni.

Despite the multitude theoretical advantages for MoM THA, high complication rates have been demonstrated and *in situ* results have been less favorable compared with *in vitro* testing [334]. Although there does not seem to be a role for MoM THA, there are still unique advantages for MoM hip resurfacing, and certain centers are still implanting a large number of these devices in patients that are properly indicated for the procedure. Despite this, sizable patient populations currently exist with a MoM arthroplasty *in situ*, and it is imperative these patients undergo routine surveillance including history, physical examination, and evaluation of metal ion levels. Even with this increased rate of MoM THA revisions, 80% of MoM THAs remain *in situ* today [335]. Since 1996 more than one million MoM articulations have been implanted world-wide to alleviate pain, restore hip function, and improve overall quality of life [314]. Although, multiple studies and national registry data showed high failure rates and the 10-year survival rate threshold of 95% set by The National Institute for Health and Care Excellence (NICE) was not achieved [336].

9. Conclusion

Implanted metallic biomaterials play a key role in the current success of orthopedic procedures. Pure metals and its alloys are the most commonly used materials for permanent implants in contact with tissue, bone and human body fluids. Potential health risks are associated with metallic wear debris in the form of nanoparticles *in situ* generation and the release of *in vivo* trace metal ions into human biological specimen's circulation. This overview explores how migration of metallic wear nanoparticles and ultratrace metal ions in the area of metal-on-metal orthopedic implants influences the surrounding tissues and bodily fluids, and what the toxicological consequences of this process may be. The present article is more informative of indicative multilevel *in situ/in vivo/ex vivo* analytical/clinical methodologies which will be helpful in a way to plan, understand and lead the analytical innovations in the area of nano-analysis to improve patient outcomes.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors declare no conflicts of interest associated with this manuscript.

Statement of informed consent

Not applicable

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