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BIOCOMPATIBILITY STUDIES

Review Article

An update on the effect of metals on stemness properties of mesenchymal stem cells

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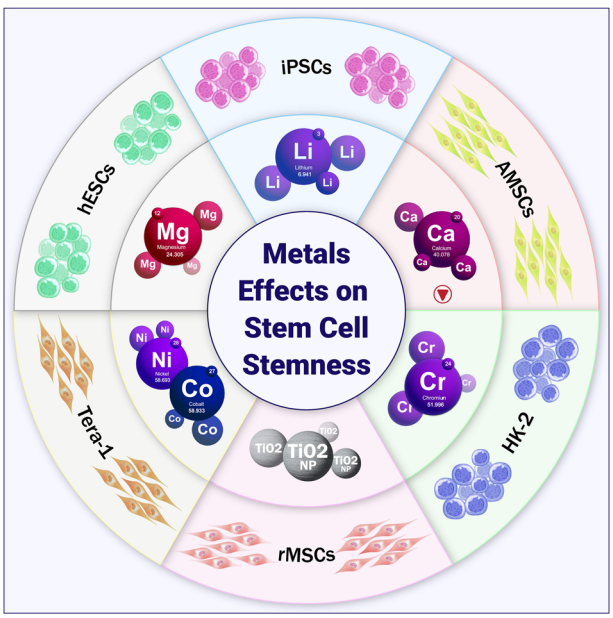
Abstract

The metal-based devices may corrode, degrade, or release metal ions and fragments after being implanted in the body, exhibiting their own consequences on hosting organs/tissues. The biocompatibility of metal implants has been investigated in various studies using a number of cell types. Mesenchymal stem cells (MSCs) are more relevant cells than others for evaluating the cytocompatibility of metal-based orthopedic implants because they are essential cells for bone regeneration and a promising cell population in regenerative medicine. In this regard, stemness preservation of MSCs is a key property in both body's own repair process and success of renewing/compensating approaches. In general, MSCs adhesion, viability, and function at the cell–metal interface is directly dependent on the metal alloys composing elements, which, along with consideration of compatibility, could guarantee the success of implants. This review scrutinizes the effects of orthopedic metal materials on the biocompatibility and stemness of MSCs at metal interface. Additionally, in vivo, host responses to metal implants are investigated.

Graphical Abstract



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1 Introduction

The most popular types of medical implants which are employed to anchor for fractured bones include the plates, pins, rods, and screws [1]. The type of materials used in making implants could be a way for implant survival/success [2]. When choosing the resources for orthopedic applications, the matching of the material properties with their applications is necessary for the best performance of the device. Since orthopedic implants are used for medical purposes, biological requirements should be covered by their compositions [3]. Thus, bio-adaptivity-related criteria comprising biocompatibility, bioactivity, osteoinduction, osteoconductivity, foreign body reaction, and stress shielding need to be fully examined and addressed before clinical applications [4]. Three types of materials were harnessed for the fabrication of orthopedic implants including polymers, ceramics, and metals. Definitely, metals were used much earlier than the other implant materials [5]. Among the metallic materials used in manufacturing of orthopedic implants, stainless steel and cobalt (Co)-chrome (Cr) alloys were successfully employed for the first time in the twentieth century [4]. Afterward, the Titanium (Ti) and its alloys were entered into lab and then clinic. The metals of manufacturing implants for instance Co, Nickel (Ni), Ti, Fe, Cr, Tantalum (Ta), Tungsten (W), and Molybdenum (Mo) are tolerable in the body [6]. The essential property for implant metals is the biocompatibility since the body environment has the potential to corrode them. The consequences of corrosion are undesired because the implants will loss material and the corrosion by-products can cause considerable negative effects [7]. Efforts have been made to design metal implants with high performance and minimum undesired side effects.

The cells are present adjacent to the implant surface, therefore the study of cytocompatibility of implants is necessary. The cytotoxicity evaluations of metal compounds were done using various kinds of cell lines, however, comparing them is difficult, because of heterogeneity of cells [8]. The bone marrow-derived mesenchymal stem cells (BMSCs) are key cells in bone regeneration progress [9] besides, they are extensively exploited for clinical applications in particular bone healing. Hence, in the present literature overview, we examined the effects of the different metal implant compositions on viability, compatibility, and stemness of mesenchymal stem cells (MSCs). We mainly focused on aluminum (Al), copper (Cu), iron (Fe), nickel (Ni), titanium (Ti), and zinc (Zn). Furthermore, other rare or precious metals encompass gold (Au), silver, platinum (pt), cobalt (Co), tungsten, lithium (Li), magnesium (Mg) Calcium (Ca) and zirconium (Zr). Meanwhile, implanted biomaterials are permanently documented as foreign entities by the host immune system, regardless of the degree to which biocompatibility was previously confirmed. Moreover, the host responses to act against metal orthopedic implants are also reviewed in the final heading. The innovative aspect of this study lies in our investigation of the impact of metals at biointerfaces on the stemness of neighboring stem cells.

2 Bone marrow stromal stem cells or mesenchymal stem cells

The human bone marrow-derived stromal stem cells (hBM-MSC) were recognized as osteogenic stem cells, for the first time by Friedenstein and colleagues in 1970, and reported to be different from hematopoietic stem cells [10]. Twenty years later, they were named MSCs by Caplan in 1991 [11], but Bianco & Robey in 2015 specified them as skeletal stem cells [12]. These evidence highlight the remarkable potential of them for active contribution in bone regeneration [13]. A large body of documents indicates that surface topography could influence the neighboring cells' functions such as bone matrix bio-fabrication and mineralization [14].

Usually, orthopedic implants come into contact with myoblasts, fibroblasts, osteoblasts, resident or entering MSCs [15]. The MSCs are particularly interesting in regenerative medicine owing to their capacity to properly differentiate into the osteogenic lineages and accordingly direct bone curing [16]. The main four groups of bone cells are osteoprogenitors, osteoblasts, osteocytes, and osteoclasts which were discovered in periosteum [17]. Osteoprogenitors are a group of MSCs residing in the bone marrow, they can differentiate into the specialized

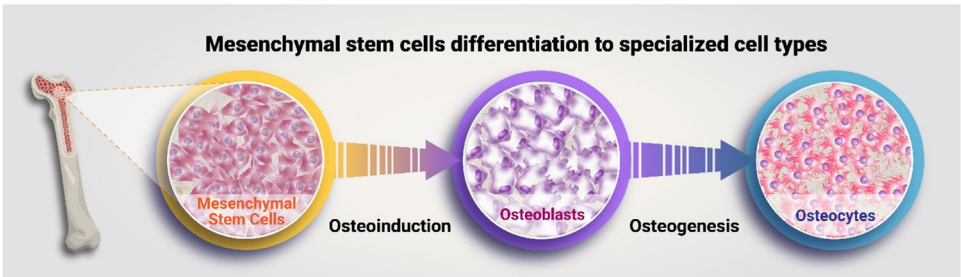

Fig. 1 MSCs differentiation in bones. Osteoprogenitors are a group of MSCs that exist in the bone marrow, they can differentiate into the specialized cell types including osteoblasts and osteocytes, and can contribute to bone regeneration

populations of bone-constructing cells including osteoblasts and osteocytes (Fig. 1).

In growing bones, for instance in fetal bone or during high turnover of adult bones, MSCs are larger and abundant, showing plump oval nuclei and high amounts of spindle-shaped cytoplasms. They convert into cuboidal-shaped active osteoblasts. Nevertheless, in mature bone, the active new bone formation or remodeling is impossible. In such conditions near the surface of the bone, the osteoprogenitor cells completely reshape and become flattened into spindle cells [18].

The differentiation of osteoprogenitors into osteoblasts could be directed using Bone morphogenic protein (BMP2), which has the potential for osteogenesis stimulation, angiogenesis during bone healing, and chondrogenic promotion under the hypoxic conditions [19]. The osteoblasts can express collagen, glycoproteins, and proteoglycan, immediately after differentiation into osteocytes they produce alkaline phosphatase (ALP) as an early marker of bone formation. In fact, the osteocytes as mature bone cells are originated from osteoblasts and trapped in their lacunae. They can communicate with each other using cytoplasmic processes besides ions or tiny molecules could be exchanged among them [20]. The metallic implants have been studied in vitro and in vivo animal models which have also been discovered that metal-based bone devices have stimulatory influence on bone repair [4, 15, 19, 21, 22].

However, prior to clinical applications, their effects on BMSCs should be evaluated because of their great importance for bone regeneration. Therefore, biological examinations must be carried out in order to fully assess the metal-based alloys' impacts on the neighboring tissues and their resident stem cells.

3 Metal materials as orthopedic implants

In the former two decades, there have been significant advances in the creating materials that are both biocompatible and biodegradable in medicine for different applications considering their unique properties. Based on recent findings, metal biomaterials in the form of complex implants could be useful in treatment of fractures and bone reconstruction [23]. In addition, recently, implants have gained such renown that they are frequently being applied as the first option for supportive treatment procedures [24]. Metals and their alloys, two important groups of prosthetic materials, exhibit a broad range of medical uses for bone and tooth tissue reconstruction. Metals are effectively transferred thermal energy and electrical charge due to the presence of independent electrons. High thermal and electrical conductance present in metallic biomaterials lead to using them in medical devices [25]. In fact, two items for metal implants are stated to be critical including mechanical properties and corrosion. The corrosion process is defined as the release of ions from metallic surfaces to the adjacent milieu. There are four types of corrosion including; crevice, pitting, galvanic, and electrochemical. The crevice corrosion happens in narrow interfaces like screw/bone. The release of ions from metals can create a positively charged region which may result in crevice corrosion [2]. The pitting corrosion causes cavities in the material; is considered to be more hazardous than other ones owing to its harder to detect and design encountering it due to the fact that corrosion debris frequently covers the pits. The galvanic corrosion is a result of electrical gradient differences. The Cr and Ni ions released from the artificial prosthesis could arrive in the tissues around implants which may cause instability of the implant, and bone reabsorption [2]. In electrochemical corrosion, free metal ions are released which can activate the human immune response; Although dermal metal hypersensitivity is frequent (10–15%), the immunologic reactions to implant metals are rare (<0.1%), but metal allergy and hypersensitivity may contribute to patient symptoms [26]. Implant biomaterials must be resistant to corrosion because it can give rise to roughening of surface, release of elements from metals or alloys, toxic reactions, and weakening of restoration [2]. Some metals as a consequence of mechanical characteristics and resistance against corrosion in broad range of environments are utilized for tissue replacement which includes total hip and knee joints.

Among metallic materials, the suitable corrosion resistance was observed in the noble metals, including Ag, Au, Pt, etc. In the meantime, from the beginning of the 1970s, the metal Pt has been applied in a wide variety of medical tools worldwide for treatment of stroke, cardiovascular disorders, persistent discomfort, stroke and relevant neurological afflictions, and emerging serious health subjects [6].

In the field of orthopedics and dentistry, the most widespread metals or alloys are Co–Cr–Ni, Ti–Al–V, and commercially pure (cp) Ti which is implicated in metabolism and differentiation of osteoblast-like cells [27]. Furthermore, cpTi and casting alloys have profited extensive applications in advanced dentistry for both momentary and lasting restorations, as well as for splints, and transferrable or static orthodontic appliances [28]. Current studies have reported that cultivation of MSCs on Ta and Ti induced considerable effects on cell biology and viability, which were similar in both cultures [29].TiO_2 nanotubes have been found to improve osseointegration compared to conservative Ti surfaces. In other words, the surface holds potential for improving the permanence of dental implants. Then, osteoblasts can easily attach and spread over the entire surface. It's notable that dental implants covered with TiO_2 nanotubes could suggestively advance healing

following dental implant surgery [30]. In a research effort conducted by Amirazad et al., the results exhibited that the pure hydrogels as scaffold, in comparison to the TiO_2 loaded hydrogel's rough surface, which is produced by the inclusion of TiO_2, can enhance primary cell attachment and, as a result, boost the viability and proliferation of ADMSCs cultivated on it [31]. Thus, these metals could have particular applications for clinical trials including the spinal reconstruction and fusion [29]. In this regard, implanted metallic devices are used for treatment of various neurological disorders including deep brain stimulators as well as motor deficits correlated with Parkinson's disease [32]. Because neurosurgery is invasive and the advancing complexity of interventional instruments, endovascular embolization using Pt coils has gained recognition as a therapeutic approach for intracranial aneurysms [33]. The present research suggests that lengthy linear Ti clips are comparable to the Co clips in mechanical endurance, and are safe to be used in vascular surgery [34]. Medical devices made from metallic components, through releasing metal ions or wearing of debris can expose patients to many of the same metals that are exposed to from environmental or occupational exposures [32]. However, the side effects of metal ions liberated from biomedical devices located in the body are among the primary reasons for failure of an implant system [35]. Actually, wear and corrosion occur in all total joint replacements that interface with bioenvironments, releasing soluble and particulate debris into the implant's surrounding environment [36]. Elevated levels of soluble metal ions exposed to immune cells, either in lymphoid organs or peripheral blood may potentially trigger the poisonous conditions and/or oversensitive immunologic-originated responses in susceptible subjects [36]. Particular ions such as Ti and Co ions can prevent some specific cellular biologic/physiologic jobs including ALP action, appearance of extracellular matrix calcification, and corresponding bones genes expression [27].

In various studies, biocompatibility examinations designed for dental alloys like Ti alloys have been completed [8]. The extraordinary physicochemical properties of nanostructured materials, including TiO_2, have made them useful as bone replacement materials. These advantages include low toxicity, stability, and biological compatibility. TiO_2's negative surface charge enables it to be included in both hydrophilic and hydrophobic systems. However, TiO_2 serves as a mechanical reinforcement to boost the hydrogels that are created in a stronger manner. A meta-analysis combining nine of the previous original studies demonstrated not any cancer-causing hazard associated with the metal-on-metal entire hip substitutions prosthesis, although a risk of skin/prostate cancers was detected and recorded [37]. Study of post-mortem specimens showed that similar concentrations of Co and Cr trigger initiation of carcinomas in animal models, and may also aggravate the risk of malignant transformation in excessive levels, Co inhibits cells metabolism, establishes hypoxic milieu, and has the potential to hurt various organs. Co toxicity or cobaltism, stemming from beer including additives, work exposure, or curative application, is extensively recognized [37]. Cobaltism can finally promote a wide variety of disorders such as vertigo, tinnitus, blindness, deafness, headaches, hypothyroidism, optic nerve atrophy, convulsions, cardiomyopathy, and peripheral neuropathy [38].

Since the past decade, several studies concerned with sensitivity to Palladium (Pd) have been published, describing common signs including oral mucosa contact allergies (such as stomatitis burning mouth, orofacial granulomatosis, or swelling of the lips and cheeks, cheilitis, and lichenoid reactions), along with asthma manifestations, dizziness, and chronic urticarial [39].

The first employed metal implants were stainless steel as well as Co–Cr combination alloys. Later, Ti alloys emerged and became public in clinical applications. The stainless steel is unaffected through corrosion due to high (>12 wt%) Cr content. The high Cr content agrees to the construction of an adhesive, self-restoring/curative, and resistant to corrosion, Cr2O3 surface covering. The austenitic stainless steel is the most extensively applied implants material, the Ni or Mn were used as austenite stabilizing elements. In clinical applications, AISI 316L is the most commonly used stainless steel type. This stainless steel has a number of other elements 17–20 wt% Cr, 0.03 wt%, 14 wt% Ni, 2.5 wt % Mo which provide greater corrosion resistance, other minor important elements are Mn, P, Si, S, and N. The stainless steel, due to its low price and availability is applied in traumatological devices for instance in fracture plates, hip nails, and screws [4]. The biomaterials have been classified into three generations, the first generation are bio passive or inert response biomaterials and have minimum immune responses [4]. Second generation is named bioactive biomaterials with potential for management of biomaterials bio-interface. Third-generation biomaterials are named bio interactive biomaterials which promote cell and molecular desirable responses [40].

Among the biodegradable metallic materials, three distinct categories have attracted great attention including Mg, Ta, and Pt.

The Mg is very important for biological processes and is biodegradable. Thus, Mg is nontoxic for body cells and its excess amounts can be easily removed via kidneys and urinary tract. Conversely, Mg alloys are able to corrode quickly in body's physiologic milieus which leads to the production of hydrogen pockets at implant interface and hinders the healing process. Studies continued to use Mg in alloy forms to reduce the undesired effects of Mg corrosion, for instance, Mg–Zn alloys (high tensile strengths) [41–43],

Table 1 The biocompatibility of metal implant materials checked on MSCs or related cell types

Metal/Alloy	Application	Antibacterial/Anti-fungal activity	Tested cell types	Results	Ref
Silver nanoparticles	Coatings for orthopedic implants	Staphylococcus epidermidis	Osteoblasts (OBs) and Osteoclasts (OCs)	At 50 nm exhibited cytotoxic effects on OBs and OCs	[89]
Magnesium–calcium–strontium	Selection of alloying implants for improving rapid degradation of Mg orthopedic implants	–	Mouse osteoblasts	No significant toxicity to MC3T3-E1	[90]
Stainless steel	Enhance integration of orthopedic implant	–	3T3 mouse fibroblast cell line	Proper neo-osteogenesis on implanted orthopedic surfaces	[3]
Silver coated materials	External fixation devices	–	Human peripheral blood lymphocytes for genotoxicity and fibroblasts (NIH 3T3) and osteoblast-like cells were used for cytocompatibility	Good cytocompatibility	[91]
Tantalum	Antagonize the cytotoxic effect of doxorubicin	–	Rabbit rectal tumor cells (VX2)	Higher intracellular ROS activity, reported in culture medium incubated with the Ta implant	[92]
Titanium	Dental implant	Staphylococcus aureus	Human lymphocytes and granulocytes	Good cytocompatibility	[93]
Nanostructures formed on a Titanium (Ti) surface by a simple non-lithographic bottom-up method	Formation of the focal adhesion points required for intracellular signaling	–	Human primary osteoblastic cells	Best biocompatible nanostructures on metallic Ti surface applicable for orthopedic implant	[94]
Silver with hydroxyapatite (Ag-HA)	Anchorage strength of implants inserted into the femur of Sprague–Dawley (SD) rats	Antibacterial activity of silver	Osteoblast cell line MC3T3-E1	combines the osteoconductivity of HA and the antibacterial activity of silver, to inhibit infections	[95]
Magnesium–zinc–calcium	Orthopedic surgery	–	Adipose-derived mesenchymal stem cells (ASCs)	cell viability and proliferation increased in the cells exposed to pure Mg and Mg–Zn–Ca extracts	[96]
Silver-loaded nano-titania coating	Antibacterial property	Staphylococcus aureus		Good antibacterial effect	[97]
Silver and strontium in hydroxyapatite coating on Titanium surface and silver calcium coatings	Orthopedic implant modification	Growth inhibition	Osteoblast-like MG63 cells	Deposited calcium phosphate coatings doped with silver and Strontium exhibited biocompatibility and antimicrobial properties	[25]
Magnesium–strontium (Mg–Sr)	Orthopedic biodegradable metals	–	Osteosarcoma cell lines MG63	Micro-computer tomography and histological analysis showed an enhanced mineral density and thicker cortical bone around the experimental implants	[98]
Hydroxyapatite coating on Mg–4.0 Zn–1.0 Ca–0.6 Zr	Load-bearing orthopedic implants	–	Fibroblasts	Good cytocompatibility coating material	[99]

Table 1 (continued)

Metal/Alloy	Application	Antibacterial/Anti-fungal activity	Tested cell types	Results	Ref
High-purity magnesium (HP Mg)	Internal fixation devices in intra-articular fracture operation	–		Good osseointegration was revealed surrounding HP Mg screws and increased bone volume and bone mineral density were detected at fracture gap	[100]
Zinc-incorporated TiO_2 coatings on titanium	Bacterial inhibition ability and bone-formability	Staphylococcus aureus and Escherichia coli	Rat bone marrow stem cells (bMSC)	Excellent antibacterial activity and biocompatibility	[101]
Multilayered coating on titanium	Controlled release of antimicrobial peptides for the prevention of implant-associated infections	Gram-positive (Staphylococcus aureus) and Gram-negative (Pseudomonas aeruginosa) bacteria	Osteoblast-like cells (MG63)	This multi-layer assembly can be a potential approach to locally deliver AMPs to prevent peri-implant infection in orthopedics without being toxic to host cells.	[102]
Magnesium alloy LAE442	Degradable alloy	–	Mouse L929 (connective tissue)	Excellent viability of cells but development of a corrosion-resistance coating is necessary to prevent early failure of the implant	[103]
Magnesium ions	Repair and regeneration of bone defects in orthopedic and dental fields	–	Human bone marrow-derived stromal cells (hBMSCs)	Biodegradable material	[51]
Strontium-based bulk metallic glass (BMG) with nominal composition of Sr40 Mg20 Zn15 Yb20 Cu5 (at.%)	Orthopedic implant	-	Osteoblast-like MG63 cells	Increased mechanical strength, high corrosion resistance, and good biocompatibility	[104]
Silver nanoparticles-doped titanium specimens	Application in orthopedics, dentistry, and other biomedical devices.	Silver-incorporated titanium shows excellent antibacterial ability against planktonic bacteria and Staphylococcus aureus in the suspension and ability to prevent bacterial adhesion	Osteoblasts	Optimized titanium/silver ratio promotes osteoblast differentiation	[105]
Chitosan-coated porous titanium	Better clinical performance of titanium implant in diabetic patients	–	Primary rat osteoblasts	Chitosan coating (as antioxidant) ameliorated diabetes-induced reduced bio-performance of TI via ROS-mediated reactivation of PI3K/AKT pathway	[106]
Zinc-loaded titania-nanotube-coated titanium substrates	Enhanced osseointegration and antibacterial action	Staphylococcus aureus	MC3T3-E1	Coated material, enhanced osseointegration, and antibacterial action	[107]
Magnesium–aluminum–zinc	In vitro biocompatibility and macrophage phagocytosis	–	L929 cells, MC3T3-E1 cells, and BMSCs and Macrophages	Biodegradable material	[108]
Titanium–silver alloys with nanotubular coatings	Preventing implant-related infection.	Staphylococcus aureus	Bone mesenchymal stem cells (BMSCs	In situ, plasma fabrication of an antibacterial ceramic-like structure improved antibacterial property and cytocompatibility.	[109]

Table 1 (continued)

Metal/Alloy	Application	Antibacterial/Anti-fungal activity	Tested cell types	Results	Ref
Silver-containing borate bioactive glass	Bacterial inhibition and enhanced bioactivity of orthopedic implant	–	MC3T3-E1 and L929 cells	Borate glass can be a coating material for good antibacterial and bioactivity of orthopedic implants	[110]
Magnesium treated with micro-arc oxidation (MAO)	Biodegradable implant with enhance the corrosion resistance of the magnesium implants	–	Saos-2 cells-human primary osteogenic sarcoma	MAO-coated Mg material showed excellent cytocompatibility	[52]
Hydroxyapatite/titanium composites	Bone-implant	–	Osteoblast cells	The addition of beta-tricalcium phosphate (TCP) with Ti increased cell viability, cell-composite interface attachment, and proliferation. Osteoblasts seeded on TCP showed higher Osteopontin and collagen type II protein expression. It showed excellent bone-implant interface compared with a pure Ti metal type.	[111]
Nickel-reduced stainless steel(Bohler P558)	Orthopedics	–	L929 fibroblasts and MG63 osteoblasts CHOK1 cells (cytogenetic effects study)	Ni-free alloy exhibited good in vitro biocompatibility and could be used for orthopedic applications	[112]
TiO(2)–silver(Ag)	Cytotoxicity for human fetal osteoblasts	Methicillin-resistant Staphylococcus aureus (MRSA)	Human osteoblastic cell line (SV-HFO)	Optimum in 0.3 Ag for cell viability and good bactericidal effect	[113]
Titanium with bacitracin immobilization	Anti-bacteria, osteogenesis, and reduction of macrophage inflammation	Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus (MRSA)	Human bone marrow mesenchymal stem cells (hBMSCs	Macrophages could not spread or activate on its surface, the secretion of inflammatory factors inhibited showed excellent cytocompatibility.	[114]
Magnesium- Neodymium (Nd) Yttrium (Y) Zinc (Zn) (MgNd2, MgY4, MgAl9Zn1, and MgY4Nd2)	Bone repair in the orthopedic field	-	Osteosarcoma cell line Saos-2 or with uninduced and osteogenically-induced human mesenchymal stem cells (MSCs) isolated from bone marrow	Cytocompatibility evaluation is needed for new biodegradable Mg alloys with cells that would be in direct contact with the implants.	[15]
Metal ions : Ag^{+}, Zn^{2+} and Cu^{2+} Cu(Copper)	Highest antibacterial efficacy but the least cytotoxicity against mammalian cells	Staphylococcus aureus and Escherichia coli	Fibroblasts	Metal ions caused ROS-mediated antibacterial effect	[115]
Titanium–copper oxide coating may be	Reduce Periprosthetic Infection	Staphylococcus epidermidis and planktonic bacteria	Gingival fibroblast and normal human osteoblast	Cytocompatibility with antibacterial effects	[116]
Electrodeposited chitosan-vancomycin composite coatings on titanium foils	Prevention of implant-associated infections	Staphylococcus aureus	MG63 osteoblast-like cell line	Good viability and antibacterial activity	[117]

Table 1 (continued)

Metal/Alloy	Application	Antibacterial/Anti-fungal activity	Tested cell types	Results	Ref
Nickle-free Zirconium (Zr) copper (Cu) ferrum (Fe) aluminum (Al), silver (Ag)	replacement material for the orthopedic surgical implant	–	MG63 cells (Human osteosarcoma cell line)	The Zr-based bulk metallic glass can be used potentially for replacement of materials in orthopedic surgical implants	[118]
Nano- and micron-sized particles of cobalt-chromium	The cytotoxic and genotoxic effects on human fibroblasts	–	Human fibroblasts	Nano-size particles caused more aneuploidy and cytotoxicity than micro-sized group	[119]
MTA Angelus (Angelus)	Cytocompatibility and antibacterial	Streptococcus mutans, Streptococcus salivarius, and Streptococcus	Rat MDPC-23 cells	MTA-based group exhibited valuable antibacterial activity and low cytotoxicity but calcium hydroxide-based materials showed higher antibacterial activity and cytotoxicity.	[120]
Silver nanoparticles immobilized on titanium	Prevention of periprosthetic infection	Staphylococcus epidermidis		Decrease the risk of implant-associated infections	[121]
Nanoscale silver nanoparticle layers are attached to the titanium orthopedic implant	reducing microbial colonization of implantable orthopedic devices	Escherichia coli Staphylococcus aureus	Murine 3T3 cells	Cost-effective and biocompatible for decreasing microbial colonization in orthopedic devices	[122]
Biomimetic coatings of plasma sprayed hydroxyapatite and titanium	Cytotoxicity analysis of plasma sprayed coatings on titanium	–	Osteoblast cells	Coating by hydroxyapatite and titanium improves corrosion resistance and cytocompatibility	[123]
Copper-bearing stainless steel (Cu-SS)	Osteogenic ability	–	Osteoblast cells	Good biocompatibility and osteogenic potential	[124]
Titanium surfaces were coated with the glycine-phenylalanine-hydroxyproline-glycine-glutamate-arginine (GFOGER) collagen-mimetic peptide	Enhance orthopedic tissue healing and integration	–	Bone marrow stromal cells	Bioactive and clinically relevant implant coating method, enhancing bone repair and integration of orthopedic implant	[22]
Iodine-supported titanium megaprostheses	Prevention and treatment of infections in large bone defect	–	Patients cells	Strong bone outgrowth and ingrowth, good antibacterial effects	[125]
Silver-polysaccharide nanocomposite	prosthetic applications in orthopedics and dentistry	Gram− and Gram+ bacterial strains	Osteoblast-like cell lines, human adipose-derived stem cells, and primary human fibroblasts	Polymeric films With good biocompatibility and antimicrobial effect	[126]
Iodine-supported titanium	Preventing and treating infections after orthopedic surgery	–	Patients cells	No infections and good ingrowth and outgrowth of bones	[127]
Calcium phosphate substituted with silver (CaP-Ag)	Bone substitute materials	Escherichia coli	Osteoblasts	Could inhibit, or reduce the incidence of postoperative bacterial infections	[128]
ZK60 magnesium alloy coated with hydroxyapatite	Improved cytocompatibility of ZK60 alloy for orthopedic application	–	Murine fibroblast L929 cells	Improved cytocompatibility	[54]

Table 1 (continued)

Metal/Alloy	Application	Antibacterial/Anti-fungal activity	Tested cell types	Results	Ref
Magnesium–aluminum- layered double hydroxides (LDH)	Orthopedic applications	–	Murine fibroblast cell line NIH 3T3 and the mouse osteosarcoma cell line MG63	In vivo, tests showed the fibrous capsules formation around $Mg(OH)_2$ and Mg–Fe–LDH but the host response of the Mg–Al–LDH was good, so it can be used as potential candidate biomaterial for implant coatings	[129]
Mg-2La: 98% magnesium and 2% lanthanum	Orthopedic implant material	–	L929 and human osteoblastic cells	Promising composed material for orthopedic implant biomaterials	[55]
Titanium (Ti), zirconium (Zr), hafnium (Hf), vanadium (V), niobium (Nb), tantalum (Ta), chromium (Cr), molybdenum (Mo), manganese (Mn), iron (Fe), ruthenium (Ru), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), silicon (Si), and tin (Sn)	Metals with potential for alloying	–	Osteoblast-like cells (SaOS2)	Group 1: Ti, Zr, Hf, Nb, Ta, Cr, Ru, and Si, exhibited excellent proliferation in SaOS2 cells. Group 2: Mo and Sn, no proliferate over time. Group 3: V, Mn, Fe, Co, Ni, Cu, and Zn, showed cytotoxicity	[5]
Multifunctional bilayer composite coating of poly(lactic acid)/brushite with high interfacial bonding strength on a Mg–Nd–Zn–Zr alloy	Orthopedic clinical applications especially for localized bone therapy	–	MC3T3-E1 osteoblastic cells	Good cell adhesion and proliferation, osteogenic differentiation, and greater osteoinductive potential	[56]
Magnesium–strontium	Biomaterials for orthopedic implants	–	MG63 cells	Good mechanical properties and corrosion resistance as well as cytocompatibility	[130]
Magnesium (Mg)–stannum (Sn)	Used as biodegradable implant	–	MG63 cells	Promising good cell compatibility and corrosion	[131]

MSCs mesenchymal stem cells, *Ref* references

Mg–Zn–Ca [42], Mg–Y–Zn [41, 44], Mg–Ca [42], Mg-Dy [45] which showed significant capacity for employing in manufacturing of fixation implants.

The second group, Ta exhibits excellent toughness, ductility, corrosion resistance, high biocompatibility, and cell adhesion, induces extensive ECM production, proliferation, and differentiation. However, poor mechanical properties, and processing challenges restrict its applications [46].

Although the Pt groups of metals including Pt, Rhodium, Iridium, Osmium, Palladium, and Ruthenium have poor mechanical properties, they are not applicable for making bone plates, but they exhibit an extreme corrosion resistance [1].

4 Biocompatibility of orthopedic metal materials for MSCs

4.1 Cytocompatibility

The concept of biocompatibility is a general description of the properties of a biomaterial compatible with cells or tissues without producing any toxic or immunological responses. The cytocompatibility is sub-classified as a type of a wider term biocompatibility and refers to compatibility with cells [47]. Cytocompatibility is necessary for implant materials, which demonstrates a favorable response to certain biological environments. Regarding metal implants, cytocompatibility relies on the characteristic corrosion resistance and toxicity of products which originate from corrosion [2]. Thus, minimum toxic response of host is very imperative. Most of the recent investigations were focused on mRNA transcription profiles in cells neighboring to tissues at implant or attached to surfaces of the implants. The results revealed strong expression of mRNAs associated with the control of propagation, osteoinduction, vascularization, and osteogenesis (Table 1).

Among different implant alloys, Ti alloys were first announced in the 1940s. The Ni–Ti alloys appeared by the 1960s which have excellent mechanical behavior, but the Ni showed some undesired allergenic effects which hampered its use [4].

The study by Ghaffari et al. explored the reaction of hBM-MSCs to Ti alloy implants having substandard crystalline apatite coatings [48].

The hMSCs were cultured on variable substrates then cell adhesion and proliferation were evaluated at different time points [48]. Both coated and non-coated substrates supported cell attachment, however non-coated group showed significant differences in proliferation and morphology of hBM-MSCs, as compared to cultured over the coated group. Researchers checked the cell migration which is associated with the osteoconduction. They concluded that the coated alloys are nontoxic, biocompatible, and excellent for constant osteogenic applications [48].

The doping of polyamine 66 with silver enhanced the antibacterial activity, and caused upregulation of bone marker genes expression in contacted BM-MSCs. This osteogenesis was mediated through two pathways including iNOS and Nnos signaling [49].

Ti–6AI–4V, alpha-beta Ti alloy, the widely used alloy in orthopedic implants, presents low weight ratio, high strength, and a perfect corrosion resistance property. In a study, with the aim of improving biological response to metals, chitosan was employed as a novel coating for Ti6Al4V.

The cytocompatibility of coating was determined by an MTT assay for Rat BM-MSCs. The coating was cytocompatible and supported rat BM-MSCs proliferation plus osteogenic differentiation. They concluded that since the coating is a hydrogel, it could be employed for the encapsulation of bio-factors and improving osteogenic potential at the interface of tissue-implant [50].

4.2 Biodegradability

The long-lasting implants have shown a number of side effects including cytotoxicity, sensitization, and allergy, for that reason the biodegradability seems essential in orthopedic applications. The biodegradation and mechanical characteristics of Mg alloys have attracted substantial interest as innovative bone implants. In a study by Leem et al., the effect of Mg ions released in abundance from alloys on proliferation and differentiation of hBMSCs was evaluated. They stated that Mg ions showed no cytotoxicity in hBMSCs, and even Mg ions treatment for 2–3 days significantly augmented hBMSC proliferation, ALP activity, and osteoblast differentiation. It is demonstrated that upregulation of integrins α2 and α3, but not β1 was observed after Mg treatments [51].

Although, Mg plus its alloys are employed in fabrication of lightweight biodegradable orthopedic implants. The high corrosion rate of them restricts the clinical applications. In a study by Ma and colleagues, the biomechanical and degradation behaviors of Mg materials with corrosion resistance surface treatment of micro-arc oxidation (MAO) were investigated. They concluded that the oxide coating may exacerbate the corrosion of Mg and decrease its degradation. The MAO-coating did not show any cytotoxicity and exhibited better bone formation nearby in vivo. Additionally, resistance to corrosion and mechanical characteristics were improved in MAO-treated Mg. Finally, MAO-Mg showed excellent cytocompatibility plus biocompatibility [52].

The degradation of Mg alloys causes ion discharge with severe cytotoxicity and annoying effects after implantation. The Mg alloys' cytological effects on cells have been studied in eight different Mg alloys containing various amounts of Al, Zn, Nd, and Y directly or indirectly using the Saos-2 (osteosarcoma cell line) or using hMSCs. These hMSCs were extracted from femoral shaft bone marrow samples in patients experiencing hip replacement. Generally, Mg alloys including, MgY4, MgNd2, MgAl9Zn1, and MgY4Nd2 showed satisfactory cytocompatibility. These studies emphasized on the obligation of cytocompatibility studies of novel biodegradable Mg alloys with hMSCs or other cells possibly near to the implants [15].

Moreover, Mg alloys show a natural degradation in water-based solutions owing to their corrosion activity and are good for orthopedic requests. The control of the degradation speed in the physiological environment defines the implants success. Three different scores of Mg alloys including, AZ91E, AZ31B, and ZK60A were studied for biocompatibility and corrosion resistance [53].

Wang and colleagues, developed a hydroxyapatite (HA) coatings on ZK60 Mg alloy to mediate the quick degradation besides improving the cytocompatibility. To determine the cytocompatibility Murine fibroblast (L929 cells) were cultured on coated or non-coated ZK60. The HA coatings reduced the rate of degradation in ZK60 alloy. After 4 weeks of immersion in simulated body fluid, no significant deterioration was observed as well improved cytocompatibility was observed by ZK60 alloy [54].

An Mg Alloy, Mg-2La, composed of Mg (98%) and lanthanum (2%), was investigated as a potential implant for medical applications. In vitro cytotoxicity test using L929 and human osteoblastic cells showed no lethality at physiological conditions. In the 100% extract, the metabolic activity of human osteoblasts was reduced to less than 70% which is harmful. The degradation speed was shown to be changed by the composition of the media, and fetal bovine serum accelerated the corrosion [55].

A bilayer composite coating of poly (lactic acid)/brushite exhibiting high interfacial bonding strength on a Mg/Nd/Zn/Zr alloy was developed by Zhang and colleagues. The poly (lactic acid) is used as drug carrier in inner layer of the composite and for outer layer of brushite by chemical solution deposition. A facile UV irradiation pretreatment was employed to facilitate the heterogeneous nucleation of bruthite [56].

The coating of composite caused a considerable decrease in Mg degradation. The coated Mg induced no cytotoxicity for MC3T3-E1 osteoblasts, better cell adhesion, proliferation, and triggered osteogenic differentiation. The in vitro Paclitaxel release profile from the composite checked by UV-vis spectroscopy, showed a burst release at initial stage followed by a sustained/controlled release. Hence, the poly(lactic acid)/brushite coating provided active protection of Mg alloy, and improved cytocompatibility, drug delivery, and bioactivity for orthopedic applications [56]. In bone tissue engineering it is preferable to employ a composite system in the scaffolding situation because it has both osteoinduction and osteoconduction qualities in addition to superior mechanical properties. Applying various elements concurrently to three-dimensional composite scaffolds enhances the effectiveness of biological molecules, stem cells, and tissue engineering. Although their stability and mechanical qualities are poor, hydrogels are water-soluble, tissue-like substances with hydrophilic surfaces that control cell adhesion, proliferation, and differentiation. This biomaterial is typically loaded with Ti to get around this hydrogel constraint, and enhance the mechanical characteristics and stability of hydrogel [31]. These findings are consistent with research by Anaya Esparza et al., which supports the benefits of TiO_2 nanoparticles as a strengthening agent in polysaccharide loaded with Ti. When compared to pure hydrogel, ADMSCs' mitochondrial activity (proliferation and viability) enhanced when TiO_2 was included in the hydrogels loaded with TiO_2. This good viability is the outcome of an appropriate composite. This viability is the outcome of a well-designed composite structure that can offer a matrix that makes it easier for nutrients and oxygen to reach the cells [31].

Recent evidence designates the positive role of strontium comprising biomaterials in improving bone restoration and radiodensity for fast imaging. The ability to support proliferation of rabbit adipose-derived mesenchymal stem cells (AMSCs) was studied on scaffolds containing strontium calcium (Ca) phosphate and HA. Also, the biodegradation was checked by simulated body fluid and PBS for 28 days at 37 °C which showed good compatibility as bone implants and in tissue engineering [21].

The viability of human MSCs was checked on medical-grade type of stainless steel surface covered with ZrTiO4/hybrid ZrTiO4-PMMA. Their outcomes confirmed the improvement of the hydrophilicity, corrosion resistance, and cytocompatibility of the ZrTiO4 substrates. The sample coated with the thin inorganic film displays a better cellular response. The ZrTiO4 grounded film with solution-to-gelation properties could remain a candidate strategy for improving the cytocompatibility of metal implants [57].

The adhesive behavior of human adipose stem cells (ASCs) on the surface of Ni-free stainless steel was investigated by Salahinejad and colleagues. They reported that these implants exhibited no harmfulness for MSCs [58].

The quick degradation observed in Mg alloys can elevate the pH of the local area, subsequently because gas-derived cavities are produced. Therefore, monitoring their biodegradation is essential for applying in clinic. The study by

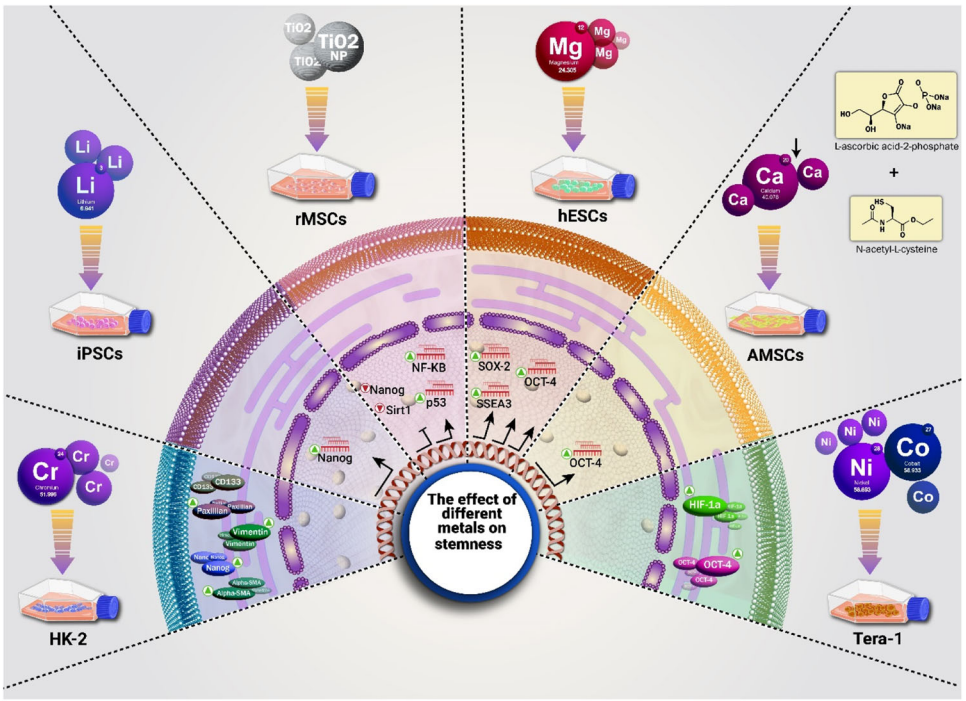

Fig. 2 The impacts of different metals treatment on stemness genes/proteins expression of stem cells: the effects of metals on different stem cell types and one renal epithelial cell (HK-2) were summarized in the figure. Each metal type caused different genes up or down regulations (mRNA of genes: comb-like figures) or proteins (oval shapes). iPSCs induced pluripotent stem cells, AMSC adipose-derived mesenchymal stem cells, rMSCs rat mesenchymal stem cells, hESCs human embryonic stem cells, Tera-1 human embryonal derived cells, HK-2 human kidney cells. Green triangle: upregulation, Red triangle: downregulation

Jonson et al. investigated just how the Mg–yttrium (Y) alloy with oxidized or polished surfaces can affect the degradation behavior and speed up in cell culture medium in competition with deionized water. In comparison polished surfaces remained more constant than that oxidized in cell expansion medium, on the other hand in water, it showed less stability. Although their degradation was different in medium, it was comparable in water. Remarkably, the polished surface presented extra cell adhesion potential as compared to the oxidized surface, generally owing to its gentler degradation speed and less significant influence on the local area pH level. The concluding statement is that the Mg alloy surface plus the immersion fluid show central roles in monitoring the ruin and cell communications [9].

The wear resistance of implants in orthopedic could be amended by ultra-smooth nanodiamond (USND). In this way, surface modification and cytocompatibility studies were performed on USND. The results indicated that despite the fact that fluorine and oxygen-terminated surfaces inhibited cell adhesion, hydrogen-terminated USND surfaces encouraged strong MSC adhesion and growth. Hence, USND could be modified to either stimulate or prevent cell and biomaterial interactions. In a comparison among two popular biocompatible metals, CoCrMo and Ti alloy (Ti–6Al–4V) with USND for the favorable MSCs cellular responses, Ti–6AI–4V showed the greatest cytocompatibility but USND performance was considerably better than CoCrMo. Additionally, upon osteoblastic differentiation, mineralized matrix formation was higher in Ti–6Al–4V while comparable in CoCrMo and USND. Therefore, USND wear composition could reduce debris release from implant along with improving osseointegration [59].

5 Stemness of MSCs at implant interface

The regenerative responses of MSCs on bio interactive metal implants promises to obtain a profound impact on clinical applications for skeletal tissue regeneration. As a result, biomaterials development in terms of production of implants is rapidly advancing to show properties that, in physiological conditions, could direct and stimulate desired stem cell fate in vivo. In this way, there are many efforts for the design of innovative materials to go over the molecular procedures involved in the production, degradation, and dealings of biomolecules in bone tissue in pathologic conditions also restoration of the corresponding tissues [60]. Although bio/cytocompatibility studies on metal orthopedic implants widely focused on viability, proliferation, and even osteointegration potentials of metals, there are little studies concentrating on long-term effects of metal implants over stemness of the adjacent MSCs. MSCs show two key properties including self-renewal power and multi-potent differentiation capability which designate their stemness. The stemness is critical factor for stem cells used in regenerative therapies [61]. The three known transcription factors: OCT4, NANOG, and SOX2 are the chief regulators of the pluripotency in all stem cell types and accordingly in MSCs [61]. The metallic biomaterials are expected to be biocompatible and not to affect the stemness properties of

stem cells at implant interface. However, checking the long-term effects of materials on stemness of MSCs rather than just compatibility studies is necessary before applications of them in clinic. The OCT4 (POUF5) gene is a chief regulator of self-renewal in embryonic stem cells (ESCs) [62]. It has been documented to play a central character in reprogramming process of fibroblasts into induced pluripotent stem (iPS) cells [63]. Co and Ni induced a dose dependent higher levels of OCT4 and HIF-1α, on the other hand, not KLF4 nor NANOG in embryonic Tera-1 cells, plus stem cells (Fig. 2). The OCT4 upregulation which is induced by Co or Ni was due mainly to protein stabilization as MG132 stabilized OCT4 expression in cells [64] (Fig. 2). Reactive oxygen species (ROS) had a major role in the stabilization of OCT4 upon Co and Ni treatment because the co-treatment of ascorbic acid eliminated the rise in OCT4. These findings imply that Ni and Co may cause reproductive cytotoxicity by interfering with OCT4 function in stem cell [64]. Also, our recent work on rat MSCs showed upregulation of aging-related genes P53 and NF-KB versus downregulation of Nanog and Sirt1 after exposure to TiO_2 NPs [65].

Although, there are some reports of negative effects related to the stemness properties of stem cells at metal implant interfaces [64] other information regarding a number of metals is desired for scientists in this field. For example, cell responses to Mg breakdown were investigated using hESCs as the in vitro model system. The expression of OCT4, SOX2, and SSEA3 indicated that the hESCs were proliferating and maintaining pluripotency regardless of the examined Mg ion concentrations (Fig. 2). However, at doses higher than 10 mM, the morphology of hESC colonies shifted, and the number of cells decreased. Furthermore, the hESC culture system may be used as a standard model for cytocompatibility studies of Mg ions in vitro, and a known harmful dosage of Mg ions (10 mM) might be used as a design suggestion for the safe degradation of implants based on Mg [66].

Also, a group reported that Lithium (Li) greatly boosts the generation of induced pluripotent stem cells from HUVEC cells or mouse embryonic fibroblasts. They claimed that Li facilitates iPSC production via increasing the expression of Nanog and its transcriptional activity (Fig. 2) [67]. Another team showed an interesting effect of Lithium chloride (LiCl) on osteoporotic females. They investigated whether LiCl improves Ti tibia implant osseointegration potential, and bone development in osteoporotic female rats from Sprague–Dawley type. The LiCl treatment boosted implant fixation plus bone formation in osteoporotic rats [68]. Also, similar to Li Cr(VI) stimulates expression of MSCs markers, for instance, Nanog, paxillin, CD133, alpha-SMA, and vimentin [69]. The study by Lin et al. demonstrated that using an expansion medium with little Ca and supplemented with antioxidant L-ascorbic acid-2-phosphate and N-acetyl-L-cysteine for AMSCs enhanced their growth rate, OCT4 expression, and lifespan [70]. Interestingly, Cr treatment of HK-2 cells induced markers of MSCs (Fig. 2) [69].

The adherent cells react with substrates, the factors for instance hydrophobicity, topography, surface energy, and chemistry of them is substantial. Thus, the MSCs-substrate interface is a key design parameter which is used to influence cell responses in regenerative medicine.

6 Host response to implant metal ions

The implant devices and known prostheses inserted in the body's connective tissues can stimulate a primary host immune reply facing the extraneous material. The tissue response to xenoimplants can be classified according to Hench classification [24], briefly: (1)the toxic material which causes the death of the adjacent tissue, (2) not toxic and bio-inactive (inert), causes a fibrous tissue with variable thickness, (3) not toxic and bioactive, interfacial bonds could form, and (4) not toxic and dissolvable, the nearby tissue can absorb and replaces it [19].

Numerous studies have been performed regarding allergic responses to synthetic materials especially to metal constituents being utilized in orthopedic surgeries [4]. Historically, Allergy responses to metal implants include restricted or widespread eczemas, urticaria, chronic swelling, sterile osteomyelitis, and aseptic implant loosening [71].

Ni, Co, and Cr are prominent classic allergens upon contact. Reportedly, only a small number of patients experience allergies to implant materials, even though up to 12% of the general population is susceptible to Ni and up to 5% to Co and Cr [72].

Several patients having revision surgeries had peri-implant inflammatory infiltrations that showed symptoms of late-type allergic responses. These infiltrations were linked to problems. An increasing number of complaints of incompatibilities with Ti materials have been received [73]. It is evident that all of the Ti samples evaluated/analyzed had consistent trace levels of other elements, such as Ni. It is suggested that an immunological reaction to metals may be the cause of poor wound healing or slowed down bone fracture repair, in part because of an exaggerated allergic reaction [74]. Thus, allergenic responses to orthopedic implants may also entail the deletion of the implant. Infiltration of lymphocytes was detected in tissue around prosthetic area, being a component of T-lymphocyte-related inflammation [73] recognized as delayed-type hypersensitivity [75]. Besides vascular wall inflammation by lymphocyte infiltration and extensive fibrin transudation have been observed. The mean sensitization value in the overall

population fluctuates between two to twelve percent, mainly in the form of typical findings, namely hand eczema, unusual appearances, for example, implant-associated intolerance reactions, and pseudo-lymphomas [76, 77].

There are fallacious reports on eczematous reactions believed to be elicited by means of contact allergy in response to the metals implanted. In most cases, it has largely been the orthopedic material of stainless steel or vitallium used for fixation of extremity fractures thus leaving residual deposits just under the skin [78]. Albeit, in prospective studies on patients operated in emergency situations for extremity fractures, there wasn't observed to be any induction of contact allergy to metals or any eczematous reactions [79]. Any orthopedic implant's breakdown products primarily consist of two categories of waste: particles and soluble (or ionic) debris. Because particle debris and the simultaneous release of Co/Cr ions may eventually cause unfavorable tissue responses, such as necrosis, hypersensitivity, and pseudotumors, the wear of MoM joints is especially concerning [80].

Three kinds of mechanical wear processes are proposed to exist: sticky, abrasive, and fatigue [81]. The deterioration process known as metal corrosion affects the surface of metallic objects and is mostly caused by how those materials interact with their surroundings. Because the physiological environment is corrosive, the deterioration of metallic materials occurs gradually and continuously, releasing metal ions in the process [82]. It is well-recognized that proteins, amino acids, and chloride ions speed up the body's deterioration [83]. In aqueous solutions, following Co–Cr alloy MoM hip replacement, the surface oxide transforms into chromium oxide containing a trace quantity of hip synovial fluid, and Co is entirely dissolved when Co–Cr alloy comes into contact with bodily fluids [84].

The wear of Co–Cr products could cause cancer in patients, particularly Cr (VI), causing abnormalities in cellular DNA [85]. Cr (VI) can enter cells much more readily than Cr (III) and is typically attached to nucleoproteins. The reduction of Cr (VI) to the more stable Cr (III) is harmful to chromosomes and occurred mutation, genomic instability, aneuploidy, and cell transformation [86].

There are no significant corrections between chromosome translocation and Co or Cr concentrations but they correlate with Mo levels regardless of their low levels. Also implanted Ti induces abnormal proliferation of cells, which can lead to the development of malignant tumors and cancer. It is worth to mention that allergy to metal implants could produce rare skin cancer. The chronic inflammation can be developed in the people with sensitivity to metal alloys such as Ni, Co, and Cr that promotes the development of skin cancers [87].

As a result, individuals with metal implants near their skin should be examined for this category of inflammation. Experiments using mice models revealed that chronic skin inflammation caused by constant skin contact with allergens leads to tumor growth [88].

7 Conclusions

The metal-based implants when transplanted at required sites possibly will corrode, destroy, or diffuse around ions or particles to the body, causing some effects on accommodating organs/tissues. In this regard, MSCs are the prevalent population of body stem cells and very critical cells in regenerative treatments. An intrinsic capability of MSCs to sustain self-renewal and differentiate into certain lineages generally is designated as stemness. Generally, MSCs' stability and performance at the metal interfaces are dependent on the type, diversity, and density of implant constituting elements. Some elements such as Cr and Ca presented positive influences on stemness markers Nanog and OCT4, respectively. Inversely, other cases may reduce the stemness ability of them and generate unwanted incompatibility. Hence, considering the stemness of MSCs is crucial to reach safe and efficient restoring/remedying by means of metal implants.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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