Artículo de revisión

Poisoning by metals used in prothetic materials in orthopedics and its current management

Envenenamiento por metales utilizados en materiales protésicos en ortopedia y su tratamiento actual

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ABSTRACT
Poisoning by metals present in prosthetic materials used in orthopedics is caused by the release of waste metals that are generated mainly by wear and corrosion. The objective of this study is to detail which are the current clinical and pathophysiological manifestations of the prosthetic metals used in orthopedics as well as the management of the most frequent arthroplasty associated with metal toxicity, hip arthroplasty, mentioning the most frequent metals that produce toxicity and implants or arthroplasties that carry a risk of developing intoxication. A narrative review was carried out through various databases from January 2005 to January 2021; the search and selection of articles were carried out in journals indexed in English. The results provided updated and organized information on the clinical and pathophysiological manifestations caused by the different types of frequent metals that produce toxicity present in prosthetic materials, as well as the management of hip arthroplasty.
Keywords: intoxication; metals; materials; prosthetics; orthopedics; arthroplasty; implants.

RESUMEN
La intoxicación por los metales presentes en materiales protésicos utilizados en ortopedia se produce por la liberación de metales de desecho, que se generan principalmente por el desgaste y la corrosión. El objetivo de este estudio es detallar cuáles son las manifestaciones clínicas y fisiopatológicas actuales de los metales protésicos utilizados en ortopedia así como el tratamiento de las artroplastias más frecuentes asociadas a toxicidad por metales, la artroplastia

de cadera, mencionando los metales más frecuentes que producen toxicidad e implantes o artroplastias que conllevan riesgo de intoxicación. Se realizó una revisión narrativa a través de varias bases de datos desde enero de 2005 hasta enero de 2021; la búsqueda y selección de artículos se realizó en revistas indexadas en inglés. Los resultados proporcionaron información actualizada y organizada sobre las manifestaciones clínicas y fisiopatológicas provocadas por los diferentes tipos de metales frecuentes que producen toxicidad que están presente en los materiales protésicos, así como el manejo de la artroplastia de cadera.

Palabras clave: intoxicación; rieles; materiales; prótesis; ortopedía; artroplastia; implantes.

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Introduction

Metals and metal alloys have been used for a large number of medical implant applications, in most medical specialties. During the last 30 years, orthopedic surgery has been improving, thus providing a better quality of life, restoring mobility and relieving pain. The prostheses to replace arthritic joints and devices to repair fractures and stabilize the spine are the most used.[1,2]

Knee and hip joint replacements have provided the best clinical results. Therefore, joint replacements have proven to be a highly reliable treatment even in the long term.[2]

However, despite the success of this type of surgery, it is essential to improve and to provide a better quality of life. The average life expectancy is increasing, which requires implants of longer duration, taking into account that complications and adverse effects are not uncommon in this type of orthopedic surgeries and prosthetic materials, leading to a replacement of the prosthesis. The deterioration of the prosthetic components is one of the complications associated with joint replacement with subsequent biological reaction caused by the body to the material released by the implant.[2]

The problem of adverse reactions to implants is rare, but it is increasing due to the increasing use of prostheses or arthroplasties. As evidenced by reports of adverse effects associated with the release of metal ions from certain types of joint replacement, such as hip replacement.[2,3]

Thanks to investigations of adverse reactions to metals, there has been a growing improvement in orthopedic investigations. However, there is little precise or exact information on the manifestations of toxicity by the different types of metals used in the various implants or orthopedic arthroplasties. Given this lack of data and the growing problems in the field of orthopedic implants, we have conducted a review of the literature on toxicity from prosthetic materials or orthopedic implants. The purpose of this review is to provide a comprehensive update on the manifestations of toxicity ~~present~~ in the different types of materials used by various implants or orthopedic arthroplasties and their current management.

Methods

Design of the investigation

A narrative review was carried out. The collection and selection of articles was carried out in indexed journals in English from 2005 to 2021.

Data source

The databases of PubMed, Scielo and ScienceDirect, among others, were searched. As keywords, the following terms were used in the databases according to DeCs and MeSH methodology: intoxication, metals, materials, prosthetics, orthopedics, arthroplasty, implants.

Data collection method

In this review, 70 original and review publications related to the subject were identified, of which 25 articles met the specified inclusion requirements, such as articles that were in a range not less than the year 2005, which were text articles complete information on metal poisoning in prosthetic materials in orthopedics. As exclusion criteria, it was taken into account that the articles did not have sufficient information and that they did not present the full text at the time of their review.

Data analysis

Data expressed as correlation between Cobalt (Co), Chromium (Cr), Nickel (Ni), Iron (Fe), Manganese (Mn), Molybdenum (Mo), Silver (Ag), Gold (Au), manifestations of toxicity and implants or arthroplasties were analyzed in Excel Software (Table 1).

Table 1 - Correlation between metals, manifestations of toxicity and implants or arthroplasties

Material	Manifestations of toxicity		Orthopedic implants or arthroplasties
Cobalt (Co)	Allergic contact dermatitis		Hip prosthesis
	Cardiomyopathy, polycythemia, and granulomatous lung disease		Knee replacement
	Altered thyroid function		Spinal Disc Implants
	Visual changes		Shoulder arthroplasty
Chromium (Cr)	Possible liver and kidney problems		Knee replacement
	Visual changes		Stainless steel spinal implants
	Respiratory symptoms and granulomatous lung disease		Spinal Disc Implants
	Dermatitis and ulcerations		Hip prosthesis
	Gastrointestinal symptoms		Shoulder arthroplasty
	Lung cancer		-
Nickel (Ni)	Acute delayed hypersensitivity	Gastrointestinal symptoms	Knee replacement
		Headache	Stainless steel spinal implants
		Vertigo	Hip prosthesis
		Vision changes	-
	Chronic delayed hypersensitivity	Altered iron metabolism	-
		Cardiovascular, respiratory, or kidney disease	-
		Alteration in calcium, magnesium, manganese, zinc homeostasis.	-
Iron (Fe)	Generation of free radicals		Hip prosthesis
	Acute gastrointestinal symptoms		-
	Hemochromatosis	Cardiomyopathy	-
		Cirrhosis	-
		Diabetes	-
		Arthritis	-
Manganese (Mn)	Headache, Psychiatric symptoms, Gastrointestinal symptoms and Parkinsonism		Hip prosthesis
Molybdenum (Mo)	Elevated uric acid / Gout, Secondary copper deficiency and Reduced testosterone		Hip prosthesis and Spinal Disc Implants

Silver (Ag)	Local argyria	Bone fixation devices (plates, screws, wires, pins, rods)
Gold (Au)	Bone marrow suppression, Dermatitis, Glomerulonephritis, Vasculitis, Hepatotoxicity and Neuropathy	Bone fixation devices (plates, screws, wires, pins, rods)

Results

Frequent metals used in prosthetic materials

Implants have provided a better quality of life for people who do not have an alternative treatment. Thanks to the advantages they provide, advances have been made in the formation of implanted devices.[4]
Metal-based arthroplasties are preferred for their high mechanical strength, durability, good thermal and electrical conductivity, ductility, and chemical/biological compatibility. Only in the last century ~~have~~ implantable medical devices become commonplace in healthcare.[2]

Cobalt (Co), Chromium (Cr), Molybdenum (Mo), Titanium (Ti) and their alloys and Stainless Steel (SS) are commonly used in implant design. CoCrMo alloys are known for their rigidity and long-term corrosion resistance, but their disadvantage is due to the cost of manufacture due to their high rigidity. These metals are used with great frequency in joint replacements, especially knee and hip.[3]

The metals that produce toxicity from metal orthopedic implants are frequently attributed to Cobalt (Co), Chromium (Cr), Nickel (Ni), Iron (Fe), Manganese (Mn), Molybdenum (Mo), Silver (Ag) and Gold (Au).[2,3,5]

Depending on the application, different types of metal will be used, we will find that Co-based alloys (for example, Co-Cr-Mo, Co-Cr-W-Ni) are highly resistant to corrosion but have lower ductility and are more difficult to work and configure by machines. Therefore, Co-based alloys are used more in long-term permanent implants and those that require high resistance to wear.

Nitinol (Ni-Ti) alloy is used in implants due to its shape memory behavior, its superelasticity and its biocompatibility, when it coexists with living tissues without being harmful or toxic and without generating rejection.[5] Ni-Ti is also used as orthopedic fixation devices, where its unique properties can be advantageous.[6]

Clinical manifestations

The clinical response is diverse and there are no specific symptoms attributable to metal toxicity. Given the diversity of the patient's context: patient history, genetic background, variations in environment and lifestyle, underlying disease, and comorbidity, the response will vary from patient to patient. The terms "metal allergy", "metal hypersensitivity" or "metal toxicity" alone do not explain most responses to metal implants.[7]

Prosthetic metal toxicity can occur locally or systemically, but it is not clear whether metal toxicity is caused by device failure. For this reason, harmful responses are often the result of device, biomaterial, and patient factors.[2]

Prosthetic metal toxicity can present neurological, cardiological, hematological, and endocrine symptoms.[2]

In this study we have found a record of toxicity manifestations attributed to Cobalt (Co), Chromium (Cr), Nickel (Ni), Iron (Fe), Manganese (Mn), Molybdenum (Mo), Silver (Ag) and Gold (Au) implemented in implants or orthopedic arthroplasties, such as hips, knee arthroplasties, or among other implants described in table 1. These data suggest that implants or arthroplasties containing these metals are at risk of developing intoxication.[8,9,10,11,12]

Pathophysiological manifestations of prosthetic metals

Degradation, which is caused by wear and corrosion, is responsible for the response to implanted materials. These wastes appear in various forms: free metal ions; colloidal complexes; inorganic metal salts or oxides; organic forms (such as hemosiderin); and finally, particle wear.[13,14,15]

Unfortunately, there is little data to report on the effects of metal used in orthopedic prostheses. Most of the *in vitro* and *in vivo* studies that have been published in the literature are related to the effects induced by Cr and Co.[4] It has been reported that most metals, especially Co and Cr, are located at the synovial level as a consequence of degradation, either due to wear or corrosion. The release of metallic residues occurs mainly in the form of micro, nanoparticles, ions of different valences and oxides composed of Co and Cr.[3,17,18]

Cellular absorption of metals due to their degradation

Metallic nanoparticles (< 150 nm) are taken up by cells through the endocytocis and pinocytosis process, through nonspecific receptors. In contrast, larger particles (> 150 nm) can stimulate phagocytosis in specialized cells such as

macrophages. After the particles are internalized, they can cause cytotoxicity, chromosomal damage, and oxidative stress. The toxicity of the particles is changed by passivation and the size of the particles. Both processes contribute to the dissolution of the metal from the surface, which may explain the biological activity. Therefore, the particles can cause irregular cell membranes and enlarged mitochondria.[16]

Local effects

Despite the reintroduction of metal-on-metal bearings to metal-on-polyethylene joints, aseptic loosening and osteolysis remain the initial cause of implant failure. In contrast, metal-on-metal bearing particles have a limited ability to activate macrophages and can cause osteolysis by some immune reaction involving hypersensitivity. We will find that the pattern of inflammation in the periprosthetic tissue of loose metal-metal junctions is significantly different from that of metal-polyethylene junctions and is distinguished by perivascular infiltration of lymphocytes and accumulation of plasma cells.[13,18]

Systemic metal toxicology

Epidemiological and experimental studies that include in vitro and in vivo models have contributed information on metal-induced toxicity in arthroplasty patients. Unfortunately, few data speak of systemic effects.[19,20] But, it is known that the lymph nodes, bone marrow, liver and spleen are circulated by metallic and polymeric particles through the lymphatic vessels. In addition, they are concentrated in the erythrocytes when entering the bloodstream, these, at the same time, circulate throughout the body, causing cytotoxic, genotoxic and immunological effects.[3]

Currently, the following toxic responses have been documented:

- The blood: Metals can induce changes in hemoglobin and hematocrit values that are related to their ability to disrupt cellular utilization of iron, especially chromium. In patients with impaired renal clearance, metals have been associated with the development of microcytic anemia.[13]
- The immune system: Immunostimulators or immunosuppressants are the mechanisms that metals use to modulate immunocompetent cells. Metals have been found in macrophages of the liver and spleen by their dissemination through lymph and blood. With respect to orthopedic metal ions, such as Co, Cr, and Ni, alteration of T cells, B cells, and macrophages, release of modified cytokines, formation of immunogenic compounds, and direct immunotoxicity are effects caused by metals, as is a reduction in circulating lymphocytes, especially CD8 + T cells.[20,21]

- Carcinogenesis: Damage to DNA has been found to be caused by Co-Cr nanoparticles through a cellular barrier. Furthermore, a reduction in the number of circulating cytotoxic CD8 + T cells has been found, which are responsible for killing tumor cells.[20]
- The liver: Hepatocellular necrosis can be caused by high levels of metal in the body, as seen after acute ingestion of Cr in humans. Also, the inhibition of macromolecular synthesis in the liver can be caused by high concentrations of Cr (10-25 μM).[21]
- The kidney: The alteration of renal function, tubular necrosis and marked interstitial changes in experimental animals and humans, can be caused by high concentrations of Cr in the epithelial cells of the renal tubules.[13]
- Respiratory system: The increase in the incidence of asthma and inflammatory conditions is caused by exposure to Co, Ni and Cr.[13] Granulomatous lung disease has also been reported, along with chorioretinitis, erythema nodosum, and cardiomyopathy, caused by cobalt and chromium.[21]
- The nervous system: The accumulation of metal in the brain is related to neuropathological conditions, including amyotrophic lateral sclerosis, parkinsonian dementia, dialysis encephalopathy and the senile plaques of Alzheimer's disease, as well as oxidative damage in the brain, significant alterations in the visuospatial ability and attention span, especially by cobalt, chromium.[13]
- The heart and vascular systems: Cardiomyopathy and congestive heart failure can be induced by the accumulation of Co in the myocardium.[14]
- The musculoskeletal system: Osteomalacia, bone pain, pathological fractures, proximal myopathy, and lack of response to vitamin D3 treatment have been associated with metal deposition in the bone, negatively affecting osteoblast function, which in turn can influence the bone remodeling.[13]
- The endocrine system: Aberrant estrogen signaling is contributed by the binding of metals to cellular estrogen receptors, as well as an alteration in the production or circulation of sex hormones, caused especially by nickel, chromium and cobalt.[13] Cobalt even prevents the uptake of iodine in the thyroxine hormone by its inhibition of the enzyme tyrosine iodine, which can induce hypothyroidism.[14]
- The visual and auditory systems: Severe retinal degeneration can be caused by high concentrations of cobalt and nickel. Patients with high concentrations of chromium, cobalt, and molybdenum in serum and cerebrospinal fluid have also been reported to suffer from vision loss, hearing impairment, foot numbness, and dermatitis.[13,17]
- The skin: The most common skin reactions are contact dermatitis, urticaria, and vasculitis.[13]
- The reproductive system: Chronic exposure to chromium induces a decrease in sperm count, epithelial degradation, sperm abnormalities, reduced numbers of follicles and ovules, and an increased number of atretic follicles.[13]

Current management for poisoning from metals used in prosthetic materials

For asymptomatic and symptomatic patients with elevated levels of metal ions, recommendations for their management are issued by the UK and US regulatory agencies. Therefore, the FDA defines "symptomatic" as experiencing local symptoms (pain or swelling at or near the arthroplasty, as well as noise) more than 3 months after placement of a prosthesis. The general clinical presentation of the patient, including symptoms, physical findings, and other diagnostic results should also be considered when determining treatment scenarios.[14]
For symptomatic patients, the FDA recommends the following guidelines:

- Periodic clinical evaluation: At least every 6 months.
- Soft Tissue Imaging: Consider the Benefits and Risks of MRI, CT, and Ultrasound for Each Patient.
- Metal ion test: Consider monitoring metal ion levels in series. Currently, the most reliable test results are available for cobalt in EDTA anticoagulated blood. In repeated tests, use the same sample type, measurement method, and preferably the same laboratory.[14]

For asymptomatic patients, the FDA recommends the following guidelines:

- Periodic clinical evaluation: Usually at least once every 1 to 2 years.
- Soft Tissue Imaging: Not necessary if you feel the arthroplasty is working properly.
- Metal ion test: Not necessary if you feel the arthroplasty is working properly.[14]

For symptomatic patients who have metal-on-metal hip replacement implants, the following procedures are advised per MHRA management recommendations:

- MoM Hip Rejuvenation (Stemless)
- Total Hip Replacements with MoM Stem: Femoral Head Diameter < 36 mm
- Total hip arthroplasties with MoM stem: diameter of the femoral head ≥ 36 mm
- DePuy ASRTM Hip Replacements (All Types).[14]

The only treatment for metal poisoning present in orthopedic arthroplasties is surgery, to remove and replace worn metal. This stops the release of more metal ions. When replacing metal, diseased tissue and bone around the implant must be debrided.[21]

Due to severe poisoning, excess bone and tissue necrosis establishes the result of the surgery. During revision surgery, the metal-on-metal implant should be exchanged for a ceramic-on-metal or plastic-on-metal implant to minimize future problems with metal ions. According to case studies published in the State Epidemiology Bulletin, some patients may see a dramatic improvement in their symptoms three to six months after revision surgery.[21]

Analysis and synthesis of the information

In metal poisoning, data indicate that metal particles and ions are spread throughout the body through lymph and blood. This causes various clinical manifestations, mainly caused by cobalt, chromium, nickel and molybdenum, present due to the excessive use of hip replacement and knee replacement. Therefore, other implants that contain cobalt, chromium, nickel and molybdenum, such as spinal disc implants, shoulder arthroplasty, among others (see table 1) are at risk of metal poisoning.

A study by *Chang* et al. (2018) provides updated information related to biomaterials used in hip arthroplasty, showing promising clinical results of support surfaces.[5] This study supports our work in providing updated information but is only limited to total hip arthroplasty and its management, since our work provides additional information on clinical manifestations and systemic toxicity, focusing on different implants or orthopedic arthroplasties.

Another study by *Keegan* et al. (2007) provides information on the release, dissemination, absorption, biological activity, and potential toxicity of metal wear debris released from alloys used in orthopedics.[13] This work supports ours, but it needs to be updated.

Currently published evidence suggests that allergic or toxicity mechanisms alone do not explain most of the responses to metal implants, therefore further *in vitro* and *in vivo* studies are required to demonstrate their causality. More epidemiological studies are also required, due to the lack of evidence to demonstrate the various clinical manifestations and systemic toxicity. The limitations of our study is the little evidence from large-scale epidemiological studies that confirm the theory of the possible causes of toxicity by the different types of metals.

Conclusions

In conclusion, the results of this study show up-to-date information on metal poisoning, which can lead to diverse or varied clinical manifestations and suggesting that patients with knee arthroplasty, hip replacement, spinal disc implants and shoulder arthroplasty have a risk of developing toxicity.

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Conflict of interest

The authors declare no conflicts of interest.

Author´s Contribution

Jhonnier Villero Suárez: He integrated the clinical evidence and the theoretical review to generate the first draft of the manuscript; obtained, selected and described the figures and tables.

Juan Farak Gómez: He integrated the clinical evidence and the theoretical review to generate the first draft of the manuscript; obtained, selected and described the figures and tables.

Maryurin Pérez García: She integrated the clinical evidence and the theoretical review to generate the first draft of the manuscript; obtained, selected and described the figures and tables.

Josselyn Rojas Pérez: She performed the initial review, and made subsequent corrections to integrate the final manuscript.