Hypersensitivity in patients receiving metal implants: a scoping review protocol

Dzifa Dordunoo¹,2, Judith Anaman-Torgbor³, Catherine Smith⁴, Ajjoon Shaik⁵, Michelle Hass⁶, Carol Gordon¹,2, Minjeong An⁷, Martha L. Aviles-G¹, Miriam Weinzierl¹

¹School of Nursing/Human and Social Development, University of Victoria, Victoria, BC, Canada, ²The University of Victoria (UVic) Centre for Evidence-Informed Nursing and Health (CEiNHC): A JBI Affiliated Group, Victoria, BC, Canada, ³School of Nursing and Midwifery, University of Health and Allied Sciences, Ho, Ghana, ⁴School of Nursing, University of the Fraser Valley, Chilliwack, BC, Canada, ⁵School of Nursing, Camosun College, Victoria, BC, Canada, ⁶Scripps Health, San Diego, CA, USA, and ⁷College of Nursing, Chonnam National University, Chonnam, South Korea

ABSTRACT

Objective: The objective of this scoping review is to gather the available evidence on metal hypersensitivity to determine the extent of the problem and identify gaps in the evidence about screening practices.

Introduction: Hypersensitivity to metal was first reported in 1966. Since this time, the use of metal in prosthetic devices has increased with an associated rise in reported hypersensitivity reaction to other metals. Symptoms of metal hypersensitivity can be subtle, and it is unclear whether clinicians are aware of or routinely ask about metal hypersensitivity when documenting allergies. This can lead to a delay in diagnosis, which puts patients at risk of poor outcomes. Hence there is a need to map the available evidence on hypersensitivity reaction in people who receive metallic device implantation.

Inclusion criteria: The review will consider studies published in the English language and that include patients who undergo procedures involving metal implantations. All available literature from the 1960s to the present will be included in this review.

Methods: The proposed scoping review will be conducted in accordance with JBI methodology for scoping reviews. Searches will be generated in multiple databases and updated as needed. Results will be imported into Covidence where titles, abstracts, and full articles will be screened according to the inclusion criteria. Data will be extracted and findings will be presented in tabular form with a narrative summary.

Keywords

adverse reactions; allergy; hypersensitivity; implants; metal


Introduction

Metals are a key component of many prosthetic devices, which are implanted for cosmetic or life-saving reasons. There is an increased risk of adverse hypersensitivity events, described as a delayed-Type IV T-cell-mediated immunological response to metal ions-protein complexes among patients undergoing procedures involving metal implantation.¹,² Once thought to be a rare phenomenon affecting less than 0.1% of the population, hypersensitivity reaction to metal appears to be a growing public health issue because of the increased use of metals and their alloys in prosthetic devices.³,⁴ Metals that were considered inert and non-allergenic, such as titanium, are inducing similar reactions.¹

It is estimated that 10% to 15% of the general population have hypersensitivity reactions, such as contact dermatitis, following cutaneous exposure to metal.¹ The true estimate of hypersensitivity to metallic device implantation is difficult to ascertain; however, estimates of procedures involving metal implants illustrate the potential extent of the hypersensitivity reactions. In the United States alone, it is estimated that seven million people underwent either total hip or knee arthroplasty in 2010.⁵ Metal hypersensitivity is estimated to occur in up to 60% of patients with a failed or poorly functioning metal
implant. With the projected increase in ageing of the global population, the need for procedures involving metal implants, and subsequently inducing hypersensitivity reactions, are likely to increase. First reported in 1966, nickel is perhaps the most widely recognized metal sensitizer, with an increasing prevalence rate of 19% over a 12-year period in North America alone. Nickel hypersensitivity awareness has led to legislation in efforts to reduce sensitization rates in European Union countries and Denmark. Overall, these legislations in Europe have resulted in decreased sensitization rates as well as an estimated US$2 billion cost saving over a 20-year period in these European countries. Increasingly, studies are showing hypersensitivity reactions to other types of metals; for example, patients with hypersensitivity to the iron, nickel, molybdenum, or chromium compositions of coronary stents are nearly three times more likely to experience in-stent restenosis compared to those without metal hypersensitivity. Similar findings are reported in patients undergoing orthopedic, dental, gynecologic, and neurosurgical procedures involving metal implants.

Metal hypersensitivity reactions can include allergic contact dermatitis, urticaria, vasculitis, swelling, pain, delayed healing, implant failure, and restenosis. Ultimately these reactions can lead to implant removal or revision when feasible. The term adverse reaction to metal debris (ARMD) has also been used to describe metal-related complications like pseudotumor, osteolysis, metallosis, and aseptic loosening of prostheses. Although it is postulated that hypersensitivity reaction may underlie these complications, it is unclear if the hypersensitivity reactions, such as swelling and pain, represent early manifestation that progresses to more serious reactions like pseudotumor. This review will only include studies that address metal hypersensitivity without association with ARMD.

The frequency of adverse events associated with medical procedures involving metal prosthesis is largely unknown because symptoms of metal hypersensitivity can be subtle, delaying diagnosis that can result in increased morbidity and health care costs. Factors contributing to the delay of diagnosis and recognition of this condition is the lack of awareness of metal hypersensitivity among clinicians and inconsistent clinical practice. It is not clear whether clinicians routinely ask about metal hypersensitivity when documenting allergies, thus this is often not considered in the differential diagnosis and is likely unreported; for example, only 11% of orthopedic surgeons always or often screen patients for metal hypersensitivity. Anecdotal evidence from our own clinical practice also suggests that nurses do not routinely ask about metal hypersensitivity when documenting allergies. Moreover, metal alloys are incorporated into many prosthetic devices and although the package inserts for various prostheses, such as coronary stents, note hypersensitivity to various metals as contraindication for use, clinicians without knowledge of the prosthetic composition or the package insert information are less likely to ask about metal hypersensitivity. Thus, we will conduct this scoping review of published studies to determine the scope of metal hypersensitivity, specifically mapping current practice to the available evidence.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted and no current or in-progress systematic reviews on the topic were identified. Prior systematic reviews have been identified; however, these reviews focused predominantly on the outcomes of metal implants in specific procedures. The narrow scope of these reviews, in addition to the fact that metal hypersensitivity is underreported due to general lack of awareness, may create an environment where clinicians erroneously believe that metal hypersensitivity is isolated to certain metals and/or procedures, or forgo screening patients, which could further exacerbate underreporting, delayed diagnosis, and increased risk to patient safety. The aim of this current review is to gather data from the available literature to determine the scope of the evidence about hypersensitivity reaction.

**Review question**

What is the available evidence on hypersensitivity reaction among patients undergoing metallic device implantation? Specifically, we aim to synthesize the evidence regarding populations, procedures, types of metal, clinical symptoms, and management of metal hypersensitivity. A secondary aim of this scoping review is to identify gaps in the evidence regarding screening practices for metal hypersensitivity.
Inclusion criteria
Participants
The review will consider studies published in English that include patients of all ages who undergo procedures involving metal implantations. This review will exclude studies involving animal studies, laboratory experiments, metal salts administered as medicine (eg, calcium, iron, magnesium), and non-metallic implants.

Concept
The concept of metal hypersensitivity will be explored in this scoping review. There are four broad classifications of hypersensitivity reactions. It is suggested that the type of hypersensitivity reaction seen in patients following metal implantation can be either Type I or Type IV. Evidence suggests Type I hypersensitivity to metal can be due to atopic B-cell mediated reaction aided by the production of immunoglobulin E; while most commonly experience Type IV, delayed T-cell mediated reaction. The mechanism underlying Type IV T-cell mediated, also known as delayed hypersensitivity, is a corrosive process that occurs in the biological system where metal ions are released. The metal ions act as haptens, interacting with proteins in the body to trigger the hypersensitivity response. It has also been suggested that these reactions may occur concurrently, with some people becoming sensitized following procedures such as ear-piercing or exposure to jewelry, while others presumably become sensitized following metal implantation. To the best of our knowledge, it is unclear whether nickel is the only metal known to elicit Type I reaction, thus, in this review we use the term “hypersensitivity” indiscriminately; however, in publications where the distinction is made between Type I or IV, we will highlight it. In addition, we use the terms “hypersensitivity” and “allergy” interchangeably. Such contextual information includes, but is not limited to, the type of procedure, metal(s) involved, diagnostics procedures, screening practices, treatment(s), and when available, resolution of symptoms. This data will help identify gaps in the evidence about screening practices.

Context
The context of the review is procedures involving the implantation of a device that has metal components. Implantation is further defined as a permanent integration of a foreign (non-biological) object into the human body to help restore function. Contextual information about the clinical presentation and management described in the literature will be reviewed and reported.

Types of sources
This scoping review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies, and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies for inclusion.

Qualitative studies that focus on exploring the meaning of the phenomenon including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research will also be considered. In addition, a scoping or systematic review that meets the inclusion criteria will also be considered. All available literature from 1960 to the present will be included in this review.

Methods
The proposed scoping review will be conducted in accordance with JBI methodology for scoping reviews as outlined in the JBI Reviewers’ Manual.

Search strategy
The search strategy will aim to find published studies and reports. A three-step approach will be utilized in this review. An initial limited search (Appendix I) of MEDLINE, Cochrane Database of Systematic Reviews, JBI Database of Systematic Reviews and Implementation Reports, PROSPERO, and CINAHL was followed by analyzing the text words contained in the title and abstract of relevant papers, along with the controlled language index terms used to describe the papers. No current systematic or scoping reviews addressing the review question were identified. A second search using these identified keywords and index terms will then be conducted across all included databases, adapting the strategy when necessary to the search interface of each database. In the third step,
the reference lists of all included reports and articles will be searched for additional papers. In addition, a gray literature search strategy was developed incorporating gray literature databases such as ProQuest Dissertations and Theses, greylit.org, and opengrey.eu, as well as relevant organizational websites (e.g., Food and Drugs Administration and CADTH). We used keywords based on those found in our database search strategies, and the searches were iterative, as is typical for gray literature searching.

Information sources
The databases to be searched include MEDLINE (EBSCOhost), CINAHL (EBSCOhost), Web of Science, as well as Google Scholar and a limited search in PubMed to ensure all relevant gray literature are uncovered. Additional sources of unpublished studies and gray literature to be searched include ProQuest Dissertations and Theses, greylit.org and opengrey.eu, and limited search of organizational websites identified by the expert advisory team.

Study selection
Following the search, all identified citations will be collated and uploaded into Covidence (Veritas Health Information, Melbourne, Australia) and duplicates removed. Titles and abstracts will then be screened by three independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into Covidence. The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the scoping review. Included studies will be imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide Australia). Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved with a third reviewer. The results of the search will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR) flow diagram.

Data extraction
Data will be extracted from papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers. The data extracted will include specific details about the population, concept, context, study methods, and key findings, including treatment relevant to the review objective. A draft charting table is provided (see Appendix II). The draft data extraction tool will be piloted, modified, and revised as necessary during the process of extracting data from each included study. Modifications will be detailed in the full scoping review report. Any disagreements that arise between the reviewers will be resolved through discussion. Authors of papers will be contacted to request missing or additional data, where required.

Data presentation
The extracted data will be presented in tabular form in a manner that aligns with the review questions. A narrative summary will accompany the tabulated results and will describe the current state of the research evidence and whether or not recommendations have been made about screening for metal hypersensitivity.

Acknowledgements
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References
Appendix I: Search strategy

CINAHL (EBSCOhost). Search conducted on July 3, 2019

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MEDLINE (EBSCOhost)

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# Appendix II: Data extraction instrument

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<th>Procedure</th>
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<th>Clinical symptoms (eg, type symptoms, duration of symptoms)</th>
<th>Diagnostics</th>
<th>Treatment (incl resolution of symptoms)</th>
<th>Key findings about screening practices</th>
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*RCT, systematic review with or without meta-analysis, quasi experimental, qualitative with or without meta-synthesis, clinical practice guidelines, consensus panels (ie, association), case reports, case series, nationally recognized experts, integrative literature review, scoping review, commentary, observational.