Allergic Sensitization to Nickel and Implanted Metal Devices: A Perspective

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Abstract: There is continuing interest in the interrelationships between allergic sensitization to metal allergens, metal implants, and the development of adverse reactions to implanted devices. Here, we focus on sensitization to nickel (although, in practice, it is commonly not possible to distinguish between events associated with nickel and other potentially allergenic metals used in devices). The purpose of this article was to review whether exposure to nickel resulting from implanted devices is associated with the development of de novo sensitization to nickel and also whether nickel sensitization, either newly acquired or pre-existing, has a causal relationship with adverse health effects. In addressing these issues, a variety of devices, including metal-on-metal hip implants, cardiac and endovascular stents and filters, and the gynecologic implant Essure, are considered. Also addressed is the question of whether pre-operative assessment of nickel allergy (and allergy to other implant metals) is required. The conclusions reached are that (a) sensitization can potentially be acquired as the result of exposure to implants containing nickel, but is not a common occurrence; (b) sensitization to nickel and/or other metal allergens is very rarely a cause of adverse reactions to implants; and (c) routine preoperative patch testing for sensitization to nickel is unnecessary, unless there is a significant clinical history of nickel allergy.

There is a long history of the use of metals and metal alloys in medical implants.† Naturally, this has been associated with a corresponding interest in the extent to which exposure to metals associated with implantation can result in adverse health effects. A comprehensive review of this subject has recently (2019) been prepared by the US Food and Drug Administration Center for Devices and Radiological Health.‡ Other more focused reviews are also available.§

The aim of this perspective is less broad in scope and is focused largely on the association between exposure to nickel resulting from medical implantation and skin sensitization and allergic contact dermatitis (ACD). This is a relevant question to address given the widespread use of medical devices containing nickel and the prevalence of nickel ACD. The objective is to consider generically the extent to which such exposure to nickel can drive the acquisition of skin sensitization to this metal and whether and to what extent acquired or pre-existing nickel sensitization is a cause of adverse reactions to metal implants. Although the article will focus primarily on hip implants, other implants (including stents and other orthopedic implants) that have the potential to result in exposure to nickel will also be considered.

To this end, the article will address in order: (a) skin sensitization to nickel at molecular, cellular, and clinical levels; (b) the acquisition of skin sensitization to nickel resulting from metal implants; (c) whether skin sensitization to nickel resulting from metal implant exposure, or pre-existing nickel allergy, is a cause of adverse reactions to implants and implant failure; and (d) whether metal implantation is contraindicated by pre-existing nickel allergy.

NICKEL ALLERGY: MOLECULAR AND CELLULAR MECHANISMS AND CLINICAL MANIFESTATIONS

Most contact allergens are organic chemicals. However, metals can also cause skin sensitization and ACD, and indeed, metal ions are among the most frequent causes of ACD.α–β The transition metals nickel, cobalt, chromium, and probably palladium are the most common metal allergens, being active as ions after oxidation and dissolution/solubilization.α–β

The ability of low–molecular-weight electrophilic chemical allergens to form stable associations with host proteins as being an essential first step in immune recognition and the acquisition of skin sensitization is well established as the “electrophilic theory.”α−β Naturally,
this raises questions regarding the mechanisms through which allergenic metals are able to engage with the immune system, such as to provoke an adaptive immune response that would result in sensitization. A key observation was made in 1991 by Romagnoli and colleagues who demonstrated that nickel could bind with a histidine residue in a peptide associated with a major histocompatibility complex (MHC) molecule. The argument was that metal ions could associate with 1 or more metal binding motifs displayed by self-peptides complexed with MHC molecules. Further progress was reported with the description of a human nickel-specific T-lymphocyte clone that was able to recognize Ni\textsuperscript{2+} in the context of a peptide associated with an MHC class II determinant expressed by antigen-presenting cells (APCs). It was also found that T-lymphocyte activation by Ni\textsuperscript{2+} could be achieved by nickel directly cross-linking the T-cell receptor to an MHC class II determinant, without the need for interaction with a peptide. It is clear that there may be more than 1 mechanism through which nickel can trigger T-lymphocyte responses. More detailed reviews of the cellular and molecular bases for metal allergy are available elsewhere.

In summary, metal allergy (and for the purposes of this article, nickel allergy in particular) can be distinguished from allergy caused by organic chemicals in the following way. For the induction of skin sensitization to organic chemicals, there is a need for the formation of stable (covalent) associations with host proteins to create a hapten-protein conjugate. This requires that sensitizing chemicals are naturally electrophilic or can be converted to an electrophilic species in the skin. Hapten-modified proteins are processed by APCs, and the resultant haptenated peptides are displayed in the context of MHC gene products for recognition by T lymphocytes bearing complementary antigen receptors. In contrast, metal ions form spatially highly defined coordination bonds with electron donors, such as oxygen and nitrogen, in the amino acid side chains of proteins. It is these very specific coordination complexes that facilitate immune recognition and the triggering of an immune response culminating in the acquisition of sensitization to nickel.

The brief description hereinabove summarizes the cellular and molecular mechanisms through which nickel can trigger an adaptive immune response. However, it must be appreciated that for stimulation of a robust immune response, there is a need for costimulatory signals (commonly referred to as danger signals) that result from activation of the innate immune system. This is a requirement for the induction of a fully effective adaptive immune response to both classical haptens and metal ions. Signals relevant for immune responses to sensitizing chemicals and metals are known collectively as damage-associated molecular patterns. These signals are expressed after cell damage, cell death, or inflammation. They interact with receptors (pattern recognition receptors) on immune cells, and these interactions in turn triggers events that are associated with, and required for, the initiation of an adaptive immune response. Among these events is the elaboration of cytokines and interleukins that drive effective antigen presentation and T-lymphocyte activation, division, and differentiation.

Among the pattern recognition receptors that recognize danger signals are the toll-like receptors (TLRs) of which there are many. Nickel ions can directly trigger the homodimerization and activation of TLR4 (one of the family of human TLRs), and that this is essential for the development of sensitization to this metal.

The induction of an immune response to nickel, which will result in allergic sensitization requires an appropriate interplay between the innate and adaptive immune responses and the creation of an Ni\textsuperscript{2+} recognition unit in association with MHC determinants that can be displayed by APCs to activate responsive T lymphocytes.

**EXPOSURE TO NICKEL IN METAL IMPLANTS AND THE ACQUISITION OF ALLERGIC SENSITIZATION**

**Consideration of Exposure Metrics**

The question addressed here is whether exposure to nickel ions from implants can result in sensitization in previously unsensitized subjects. The question is legitimate because there will clearly be the opportunity for some level of exposure to nickel in those with certain implants. However, whether exposure will necessarily result in sensitization is dependent on a number of factors, including the inherent susceptibility (genetic and nongenetic) of the subject, although, in the case of nickel allergy, it has proven difficult to find a genetic basis for predisposition. Of importance also will be the level of exposure (which will in turn be governed by the nature of the implant itself and the extent to which nickel ion release has been facilitated by wear), and the context in which exposure to nickel ions occurs. However, in the context of implants, there is no reason to suppose that even in susceptible subjects, the acquisition of sensitization will be a function only of the level of exposure.

Naturally, these are studies of skin sensitization and ACD that have informed much of our current understanding of the factors governing the acquisition of sensitization to low-molecular-weight chemicals and metals. It is relevant to consider briefly the factors known to affect the development of skin sensitization to illustrate some of the important variables that are likely to influence whether exposure to metal ions deriving from implants will drive allergic sensitization.

Skin sensitization is induced after topical exposure to a contact allergen. It is now clear that in most circumstances, the important metric of exposure related to the acquisition of sensitization is the dose per unit area of chemical at the skin surface. This holds true except for circumstances where the area of exposure is small. Thus, at skin surfaces, and doubtless at other anatomical locations, the local concentration of antigen (in this instance, a contact allergen) and its distribution will each have important influences on the effectiveness of sensitization. There is a requirement for a certain minimum level of antigen to be available locally for an immune response to be triggered. In the skin, antigen has to engage effectively with cutaneous antigen processing/presenting dendritic cells (DCs), including epidermal Langerhans cells, which are responsible for
processing the antigenic moiety and transporting it, via afferent lymphatics, to regional lymph nodes where it can be presented to responsive T lymphocytes.34–36

The induction of immune responses (including immune responses to Ni ions) in other anatomical locations will require a similar engagement of antigen with local DCs and the migration of antigen-bearing DCs to draining lymph nodes. Naturally, however, the effectiveness of sensitization will depend not only on the local concentration of Ni ions but also on the induction of relevant danger signals, the availability of adequate numbers of DCs, and the alignment between anatomical sites of exposure and regional lymph nodes in which adaptive immune responses are initiated.22–24 The critical point here is that it is not only the levels of nickel ions that will determine whether sensitization might develop but also the local anatomical and physiological conditions under which exposure occurs. A further consideration is that it is theoretically possible that exposure to nickel under some circumstances and, in some anatomical locations, could induce immunological tolerance rather than sensitization. In mice and guinea pigs, tolerance to nickel can be induced by oral administration of nickel sulfate.37,38 In humans, there is some evidence that early exposure oral exposure to nickel (via orthodontic braces) is associated with a reduced frequency of nickel ACD.39–41

It is now well established that contact allergens differ significantly (by at least 5 orders of magnitude) in terms of their relative skin sensitizing potency.34 In this context, potency can best be defined as the ease with which a contact allergen encountered at the skin surface is able to induce sensitization. In practice, the potency of contact allergens is reflected by the amount of chemical (measured as dose per unit area of skin) that is required to induce sensitization. The higher the potency of a chemical, the lower will be the dose required for sensitization to be acquired. Thus, for contact allergens of low potency, higher concentrations will be necessary for sensitization.34 Although the potency of contact allergens is measured conventionally as a function of the concentration of the chemical at the skin surface required to drive sensitization, there is every reason to believe that differences in potency will be manifest if exposure occurs at other anatomical sites. Considerations of potency are relevant when exploring the ability of nickel derived from implants to cause sensitization because, although the prevalence of nickel allergy is relatively high among the general population, nickel is actually regarded as having limited, and at best, intermediate, sensitizing potency in humans.42 In this context, nickel is known to be significantly less potent than many chemicals commonly associated with ACD.42 In summary, the ability of a contact allergen, in this case nickel, to induce sensitization will be influenced by the intrinsic potency of the allergen, the extent of exposure (and, in particular, local concentrations of the allergen), the availability of DCs, the stimulation of danger signals, and anatomical alignment with draining lymph nodes. Although it is acknowledged that under most conditions of exposure (other than skin exposure), it will not be possible to evaluate many (if any) of these variables, it is important to appreciate that exposure per se, especially exposure measured at a systemic level, will not necessarily equate with the risk of sensitization.

Implant-Driven Sensitization to Nickel

Implanted metal devices are of various compositions. For safety and reliability, implants are made of corrosion-resistant alloys that do not release significant levels of metal ions and are designed to be durable and resistant to corrosion. The United Nations Globally Harmonized System of Classification and Labelling define an alloy as “… a metallic material homogenous on a macroscopic scale, consisting of 2 or more elements so combined that they cannot be readily separated by mechanical means.”43

Commonly used metal alloys include stainless steel, non-stainless steel cobalt-chromium-nickel alloys, cobalt-chromium alloys, and titanium alloys (including nitinol). The stainless steel used most commonly for orthopedic implants (type 316L modified) contains nickel, chromium, and a small amount of cobalt as an impurity; all of which are well-known allergenic metals in the context of exposure via the dermal route and skin sensitization. Nitinol is a malleable alloy with a composition that comprises 55% nickel and 45% titanium. However, it is important to appreciate that composition alone does not correlate with or predict any potential for adverse health effects.

The clinical use of implanted metal devices is broad, with various applications, including orthopedic (dynamic joint and fixed devices), endovascular (stents and other devices), gynecologic (Essure), neurological (intracranial stents), and dental (dental implants).44 Clearly, there is considerable variation in anatomical locations, opportunities for wear and metal release, and the conditions of exposure to various metals. However, the exclusive focus of this article is on exposure to nickel resulting from implanted devices, considering in the first instance whether implants containing nickel can result in allergic sensitization to this metal.

There are 2 approaches available for determining whether sensitization to nickel might be associated with a metal implant. The first is, of course, conventional patch testing that is the mainstay for the diagnosis of ACD. This is typically conducted using patches containing 5% nickel sulfate in petrolatum and is considered to be a reliable basis for the clinical diagnosis of sensitization to nickel. The second is the lymphocyte transformation test (LTT). This is an experimental tool that is not used clinically for diagnosis of sensitization. This latter test seeks to determine whether the immune system of a subject has been primed to a particular antigen by culturing peripheral blood lymphocytes with a source of that antigen. The principle is that if the immune system has been primed to an antigen (in this case, contact allergen) in vivo, then culture of lymphocytes with that antigen in vitro will result in a proliferative response (lymphocyte transformation). The theoretical basis is that only if there has been prior priming to an antigen in vivo, the pool of responsive T lymphocytes will have been expanded sufficiently in number to display a discernible proliferative response in vitro. In theory, the LTT can be conducted with any antigen. However, in practice, it has
proven much easier and more reliable to conduct the LTT with metal allergens, rather than with low-molecular-weight chemical allergens. The reason for this is that to conduct an LTT with the latter, it is necessary to present the allergen in vitro in the form of a conjugate with protein, and this creates both technical difficulties and uncertainty that the antigen is being delivered in a relevant molecular context. The LTT test has been used widely in experimental systems for evaluating sensitization to nickel. Although the reproducibility of this method has been questioned, there are reports in the scientific literature of the LTT being able to distinguish between nickel-sensitized and nonsensitized subjects with some accuracy.45,46

More recently, there have been attempts to improve the LTT by the introduction of additional or alternative end points, such as analysis of activation-induced cytokine production by cultured lymphocytes,47 or by measurement of the proliferation of a particular subset of T lymphocytes (memory T helper cells).48 However, most data relating to metal hypersensitivity associated with implantation derive from the standard LTT assay.

It has been suggested that because there may be differences between cutaneous allergic reactions and systemic sensitization, the LTT might provide a more accurate method for identifying sensitization resulting from a metal implant.49 It is, however, the view of the present authors that both methods (although each has limitations) if properly conducted provide a legitimate means of determining whether sensitization has resulted from exposure to a medical device, and in practice, both approaches have been used for this purpose. It must be emphasized again, that in standard clinical practice, only patch testing is used for diagnostic purposes.

Allergy to various metals (including nickel) was first described as a complication of metal implants in the 1960s,50 and this was confirmed thereafter by other reports of allergy associated with orthopedic implants.51-53 More recently, studies using patch testing and/or the LTT have investigated the development of sensitization to metals associated with orthopedic implants. For instance, it was found by Hallab and colleagues54 that a significant fraction of patients who had received a hip implant developed reactivity to metals, including nickel, as measured using an LTT. A variety of other investigations have found that orthopedic implants may be associated with the development of sensitization to metals, including nickel, in some patients.55-59

With respect to orthopedic implants, it is possible to draw the general conclusion that although there is evidence that in some subjects, such implants may induce allergic sensitization to metals, there seems not to be a clear correlation with the estimated level of exposure or with the status of the implant.44,60,61

This conclusion leads to the important question of whether sensitization is a cause of adverse reactions to metal implants or implant failure. That question will be addressed in the next section.

Before considering the implications of metal allergy, it is appropriate to examine briefly whether other types of metal implant have been associated with sensitization to nickel (or other metals).

In addition to hip implants, there is evidence that sensitization to metals (chromium, nickel, and cobalt) can be associated with total knee replacement.62,63 In addition, as well as dynamic orthopedic implants, fixed devices, such as screws and plates, have occasionally been implicated as causes of allergic reactions.64 There is, in addition, evidence that cardiovascular stents and devices, which are frequently manufactured from stainless steel or nitinol, are rarely associated with metal allergy.65,66 Finally, allergy to nickel and other metals has also been reported in those with metallic dental implants.67

In summary, the available evidence indicates that metal implants of various types used in different anatomical regions may be implicated in the development of sensitization to nickel and other metals. Although the clear implication is that de novo sensitization will result from exposure to metal ions released from the implant, it is not possible to draw conclusions about the levels of exposure that will induce sensitization, other than the assumption that the higher the level of exposure, the greater the likelihood that sensitization may be acquired. One important reason why it is difficult to discern clear dose-response relationships is that as discussed previously, the development of sensitization will undoubtedly be influenced by a variety of factors, including the anatomical site and local microenvironment, in which interaction of metal particles or ions with the immune apparatus takes place. Perhaps consistent with this is the fact that a study of metal release and metal allergy showed that a significant increase in the levels of metal ions (in this case, cobalt and chromium ions) measured in the urine was not associated with an increase in metal allergy.68

It can be concluded that in certain circumstances where there are high levels of surface wear, exposure to nickel from implanted devices may occasionally result in sensitization. However, given the low incidence of nickel sensitization attributable to implantation compared with the large number of implants used in patients, it would seem that the potential for nickel allergy from medical implants is limited.

The more important question from a clinical perspective is whether de novo sensitization to nickel (or other metals) resulting from implantation, or pre-existing sensitization, is a cause of adverse reactions to metal implants, or of implant failure.

**Nickel Allergy and Adverse Reactions to Metal Implants**

The issue addressed here is whether allergic reactions to metals are a cause of adverse health effects in subjects with implants. In addressing this question, it is important to appreciate that although metal exposure from an implanted device can in certain circumstances cause sensitization, a positive patch test for metal allergy does not prove symptom causality.44 It is instructive to consider first the case of metal-on-metal (MoM) hip implants that contain cobalt, chromium, and nickel at ratios of approximately 64:28:1. Although nickel is a minor component compared with cobalt and chromium, MoM hip implants do provide a rich source of information for addressing the question whether allergic reactions to metals per se are an important cause of adverse health effects.

Concerns were raised regarding the potential of MoM hip implants to cause adverse reactions associated with local tissue damage. A range of reactions has been reported that have been described
collectively as adverse reactions to metal debris (ARMD).$^{69–73}$ Although ARMD is an important adverse health effect, the prevalence among those receiving a hip implant is relatively low. For example, it has been shown that despite comprehensive screening, levels of ARMD remain low at a 5-year follow-up of MoM total hip replacements.$^{74}$

Consistent with the presence of a lymphocytic infiltrate in some cases of ARMD, it has been proposed that some adverse reactions and MoM hip implant failure can be associated with an immune or allergic-like reaction in periprosthetic tissues. This has been described as aseptic lymphocytic vasculitis and associated lesions.$^{75–78}$ These observations raised the question of whether sensitization to metal ions plays a role in implant failure or alternatively (and conversely) whether increased wear debris released as a result of loosening of the prosthesis induces sensitization.$^{79–81}$

That is a question that has proved difficult to answer with certainty. However, there are reasons to suggest that allergic sensitization and allergic reactions are not a major cause of ARMD or implant failure. As cited previously, Hallab et al$^{54}$ in 2013 reported that many patients who had received a MoM hip implant developed reactivity to metals on the basis of LTT measurements. Importantly, however, the authors acknowledged that it was unclear whether such responses herald the development of adverse health effects or are associated with implant failure.$^{54}$ It is relevant also that Langton et al$^{72}$ in 2010 failed to identify responses to metal ions using the LTT, even among patients requiring implant revision. Other studies have also suggested that metal allergy seems not to play an important role in hip implant failure.$^{55,56,62,82,83}$

It would seem, therefore, that sensitization to metals may be acquired (albeit rarely) by patients who have received an MoM hip implant or that sensitization could possibly have predated implantation. Moreover, in some instances, there may also be evidence of an immune hypersensitivity reaction. However, taken together, there is no consistent evidence that sensitization to metals, however acquired, is an important contributor to ARMD or to the failure of hip implants.

Consistent with that view are conclusions drawn by other authors. Teo and Schalock$^{59}$ in 2017 found that there was no clear conclusion regarding a link between metal allergy and implant failure. Similar views were expressed by Thyssen and colleagues$^{83}$ who found that the risk of surgical revision was not increased in patients with metal allergies and that the risk of metal allergy was not increased in those who had received surgical revision compared with controls. They concluded also that the risk of complications in metal allergic patients seems limited.$^{83}$ Other investigators have reached similar conclusions. For instance, Schalock et al$^{44}$ in 2016 stated that metal exposure from implanted devices can cause sensitization but that a positive test for sensitization does not prove symptom causality.$^{44}$ Similarly, Wawrzynski et al,$^{64}$ in 2017, found that patch test reactivity to metals does not correlate with the status of orthopedic implants. Finally, Furrer and colleagues$^{44}$ in 2018 reported on a retrospective clinical study of patients with orthopedic implant complications. They concluded that factors other than allergy, such as the type of replaced joint and mechanical stress, seem to be of greater relevance for implant-related complications. Their view was that sensitization to metals (and other materials) seems rarely to play a role and is overestimated.$^{84}$

As indicated previously, nickel is not a major component of MoM hip implants, and it is likely that in this instance, sensitization to cobalt and chromium will be more common. Nevertheless, the data summarized previously illustrate that although the release of metal ions can result in sensitization, there is little evidence to suggest that allergic reactions play an important role in driving adverse responses to implants. A more plausible theory is that it is not sensitization that causes abnormal wear of metal implants, but conversely, that it is wear, and the release of metal ions, which may, in some instances, induce sensitization.

Before leaving the example of MoM hip implants, it is, for completeness, relevant to consider briefly a study that was conducted to explore the immunologic activity of wear particles in mice. It is, of course, important to emphasize that it is not possible to recapitulate in experimental animals the complexity of interactions that will occur in humans between the immune system and metal implants and wear particles deriving from such implants. It must also be borne in mind that the molecular interactions required for the stimulation of immune responses to nickel (and cobalt) are known to differ between humans and mice.$^{75,76}$

Acknowledging these limitations, studies in mice can, however, be instructive for examination of dose-response relationships under a given set of circumstances. The study was conducted by Tvermoes et al.$^{85}$ Mice were exposed to various concentrations of metal particles, metal salt mixtures, or both, and the stimulation of immune responses in draining lymph nodes measured. To summarize the results, it was found that the level of wear required for immune stimulation was 800 times higher than the amount of wear that would be expected to be released in 1 day from a normally functioning MoM hip implant ($<1$ mm$^3$/y or approximately $0.003$ mm$^3$/d)$^{86}$ and also significantly higher than the amount of wear that would result from the most extreme wear conditions ($>90$ mm$^3$/y).$^{73}$ As discussed earlier, because of a number of variables (including anatomical location, differing wear rates, the local availability of DCs, sources of danger signals, and positioning relative to lymphatic drainage), it is not possible to define clear relationship between levels of exposure to metal wear and opportunities for immune activation. Nevertheless, despite the limitations of animal studies, the results summarized previously suggest that under most conditions of exposure, there be little opportunity for the elicitation of immune responses to metals.$^{85}$

It can be argued that MoM hip implants provide a worst-case scenario for the release of metal ions and that compared with other implanted metal devices, they present the greatest opportunity for the development of de novo sensitization. It is not unreasonable to propose, therefore, that with other types of metal implants, where exposure to metal ions is expected to be lower, there will be a similar absence or low frequency of adverse health effects that might be attributable to an allergic reaction.

Nevertheless, it is appropriate to consider here other implants where nickel is a major component of the device. One such example
is nitinol, a shape memory alloy of nickel (55%) and titanium (45%). Nitinol has attractive properties for medical devices, including elasticity, biocompatibility, and fatigue resistance. As a result, nitinol has found wide application including use in cardiac devises and endovascular shunts and filters, and these are considered briefly here.87

There are case reports of possible nickel-allergic reactions to cardiac and endovascular devices. Among these are instances of a reaction after implantation of a nitinol vena cava filter,88 a systemic allergic reaction after placement of an arterial nitinol stent,89 and generalized dermatitis in a nickel-allergic patient after placement of a stent in the popliteal artery.90 However, there is no doubt that such cases are rare.65,91,92 Thyssen et al93 reported that nickel and/or chromium allergy seems not to increase the incidence of in-stent restenosis with stainless steel stents. Similar conclusions were drawn from another study that failed to find a causal relationship between nickel allergy and in-stent restenosis.94 In further agreement with this conclusion were the results of a single-center retrospective study that failed to find any association between nickel (or chromium) allergy and early or late adverse outcomes after coronary stent implantation.95

It is likely that the rare reactions reported about nickel-containing endovascular and cardiac devices that have been reported are associated with preexisting nickel allergy, rather than the acquisition of sensitization after implantation. The same no doubt holds true for other nickel-containing implant materials used for dental implants and for treatment of pectus excavatum (Nuss procedure).

Finally, given recent interest in adverse reactions to Essure, it is appropriate to consider the possible relationship between such effects and nickel allergy. Essure is a nickel-containing (nitiol) device implanted in the fallopian tube for the purpose of permanent contraception. It was approved by the Food and Drug Administration in 2002, and by 2015, an estimated 750,000 women had undergone the procedure to receive Essure.96 Since the introduction of this device, there have been increasing numbers of reports claiming adverse effects (and concerns about efficacy), and hypersensitivity to nickel was proposed as one possible cause of some of the problems.

There have been some sporadic suggestions, based on case studies and case series, of a possible role for nickel hypersensitivity.97–99 However, even then, the view of the authors of such reports has been that the incidence of confirmed reactions to nickel associated with exposure to Essure is extremely low98,99 and that such very rare complications should not dissuade patients from the use of this device.99 Indeed, the incidence of Essure-associated nickel allergy is very low, and it has been reported that a positive patch test to nickel does not correlate with adverse reactions.100,101

A recent investigation sought to determine whether a correlation exists between sensitization to nickel and adverse events attributed to Essure. A total of 39 women who had presented with adverse reactions to Essure were recruited into the study and patch tested for nickel sensitization before implant removal. It was concluded that nickel allergy was not responsible for adverse reactions of Essure.102

There is one other point to be made that may, or may not, be related to exposure to nickel via Essure. It has been found that among

**Pre-implant Patch Testing: Is There a Need?**

Some authors, commonly from an orthopedic background, have suggested that consideration be given to routine preoperative patch testing.63,104 However, it is the view of the present authors that the situation is far from clear-cut. Therefore, in addressing this question, there is a number of factors that should be considered. These are, in no particular order of importance, as follows: (a) sensitization to metals seems not to correlate with the development of adverse reactions to implants, (b) a positive patch test to nickel does not necessarily herald allergic reactions to a metal implant, and (c) an overly cautious approach might deny patch test–positive subject access to the important health benefits of metal implants.

On the basis of those considerations, it can be argued that routine pre-operative patch testing is not required. Perhaps a balanced approach as suggested by experienced physicians provides a pragmatic solution. Thus, Thyssen and colleagues60 in 2011 recommended that clinicians should “refrain from routine patch testing prior to surgery unless the patient has already had implant surgery with complications suspected to be allergic, or has a history of clinical metal intolerance of sufficient magnitude to be of concern to the patient or a health provider.” Similarly, Schalock et al14 in 2016 voiced the following opinion: “Routine pre-operative evaluation in individuals with no history of adverse cutaneous reactions to metals or history of previous implant-related adverse events is not necessary. Patients with a clear self-reported history of metal reactions should be evaluated by patch testing before device implant.”

**Concluding Comments**

Questions of whether exposure to metal implants can drive de novo allergic sensitization to nickel and other metal allergens and whether

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there exists a causal relationship between newly acquired or preexisting sensitization and the development of adverse reactions to metal devices are intriguing and important questions. Furthermore, definitive answers are far from simple as the available data typically are derived from individual cases, small case series, and meta-reviews thereof. Such a situation is likely to persist, because randomized controlled trials would be unethical. Hence, conclusions will always be expert opinion.

One conclusion drawn from this review is that sensitization to nickel can potentially be acquired from exposure to metal implants but that this is not a common occurrence. Moreover, it is not clear what factors, other than the inherent susceptibility of the subject, would predispose to the development of sensitization from a metal implant. It is probable that many variables may be influential including the nature and local concentrations of wear debris and metal ions, the anatomical site of exposure, the availability of DCs, danger signals and other components of the immune system, and alignment with the lymphatic system.

Irrespective of whether sensitization to nickel is pre-existing or has been driven by the metal implant itself, it would seem that only very rarely is there a causal relationship between allergy to nickel (or to other metals) and adverse reactions to implants. Finally, it is suggested that routine pre-operative patch testing for sensitization to nickel is not necessary, unless there is a significant clinical history of allergic reactions to nickel.

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