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Conflict of interest

None.

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DKG statement on the use of metal alloy discs for patch testing in suspected intolerance to metal implants

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Summary

Intolerance reactions to metal implants may be caused by metal allergy. However, prior to implantation, 'prophetic'/prophylactic patch testing should not be performed. Pre-implant patch testing should only be done to verify or exclude metal allergy in patients with a corresponding history. In case of implant-related complications – in particular following replacement arthroplasty – such as pain, effusion, skin lesions, reduced range of motion or implant loosening, orthopedic causes should be ruled out first. Workup of suspected metal implant allergy should then be done using the DKG standard series, which includes nickel, cobalt, and chromium preparations. Various studies assessing the usefulness of metal alloy discs for patch testing have shown this particular approach to be ineffective with respect to providing reliable information on metal allergy. Any positive reaction in such tests cannot be assigned to a specific metal contained within the alloy. Furthermore, there is a risk of broad and indiscriminate use of these readily available discs. Accordingly, given the lack of additional benefit compared to patch testing with standardized metal salt preparations, we do not recommend patch testing with metal alloy discs.

Introduction

Demographic changes also lead to an increase in the number of individuals treated with replacement arthroplasty. In Germany, 232,320 patients underwent hip replacement and

168,486 patients knee replacement surgery in 2011, with 10.4 % and 9.5 % being revision surgeries [1]. These revision figures are in accordance with figures from other countries. In case of postoperative complications following replacement arthroplasty, workup of typical causes such as mechanical

problems or infections is paramount [2]. Unlike cutaneous contact allergies to nickel, cobalt, or chromium [3], which are frequent among the population, there is no conclusive data on metal allergy as trigger for complications following joint replacement. Data from the Australian registry shows that the term *metal sensitivity* – as cause for revision surgery – has been documented in up to 5.7 % of revised hip implants and 0.9 % of shoulder prostheses [4]. Based on inconclusive data at the time, an interdisciplinary statement authored by P. Thomas [5], in cooperation with orthopedic surgeons, had given cautious recommendations (with some restrictions) in 2008. Accordingly, a patient allergic to metals was preferably not supposed to be treated with a knee implant containing those particular metals. However, taking into account orthopedic advantages and disadvantages, use of such implants could still be considered. Prerequisites for this course of action included a well-documented informed consent discussion with the patient as well as consideration of the following aspects: (i) still inconclusive data with respect to implant allergy and the frequency of symptoms in patients treated with implants that contain alloys to which a type IV sensitization exists, (ii) unclear long-term success of potential alternatives, (iii) known lifetime of standard models.

At that time, however, the primary authors Thomas and Thomsen already advised against the use of metal-on-metal (MoM) implants for total hip replacement in patients with metal allergy. Within a few years, the high complication rate observed in some MoM models has led to a complete reversal as to how MoM hip implants are viewed. In the meantime, a medical health alert issued by the British Health Services has put replacement arthroplasty using metal implants under scrutiny. The 2013 *FDA safety communication metal-on-metal hip implants* advised against the use of MoM models in patients with metal allergy. In a nationwide survey of active members of the Working Group Joint Implants (Arbeitsgemeinschaft Endoprothetik), information on the topic “allergy” was provided for 122,159 replacement arthroplasties performed in 2009 [6]. Even though this number only corresponds to a percentage of the total number of joint replacements performed that year, it allows for some conclusions: of 1,530 patients with known nickel or cobalt allergy, 1,285 (84 %) were already preemptively treated with an alternative implant suited for patients with metal allergy. These included prostheses made of alternative materials such as titanium and its alloys, ceramic materials, oxinium, or also frequently implants with ceramic-like/titanium-based surface coating as well as multilayer coatings. These alternative implants were also used in up to one-third of patients with upcoming implant exchange surgery and suspected metal allergy.

There is, however, no data yet on how frequently complications occur, if metal-allergic patients receive an implant that contains the corresponding metal. On the one hand, this

Table 1 Typical composition of a CoCrMo alloy, according to [9].

CoCrMo alloy 5832-12 (according to ISO 5832)	
Element	Weight percentage (%)
Nickel	Maximum of 1.0
Chromium	26.0–30.0
Molybdenum	5.0–7.0
Iron	Maximum of 0.75
Manganese	Maximum of 1.0
Silicone	Maximum of 1.0
Carbon	Maximum of 0.35
Nitrogen	Maximum of 0.25
Cobalt	Remainder

highlights the need for diagnostic measures with regard to “metal implant allergy”; on the other hand, it also reveals an uncertainty on the part of surgeons with respect to handling “allergies”. Thus, apart from established diagnostic procedures such as patch testing with standardized test preparations [7] and histological examination of tissue surrounding the implant [8], metal discs made up of implant alloys are also used for patch testing. Moreover, the availability of these test discs also enables our surgical colleagues to readily use them for preoperative prophetic/prophylactic tolerance testing. In the following paragraphs, we will critically discuss the use of metal alloy discs in patch testing.

Alloy components

The most frequently used materials for osteosynthesis and stents are stainless steel or titanium alloys. The main component of stainless steel is iron. Furthermore, it contains approximately 12–15 % nickel (Ni), approximately 18 % chromium (Cr), up to 2 % manganese, and up to 3.5 % molybdenum (Mo). Examples include Kirschner wires, steel wire cerclages, medullary nails, screws, and disc materials as well as stents. For replacement arthroplasty, cobalt-chromium-molybdenum (CoCrMo) alloys are most frequently used, followed by titanium alloys and rarely also zirconium-based materials. Primary sliding partners include polyethylene or ceramic. Titanium (Ti) and its alloys are also often used in pacemaker casings. Regarding weight percentages (wt %), CoCrMo alloys most frequently consist of approximately 64 % cobalt, 28 % chromium, 6 % molybdenum, and up to 1 % nickel [9] (Table 1). However, these weight percentages neither seem to exactly correspond to the percentages of these materials released by corrosion or abrasion nor to

Table 2 Components of a stainless steel alloy, according to [9].

Stainless steel 5832-1 (according to ISO 5832)	
Element	Weight percentage (%)
Carbon	Maximum of 0.03
Nitrogen	Maximum of 0.10
Sulfur	Maximum of 0.010
Phosphorus	Maximum of 0.025
Silicone	Maximum of 1.00
Manganese	Maximum of 2.00
Chromium	17.0–19.0
Molybdenum	2.25–3.5
Nickel	13.0–15.0
Copper	Maximum of 0.50
Iron	Remainder

the percentages measurable in vivo (e.g. blood level analysis) [10]. As mentioned above, stainless steel contains a much higher nickel percentage than CoCrMo alloys [9] (Table 2). Titanium alloys are usually primarily made up of titanium as well as either aluminum and vanadium or aluminum and niobium. Pure titanium consists of more than 99 wt % titanium.

The formation of abrasive particles caused by corrosion and wear of prostheses results in the release of metal ions in vivo. This has led to the conclusion that, based on the release of their components, alloy metal discs could also be used for patch testing in suspected metal allergy.

Alloy metal discs and patch testing

The release of metal ions from stainless steel as well as CoCrMo metal discs was measured in an in vitro study, addressing the question whether the amounts of metal released reached threshold values for triggering a local allergic reaction in sensitized individuals, and whether this is reproducible in patch testing using the aforementioned discs [11]. The stainless steel typically used in implants contained 20.79 wt % Cr and 9.81 wt % Ni; the CoCrMo disc, 65.2 wt % Co, 27.3 wt % Cr, and 0.3 wt % Ni. Assuming a (standard) two-day epicutaneous application, two-day in vitro elution at 37°C was conducted using artificial sweat, a culture medium containing type AB serum, and distilled water. For both disc variants, metal release values were below 0.5 mcg/cm²/2 days for nickel; they reached a maximum of 1.36 mcg/cm²/2 days for Cr, and a maximum of 18.94 mcg/cm²/2 days for Co (in CoCrMo discs). In keeping with other investigations, the study showed that the values measured for Co and

Cr release (from CoCrMo discs) indeed reached threshold values known to trigger cutaneous allergic reactions [12, 13]. None of the 52 metal-allergic test individuals (41/52 Ni, 16/52 Cr, and 15/52 multiple allergies) reacted to the stainless steel discs. Five of the 52 test individuals showed local allergic reactions to the CoCrMo discs; all five of them also exhibited allergic reactions to cobalt chloride in the patch test with standardized metal salt test preparations. Moreover, three of those individuals also reacted to nickel sulfate and potassium dichromate. However, it remains unclear, which of the metals released actually triggered the “disc reaction”. In addition, only one-third of patients allergic to cobalt and only one-fourth of patients allergic to chromium reacted to the CoCrMo discs [11].

As early as 1987, Menné et al. showed that only two of 66 individuals allergic to nickel reacted to test specimens made of stainless steel [14]. On the other hand, Haudrechy et al. reported that almost all nickel-allergic test individuals had reacted to nickel-plated test discs [15]. Julander et al. demonstrated that cobalt-containing metal objects could release enough cobalt to cause allergic contact dermatitis [16]. These studies were confirmed by Thyssen et al. [17]. Thus, contact with metal objects or test specimens may indeed experimentally trigger dermatitis. However, the degree to which this happens varies and depends on the composition and metal release performance of the metal objects. The authors are aware that tests with discs containing dental alloys as well as dental implant materials, i.e. titanium-based alloys, are also offered and performed. However, given the lack of proper evaluation, the significance of such test results – analogous to findings obtained from the above-mentioned studies with orthopedic implants – has to be questioned.

By contrast, standardized patch testing with evaluated metal salt preparations represents a procedure in accordance with guidelines. Here, delayed reading after one week may increase test success; differentiation of irritant reactions is crucial. Based on the aforementioned results, testing of metal alloy discs is unnecessary. In case of a positive reaction when using metal alloy discs for patch testing, it remains unclear to which specific metal the reaction has occurred. If the test is negative, on the other hand, there is no assurance regarding the harmlessness of the material in vivo, because of different corrosion conditions and particle abrasion. Given the particular conditions under which exposure to potential allergens is conducted in this setting, negative patch test results do not always mean that there is no allergy. Rather, false-negative findings also have to be taken into account [7].

Conclusion

Metal alloys used for implants often contain numerous different metals. Due to corrosion and abrasion, metal ions are

released into the surrounding tissue, which has been confirmed by in vivo studies and elution tests with metal alloy discs. Standardized and tested patch test preparations are currently only available for nickel, cobalt, and chromium (chromate). Testing with other metals or metal salts is inconclusive due to lack of validation. Standardized patch testing requires experience in dermatology and allergy. The few available patch test studies using alloy discs show a poor correlation with reactions to standardized test preparations such as nickel sulfate, cobalt chloride, and potassium dichromate. Thus, for example, only 7 % of patients allergic to nickel, 25 % of those allergic to chromium, and 31 % of those allergic to cobalt reacted to the CoCrMo discs [11]. However, as the alloys also contain many other metals, it remains unclear which component actually triggered the reaction. Rather than providing clear-cut results, testing with metal alloy discs creates difficulties in interpreting potential positive reactions. Given the lack of additional benefit compared to standardized patch testing with metal salts, we do not recommend testing with alloy discs. Indiscriminate testing without any corresponding patient history with respect to metal allergy also has to be rejected.

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