

Clinical Management of Joint Arthroplasty

Peter Thomas · Susanna Stea

Metal Implant Allergy and Immuno- Allergological Compatibility Aspects of Ceramic Materials

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 Springer

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P. Thomas, G. Roider, A. Beraudi, D. de Pasquale,
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and B. Summer

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Prof. Dr. Peter Thomas

Clinic for Dermatology and Allergology
Ludwig-Maximilians-University Munich
Frauenlobstraße 9–11
D-80337 Munich

Dr. Susanna Stea

Medical Technology Laboratory
Rizzoli Orthopaedic Institute
Via di Barbiano, 1/10
I-40136 Bologna, Italy

Sylvia Usbeck

CeramTec GmbH
CeramTec Platz 1–9
D-73207 Plochingen

see website:

www.bioloX.com/clinical-guides/

ISBN 978-3-662-47439-6

ISBN 978-3-662-47440-2 (eBook)

DOI 10.1007/978-3-662-47440-2

Springer Medizin

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Cover Design: deblik Berlin

Cover Illustration (collage): © CeramTec GmbH, © Fotolia

Production: Fotosatz-Service Köhler GmbH – Reinhold Schöberl, Würzburg

Printed on acid-free paper

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Preface

The growing number of endoprostheses reflects not only the demographical changes with a rising proportion of the elderly within the population but also the growing number of young people getting implants.

Besides optimizing mechanical properties, tissue integration and tribology of metal implants, biocompatibility of implant materials with respect to long-term efficacy will become more significant. Nickel, chromium and cobalt or bone cement components might trigger contact allergies and thus in turn may lead to implant incompatibility. This possibility highlights potential local and systemic adverse reactions of released implant components .

Ceramic implants are often used in patients with hypersensitivities. Trial results of two research groups that studied immuno-allergological compatibility of ceramic materials will be presented in this clinical guide.

The guide presents background information and recommendations on how to proceed in patients with suspected implant allergies since the diagnostic criteria of implant-associated allergies have not yet been defined.

Patient history and clinical findings, in addition to test results must be considered in context.

For the first time, a clinical algorithm has been developed for procedures in clinical practice when an implant allergy is suspected. The algorithm is presented as a laminated insert. The flow chart contains additional information on the histopathological particle algorithm, according to Krenn.

Enhancement of clinical-allergological diagnostic tools and interdisciplinary research approaches will help improve future patient care.

Author



Peter Thomas, MD, PhD, professor of dermatology and allergology

Peter Thomas was born on March 5, 1956, in Augsburg-Göggingen, Germany, and completed his study in medicine at the Ludwig-Maximilians-University in Munich (Germany). He spent two years in the USA as a research fellow in the Department of Immunology at the Johns Hopkins University in Baltimore, Maryland, and the La Jolla Institute for Allergy and Immunology in California.

Thomas specialized in allergology, environmental medicine and problem-based learning (Harvard Medical School). For the last 15 years, Thomas has dedicated his research to metal implant hypersensitivity. Along with his team, he offers special consultation hours on implant hypersensitivity which more than 1,000 patients with allergic reactions to implants or suspected allergies have attended.

Peter Thomas

- is an internationally renowned allergologist/dermatologist
- works with an interdisciplinary team
- is an expert allergologist for the German Society of Orthopaedics and Orthopaedic Surgery (DGOOC) and German Society of Dental, Oral and Orthodontic Implantology (DGI)
- offers special consultation for patients with implant allergies
- provides professional training of medical school students and medical personnel
- reviews articles for ten medical journals and several research foundations
- developed a diagnostic algorithm for patients with suspected implant allergies
- published more than 100 original scientific papers
- contributed articles to 42 textbooks
- has won three research awards

Along with Marc Thomsen, MD, PhD, Thomas leads the Implant Allergy Working Group of the DGOOC for which he also acts as an expert allergologist. Thomas is a member of seven medical societies. He also is the lead author of the interdisciplinary statement on implant allergy published in 2008 by the DGOOC, the German Contact Dermatitis Research Group (DKG) and the German Society for Allergology and Clinical Immunology (DGAKI).



Susanna Stea, PhD, biologist and researcher

Susanna Stea was born on March 9, 1959, in Bologna (Italy). She studied biology at the University of Bologna, Italy, and graduated in 1981. Four years later, she earned her degree as a specialist in biochemistry and clinical chemistry at the University of Parma, Italy.

Her work experience includes assignments at the Rizzoli Orthopedic Institute, the Biocompatibility and the Medical Technology Laboratories. Today, she is responsible for the biological unit at the Medical Technology Lab in Bologna, where problems related to tissue reaction to orthopedic prostheses and mechanobiology of bone and bone cells are studied. The biology unit, headed by Stea, isolates wear particles of the synovial fluid from patients with prostheses and identifies the amount of metal ions in the hair of prosthesis patients. Further research is dedicated to bone histomorphometry, cytokines in the synovial fluid of prosthesis patients, histology of periprosthetic soft tissue, and in-vitro evaluation of bone homeostasis. Innovative technologies in search of prevention, diagnosis, treatment, monitoring and rehabilitation of musculoskeletal diseases are validated and transferred into clinical practice. The lab closely cooperates with the Department for Orthopedic Traumatology and Prosthetic Surgery and Revisions of Hip and Knee Implants.

Since 2009, Stea is in charge of post-marketing surveillance of orthopedic medical devices. She is further responsible for data collection of the Register of Orthopedic Implants of the Italian region Emilia-Romagna (RIPO) and runs the Register of Explanted Prostheses of the Rizzoli Institute (REPO).

Her teaching activities at the University of Bologna include specialized courses in biomaterials in prosthetic surgery and biomedical technology in articular reconstructive surgery.

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1 Introduction

Contact allergy to nickel, cobalt, or chromium is frequent both in the work area and in private life [1]. In addition to articles of daily life, metal implants have also become a source of metal exposure. These include orthopedic–surgical implants as well as many implanted devices in other medical specialties. Allergic complications after insertion of metallic orthopedic implants encompass cutaneous changes such as eczema, urticaria, and impaired wound healing, but also extracutaneous reactions such as swelling, effusions, pain, and even loosening [2][3][4][5][6][7]. The aging population will lead to an increased use of metal implants, and consequently also to a growing number of implant failures and subsequent revision surgeries. In 2011 the numbers of total hip replacement (THR) and total knee replacement (TKR) procedures were reported to be 465,034 and 702,415 in the USA, respectively, and 232,320 and 168,486 in Germany [8]. With the rate of complication-related revision surgery at approximately 9%, the significance of metal implant allergy in the outcome of arthroplasty is receiving increasing attention.

Since the early reports on patients with *cutaneous* reactions to metal orthopedic implants in the 1960s [9], metal implant hypersensitivity has been a concern for orthopedic surgeons. Over the years a growing number of such reports on dermatitis – but also vasculitis-like reaction or even urticaria – in association with orthopedic implants were published [10][11][12][13][14]. The temporal and clinical course of symptoms before and after removal of the implants emphasizes the link between metal hypersensitivity and allergic skin reactions associated with metal implants. *Noncutaneous* complications such as recurrent pain, effusion, loosening, and reduced range of motion are not specific for a given etiology. However, especially in patients with knee arthroplasty, such symptoms – after exclusion of infection and mechanical reasons – can be associated with metal allergy [4][15][16]. Predominantly pain – but also recurrent effusions, reduced range of motion, and aseptic loosening – was noted in a series of 200 patients with complications as compared with 100 symptom-free arthroplasty patients. Again, higher rates of metal sensitization were observed in the group with the complications [17]. Cases of failed arthroplasty are more easily linked to allergy if, in addition to metal allergy, peri-implant lymphocytic inflammation is seen. In a series of 16 patients with failed metal-on-metal (MoM) hip arthroplasty and peri-implant lymphocytic inflammation, 13 were identified as metal allergic (defined as positive patch test or lymphocyte transformation test or both) [18]. However, the extent to which aseptic loosening, pain, or periarticular fibrosis (“arthrofibrosis”) may be caused by metal allergy is still an open question. Finally, there are also reports on patients with well-performing arthroplasty despite a known metal allergy [19][20]. Thus, in non-cutaneous complications related to arthroplasty a series of elicitors (including mechanical or infectious etiology) have to be excluded first [21]. Accordingly, metal hypersensitivity is often a diagnosis of exclusion and it is considered only after infection, implant malposition, instability, and fractures have been ruled out [22]. Over the years, knowledge on adverse reactions to metallic implants has been growing. Foreign-body-like reactions to metallic and polyethylene wear particles were a focus of interest for many years [23]. Other aspects include: the partly necrotic inflammatory pseudotumor formation to MoM coupling [24];

the corrosion at the head–neck taper as a cause of adverse local reactions [25][26]; and the direct *in vivo* inflammatory cell-induced corrosion of CoCrMo alloy implant surfaces [27]. As early as in 2008, the German societies for allergy and orthopedic surgery advised in an interdisciplinary statement on metal implant allergy against MoM hip arthroplasty in patients with metal allergy [6]. Two years later, the British Health Agency (MHRA) placed all MoM bearings under supervision with a “medical device alert” [28]. In the meantime, there production of two models has been halted because of complications, and the U.S. Food and Drug Administration (FDA) published a report in 2013 entitled “Concerns about metal-on-metal hip implants” [29]. Registry data may provide additional information on metal sensitivity: For the first time, the Australian arthroplasty registry listed “metal sensitivity” as a reason for revision. In the 2012 report, this was indicated in about 0.9% of the revised shoulder endoprostheses and 5.7% of the revised total hip arthroplasties [30]. In the 2013 report, the term “metal sensitivity” was changed to “metal-related pathology.”

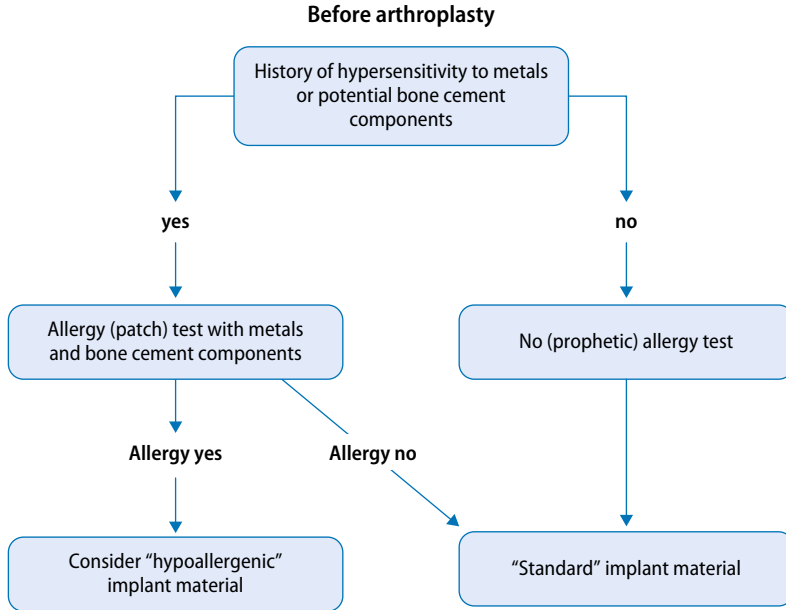
2 Diagnostic Steps in Suspected Implant Allergy

Several research groups are working on the topic “implant allergy.” Correspondingly, there are somewhat differing opinions on diagnostic approaches [31][32][33][34]. The Danish research group led by Jacob P. Thyssen has recommended extensive patch testing to clarify intolerance reactions (including previously not widely evaluated metal preparations) [35]. Donatella Granchi and coworkers from Bologna commented on “metal hypersensitivity testing in patients undergoing joint replacement” based on 22 publications [3]. She points to the limitations of allergy testing: Patients with implant failure as compared with those who have stable implant present more frequently with metal allergy, but this does not prove a causal relationship. In summary it can be stated, however, that the two most common methods of testing for metal sensitivity are (*in vivo*) skin patch testing and (*in vitro*) the lymphocyte transformation test (LTT).

Theoretically, testing could be done in patients undergoing their first implantation or in patients with metallic implant failure [36].

2.1 Testing of Patients Prior to Primary Arthroplasty

“Prophylactic–prophetic” compatibility patch testing should not be performed, since “the patch test is not suitable to predict the development of allergic contact dermatitis (in the sense of a ‘prophetic testing’)” [37]. Only with a history of previous complications/suspected allergic reactions to metals or acrylates can a possible metal allergy or potential allergy to bone cement components be clarified. ■ Fig. 1 summarizes this strategy.



■ Fig. 1 Flowchart for the evaluation of potential allergy prior to primary arthroplasty (for details, see text)

2.2 Testing of Patients with Failed Arthroplasty

After exclusion of the most frequent differential diagnoses (such as infection) by the supervising orthopedic surgeon, but also by the dermatologist in the case of skin eruptions (such as psoriasis), the patch test is performed. Histology can help characterize peri-implant inflammation – in particular to exclude infection. A T-cell metal sensitivity can also be investigated using LTT. This is, however, still restricted to scientific laboratories that evaluate the results critically case by case for clinical relevance [6]. ■ Fig. 2 presents an algorithm of the diagnostic steps. The proper evaluation of potential allergy begins with a detailed history (e.g., intolerance reaction to metallic items, to acrylate-based dental materials).

2.3 Patch Testing

The standard testing series includes nickel, chromium, and cobalt preparations, which are common implant components. There is still no official consensus on bone cement testing. The bone cement testing series of the Munich allergy group encompasses: gentamicin sulfate, benzoyl peroxide, hydroquinone, 2-hydroxyethylmethacrylate, copper-(II)-sulfate, methyl methacrylate, and *N, N*-dimethyl-*p*-toluidine. Additional metal preparations are available, but not yet standardized – and their use should be critically decided case by case [18]. It is useful to also perform a late patch test reading after 1 week. Even when a positive reaction is found, it is mandatory that the clinical relevance of the test results be evaluated.

2.4 Histology

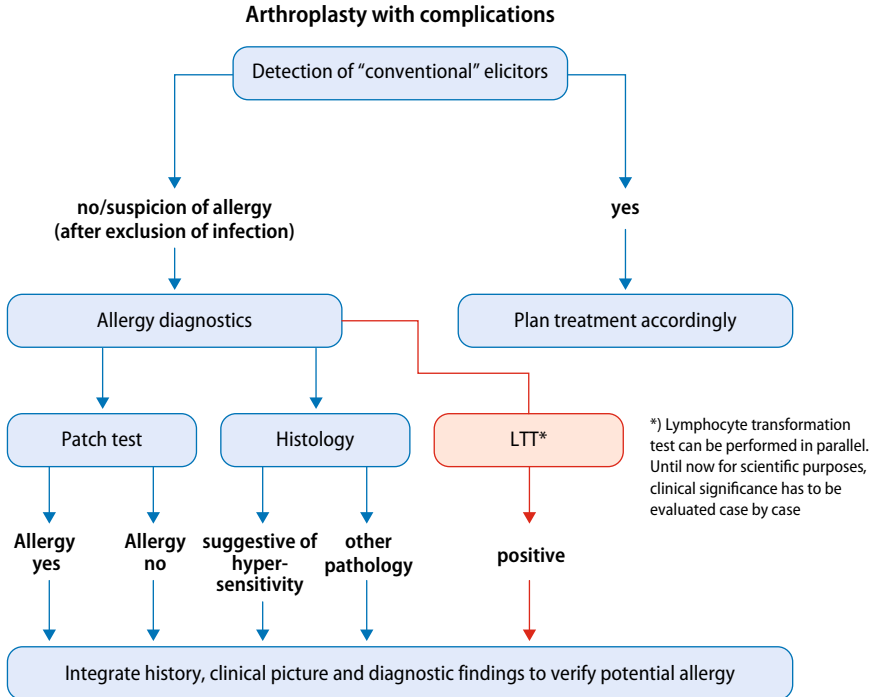
A consensus classification [38] describes four types of reactions of periprosthetic membranes: a foreign-body-like response (type I), a granulocyte-dominated infectious type (type II), a mixture of type I and II (combined type, type III), and a paucicellular fibrotic reaction (type IV, indifferent type). This has recently been completed by a particle algorithm by Veit Krenn et al. showing various reaction patterns also in relation to a composition of particles [39] (see loose insert). Periprosthetic lymphocytic infiltrates might indicate hyper-reactivity, but histological characteristics of metal allergy-induced periprosthetic hypersensitivity are still to be defined. The analysis of the local cytokine pattern might further clarify this issue [40]. Thus, different peri-implant inflammation patterns are described apart from a foreign-body reaction: particle-induced inflammasome activation [38], lymphocytic inflammation [38][40], and differential lymphocytic activation patterns [41].

2.5 Lymphocyte Transformation Test

This scientific test uses the antigen-induced (T cell) proliferation in relation to the baseline proliferation of unstimulated cultures and gives a stimulation index (SI) as a read-out. We have, like other laboratory groups, set the detection limit for sensitization at $SI > 3$ [42] and give interpretation only in view of other diagnostic parameters. If critically evaluated, the LTT is a complementary method, for example, when investigating a suspected allergic drug reaction [43]. However, LTT sensitization does not necessarily mean disease-causing hypersensitivity [44][45]. Even for the predominant “allergen” nickel, quality assessments of LTT procedures are very rare [44][45]. Accordingly, the Robert Koch Institute does not generally recommend the LTT [44]. On the other hand, several research groups are using LTT to assess “metal sensitization” in arthroplasty patients [31][46]. Future development steps [47] and a follow-up study with evaluation of the clinical relevance of LTT results can lead to LTT optimization.

Take-Home-Message

- “Prophylactic” patch testing of implant compatibility in patients prior to primary arthroplasty should not be performed
- Combined evaluation of medical history, clinical findings, patch testing, and histology
- Patch testing in patients with failed arthroplasty after exclusion of the differential diagnoses
- Histology is recommended to characterize peri-implant lymphocytic inflammation
- LTT must be carefully interpreted in the context of additional information



■ Fig. 2 Flowchart for the evaluation of potential allergy in arthroplasty with complications (for details, see text)

3 Immuno-allergological Properties of Alumina Ceramics In Vitro and In Vivo

To assess the immuno-allergological properties of alumina ceramic materials (BioloX[®]-forte), in vitro and in vivo studies were performed in the Clinic for Dermatology and Allergology of the Ludwig Maximilians University, Munich [48]. The aim was to evaluate whether:

- There was any (allergic) patch test reaction to ceramic material in individuals with other allergies (e.g., also to metals)
- The presence of ceramic discs would alter in vitro proliferative and cytokine response of human peripheral blood mononuclear cells in a cell culture model

Patch testing was done in a consecutive series of 250 patients visiting the clinic. The patch test was applied on the patient's back using a European standard series of 30 allergens (Hermal, Reinbek, Germany) supplemented by a sterilized ceramic disc (Al₂O₃-BioloX[®]-forte, CeramTec, Plochingen, Germany). The reactions were evaluated according to standard procedure on days 3 and 4 [37]. Nickel was the most frequent allergen with 17.2% positive reactions. None of the patients reacted to the BioloX[®]-forte discs. The results are summarized in ■ Tab. 1.

Tab. 1 Patch test reaction frequency in 250 consecutive individuals

Test substance	Reactions/250 patients	(%)
Nickel(II)-sulfate x 6 H ₂ O	43	17.2
Fragrance mix	38	15.2
Balsam of Peru	33	13.2
Thimerosal	26	10.4
Lanolin alcohol	20	8
Mercury(II)-amid-chloride	17	6.8
<i>p</i> -Phenylenediamine	15	6
Dibromodicyanobutane, phenoxyethanol	11	4.4
Colophonium	10	4
Potassium dichromate	6	2.4
Bufexamac	6	2.4
Neomycin sulfate	5	2
Thiuram mix	5	2
Cobalt(II)-chloride	5	2
(Chlor)-Methylisothiazolinone (Kathon CG in water)	4	1.6
Cocamidopropyl betaine (in water)	4	1.6
Benzocaine	3	1.2
<i>N</i> -Isopropyl- <i>N</i> -phenyl- <i>p</i> -phenylenediamine	3	1.2
Sesquiterpene lactone mix	3	1.2
<i>p</i> -tert-Butylphenol-formaldehyde resin	2	0.8
Formaldehyde	2	0.8
Propolis	2	0.8
Turpentine	2	0.8
Mercapto mix	1	0.4
Epoxide resin	1	0.4
Cetyl stearyl alcohol	1	0.4
Paraben mix	1	0.4
Toluenesulfonamide-formaldehyde resin	1	0.4
Zinc diethyldithiocarbamate	–	–
Vaseline album	–	–
Biolox [®] forte disc	–	–

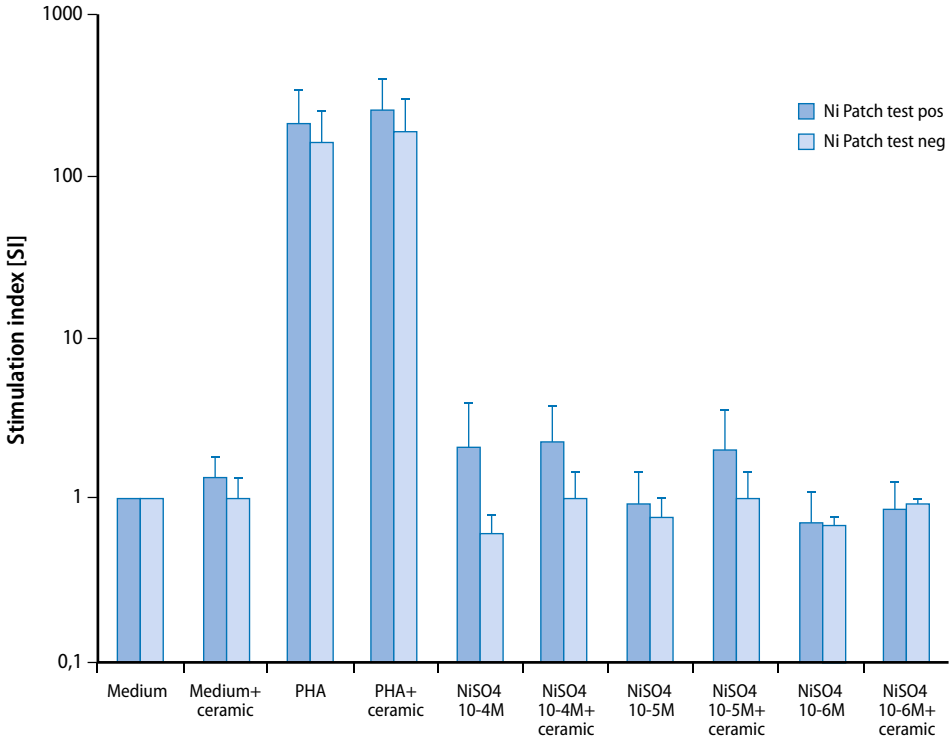
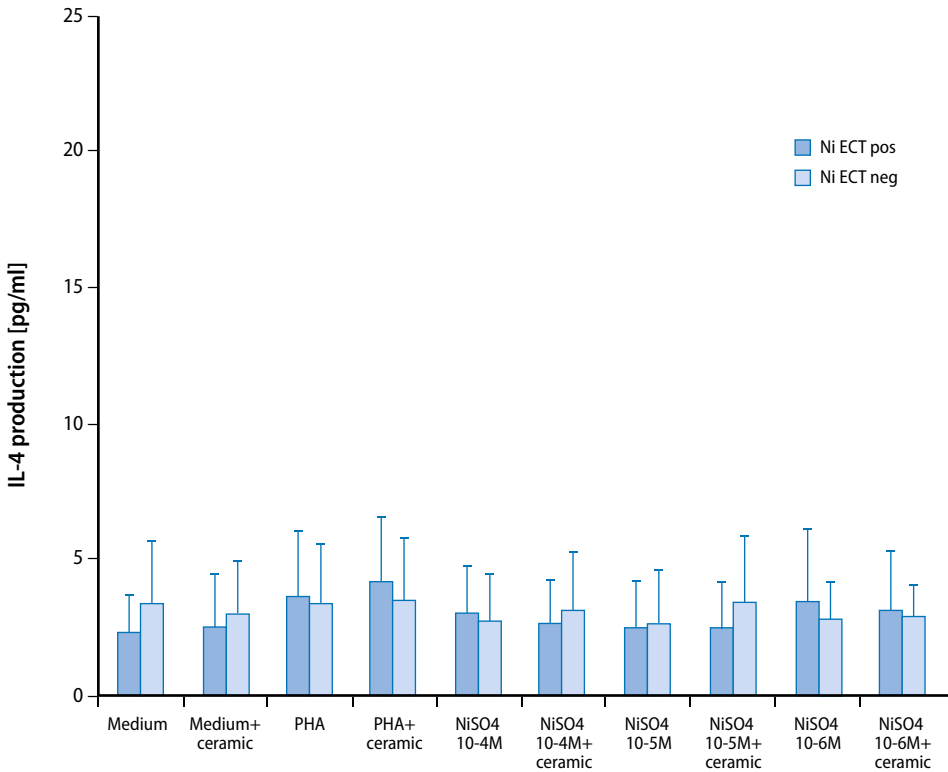


Fig. 3 Proliferative response (expressed as stimulation index) of peripheral blood mononuclear cells from 15 nickel-allergic and 15 nonallergic blood donors. Statistics: *t* test. *Medium* culture medium, *NiSO₄* nickel sulfate, *PHA* phytohemagglutinin, *SI* stimulation index, *+ceramic* additional presence of Al₂O₃ (BioloX[®]forte) disc

The *in vitro* experiments consisted of a lymphocyte proliferation assay and the analysis of the interferon (IFN)- γ and interleukin (IL)-4 cytokine production after stimulation of peripheral blood mononuclear cells (PBMC). For this purpose, heparinized blood of 15 nonallergic and 15 nickel-allergic individuals (22 women, 8 men, 24–70 years) was obtained. After isolation of PBMC by density centrifugation, cells were cultured with the pan T-cell mitogen phytohemagglutinin (PHA) at 2.4 $\mu\text{g/ml}$, NiSO₄ at 10⁻⁴M, 10⁻⁵M, and 10⁻⁶M, Al₂O₃ ceramic discs, and culture medium alone as control. For the proliferation assay, cells were pulsed after 5 days with ³H thymidine and the proliferation was assessed by incorporated radioactivity and expressed as SI. IFN- γ and IL-4 production in the supernatants of stimulated and unstimulated cultures was analyzed by ELISA (antibodies from PharMingen, San Diego, Calif.).

PBMC of nickel-allergic blood donors showed enhanced proliferative response to NiSO₄ 10⁻⁴M. The proliferative response was only marginally influenced by the ceramic BioloX[®]forte discs (■ Fig. 3).

The presence of BioloX[®]forte discs did not have an overall influence on IL-4 production in the cell cultures (■ Fig. 4).



■ **Fig. 4** Interleukin (*IL*)-4 production (pg/ml) of peripheral blood mononuclear cells from 15 nickel-allergic and 15 nonallergic blood donors. Statistics: *t* test. *Medium* culture medium, *NiSO₄* nickel sulfate, *PHA* phytohemagglutinin, *SI* stimulation index, *+ceramic* additional presence of Al₂O₃ (Biolox® forte) disc

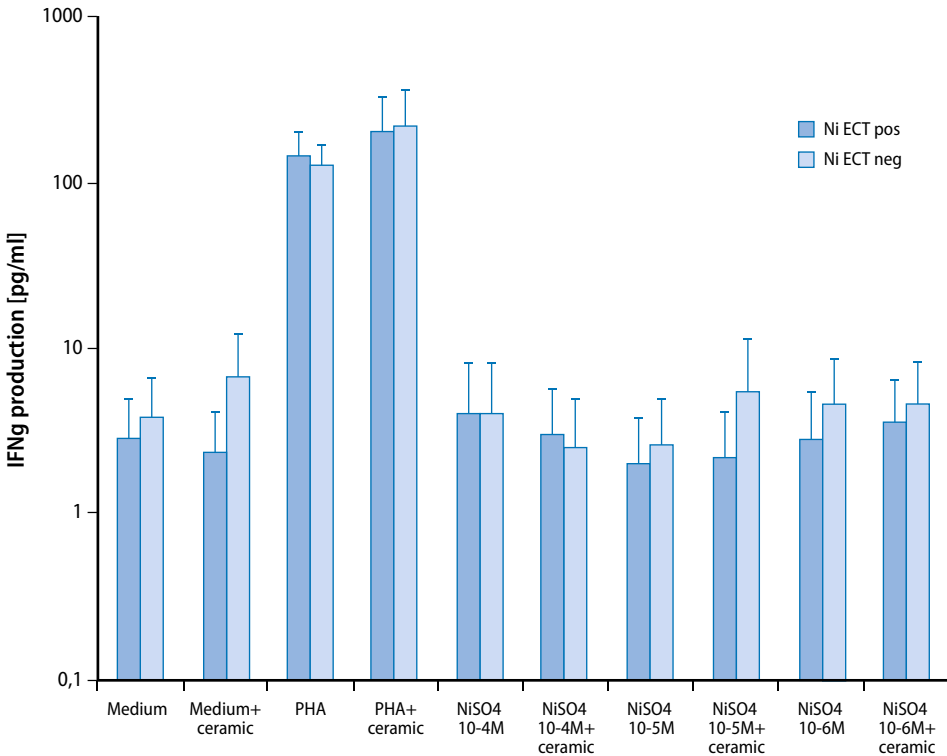
The nonallergic blood donors showed a slight increase in IFN- γ production in the presence of ceramic discs in the medium culture. On the other hand, the IFN- γ production was not altered after stimulation with PHA or NiSO₄ (■ Fig. 5).

These data show that despite a high rate of delayed-type hypersensitivity reactions to standard allergens, none of the patients had a patch test reaction to Al₂O₃ ceramic. Also, the cytokine response – which was analyzed by the assessment of IFN- γ and IL-4 production in vitro – was not influenced by the presence of Al₂O₃ discs. In summary, the results of this study gave no indication of an impaired or altered immuno-allergological compatibility of the Biolox® forte ceramic material.

Take-Home-Message

Alumina Ceramic (Biolox® forte)

- No patch test reaction
- No overall influence of cytokine response
- No indication of impaired or altered immuno-allergological compatibility



■ Fig. 5 Interferon (*IFN*)- γ production (pg/ml) of peripheral blood mononuclear cells from 15 nickel-allergic and 15 nonallergic blood donors. Statistics: *t* test. *Medium* culture medium, *NiSO*₄ nickel sulfate, *PHA* phyto-hemagglutinin, *SI* stimulation index, *+ceramic* additional presence of Al₂O₃ (BioloX® forte) disc

4 Immuno-allergological Compatibility of Ceramic Composite Material

4.1 Ceramic Composite Material and Alumina Ceramics

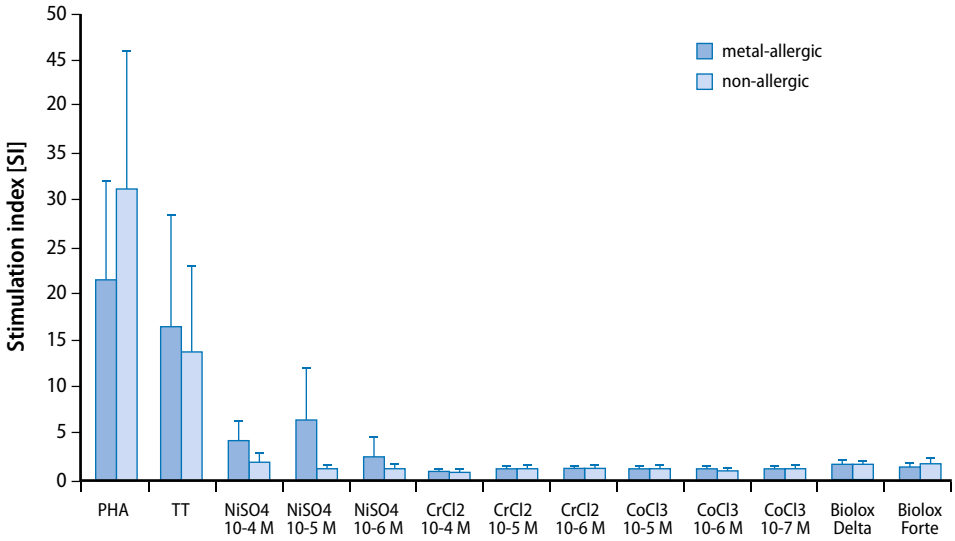
A subsequent series of experiments aimed to investigate the immuno-allergological properties of a ceramic composite material (BioloX®delta). This study was done because BioloX®delta contains chromium, which is a potential elicitor of allergic reactions. Thus, the following questions were posed:

- Will there be a positive (allergic) patch test reaction to chromium-containing ceramic material in individuals with metal allergy?
- Do human lymphocytes containing cell cultures show enhanced reactivity in the presence of BioloX®delta discs?
- Is there a release of chromium from BioloX®delta discs when they are kept for 5 days under different “elution” conditions?

Tab. 2 Positive patch test reactions in 200 consecutive individuals

Contact allergen	Reacting patients	(%)
Nickel(II)-sulfate	29	14.5
Cobalt(II)-chloride	15	7.5
Thiomersal	14	7
Fragrance mix	12	6
Balsam of Peru	12	6
Potassium dichromate	10	5
Dibromodicyanobutane, phenoxyethanol	9	4.5
<i>p</i> -Phenylenediamine	8	4
Colophonium	6	3
Neomycin sulfate	6	3
Thiuram mix	6	3
Mercury(II)-amid-chloride	5	2.5
Benzocaine	4	2
Formaldehyde	4	2
Paraben mix	4	2
Lanolin alcohol	4	2
Composite mix	3	1.5
Amerchol L-101	3	1.5
Bufexamac	2	1
Cocamidopropyl betaine	2	1
Mercapto mix	2	1
Propolis	2	1
Biolox®delta discs	0	0

Patch testing was done in a consecutive series of 200 patients visiting the clinic. The patch test was applied on the patient's back using a European standard series of 30 allergens (Hermal, Reinbek, Germany) supplemented by a sterilized ceramic disc (Biolox®delta, CeramTec, Plochingen, Germany). The reactions were evaluated according to a standard procedure on days 3 and 4 [37]. Nickel was the most frequent allergen with 14.5% positive reactions. None of the patients reacted to the Biolox®delta discs. The results are summarized in **Tab. 2**.



■ **Fig. 6** Lymphocyte proliferative response of metal-allergic and nonallergic blood donors after stimulation with the control stimuli phytohemagglutinin (*PHA*) and tetanus toxoid (*TT*) and the metal salts NiSO₄, CrCl₂, and CoCl₃ in different concentrations and the ceramic materials BioloX[®]delta and forte. Proliferation is given as a stimulation index (*SI*)

Take-Home-Message

BioloX[®]delta

- No patch test reaction

For the lymphocyte proliferation assay, heparinized blood was obtained from 30 individuals (7 women, 23 men), of whom 10 were nonallergic and 20 had nickel or chromium allergy. After isolation of PBMC by density centrifugation, cells were cultured in two parallel sets of experiments with/without the presence of ceramic discs and the following stimuli: pan T-cell mitogen PHA, NiSO₄, CrCl₃, CoCl₂, and culture medium alone as control. For the proliferation assay, cells were pulsed after 5 days with ³H thymidine and the proliferation was assessed by incorporated radioactivity and expressed as SI. ■ Fig. 6 shows that the presence of neither the BioloX[®]forte discs nor the BioloX[®]delta discs had stimulatory effects.

Take-Home-Message

- Lymphocyte proliferation: BioloX[®]delta and BioloX[®]forte showed no stimulatory effects

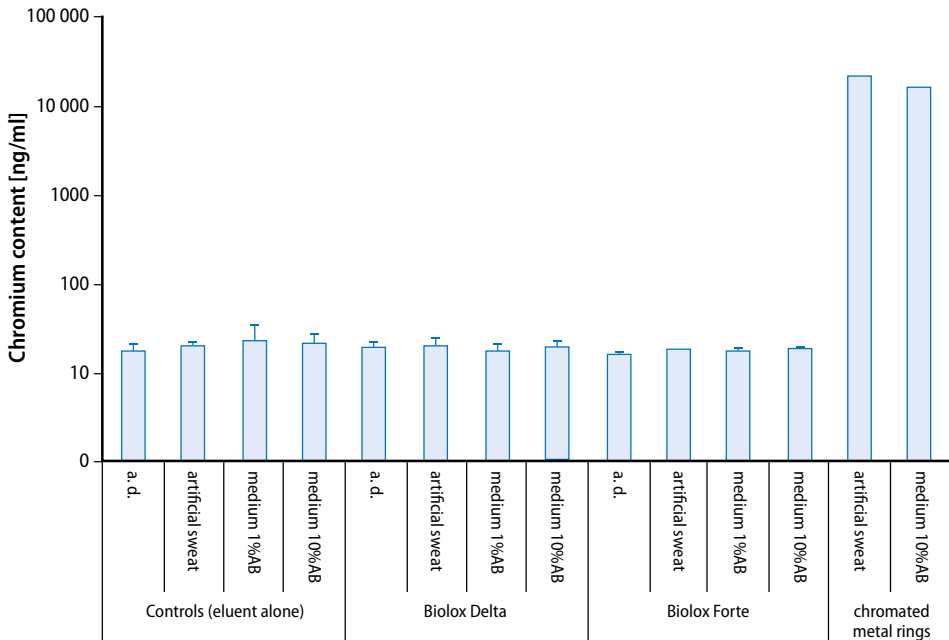


Fig. 7 Determination of chromium by atomic absorption spectroscopy in eluates (5-day incubation, 37°C, sterile. *Medium 1%AB*, elution in RPMI1640 medium supplemented with 1% human AB serum; *medium 10%AB*, elution in RPMI1640 medium supplemented with 10% human AB serum; *a.d.* elution in distilled water; *artificial sweat*, elution in artificial sweat

We next assessed the potential chromium release from BioloX[®] delta discs. In 24-well culture plates, six discs each were kept for 5 days at 37°C in the presence of 1-ml eluent. The eluates were then pooled and the experiment was repeated two more times. The eluents were:

- Distilled water
- Artificial sweat
- Culture medium with 1% human AB serum
- Culture medium with 10% human AB serum

In a further set of experiments, chromated metallic rings underwent identical elution conditions. To assess the potential chromium release, the eluates were first treated by microwave digestion with nitric acid. After three-point calibration, atomic absorption spectrometry was used to analyze the released chromium (duplicate experiments). As **Fig. 7** shows, the various elution media already contained minute traces of chromium. The different elution conditions did not lead to noteworthy chromium release from both variants of ceramic discs. By contrast, the chromated rings proved to have a high chromium release.

Take-Home-Message

- No relevant chromium release from BioloX[®] delta discs

Tab. 3 Mean values of chromium levels in the four different matrices (adapted from [49], with friendly permission by *Hip International*)

Group	Blood ($\mu\text{g/l}$) Mean (SD)	Serum ($\mu\text{g/l}$) Mean (SD)	Erythro- cytes ($\mu\text{g/l}$) Mean (SD)	Urine ($\mu\text{g/l}$) Mean (SD)	Urine normalized ($\mu\text{g/g creatinine}$) Mean (SD)
Patients ($n=20$)	0.21 (0.09)	0.21 (0.12)	0.13 (0.09)	0.14 (0.18)	0.12 (0.13)
Controls ($n=21$)	0.22 (0.14)	0.17 (0.08)	0.13 (0.09)	0.10 (0.12)	0.07 (0.08)

4.2 Evaluation of Ceramic Composite Material Under Physiologic Conditions In Vivo

The Bologna orthopedic research group at the Rizzoli Institute conducted a study to assess the potential in vivo release of chromium ions from ceramic composite material (BioloX[®]delta) bearings in arthroplasty patients. For this purpose, aliquots of blood, erythrocytes, and urine were analyzed [49]. BioloX[®]delta is a ceramic composite material used as an alternative to MoM or metal-on-polyethylene coupling. The included chromium is trivalent chromium strongly bound to the alumina lattice. Since its launch, 3.8 million BioloX[®]delta ball heads and 1.5 million inserts have been implanted around the world [50]. Because many countries decided to adopt several measures regarding the monitoring of chromium and cobalt ion levels in MoM THA owing to the high failure rates, this study was performed to evaluate the potential release of chromium also from ceramic materials in arthroplasty under physiologic conditions in vivo.

The study participants comprised 20 patients with implanted BioloX[®]delta THA couplings (THA group; 10 women, 10 men; mean age, 59.9 years; mean body weight, 71 kg) and 21 subjects with no implanted prostheses (control group; 7 women, 14 men; mean age, 57.2 years, mean body weight, 75 kg). Fifteen patients of the THA group had a 32-mm ball head and five a 36-mm ball head. The follow-up was performed between 6 and 63 months after the THA. Blood and urine was taken from all participants and the chromium content was analyzed by inductively coupled plasma mass spectrometry (ICP-MS, ELAN DRCII, Perkin Elmer, Waltham, Mass.) in the blood, serum, isolated erythrocytes, and urine.

The reference values of chromium in the general population (as internal reference range of the laboratory) were: 0.1–5.0 $\mu\text{g/l}$ for blood, 0.1–0.5 $\mu\text{g/l}$ for serum, 0.14–4.58 $\mu\text{g/l}$ for erythrocytes, and <0.05–2.2 $\mu\text{g/l}$ for urine. When comparing the individuals in this study with/without arthroplasty, the mean values of chromium in all samples were not significantly different in the two groups. In both groups, all patients had chromium levels below the upper reference range for the general population. The mean values are given in **Tab. 3** and are shown in **Fig. 8**.

In summary, the results of the study show that patch testing with the BioloX[®]delta THA coupling did not detect elevated chromium levels in vivo. Furthermore, the respective chromium levels in vivo are comparable to healthy individuals without arthroplasty. Thus,

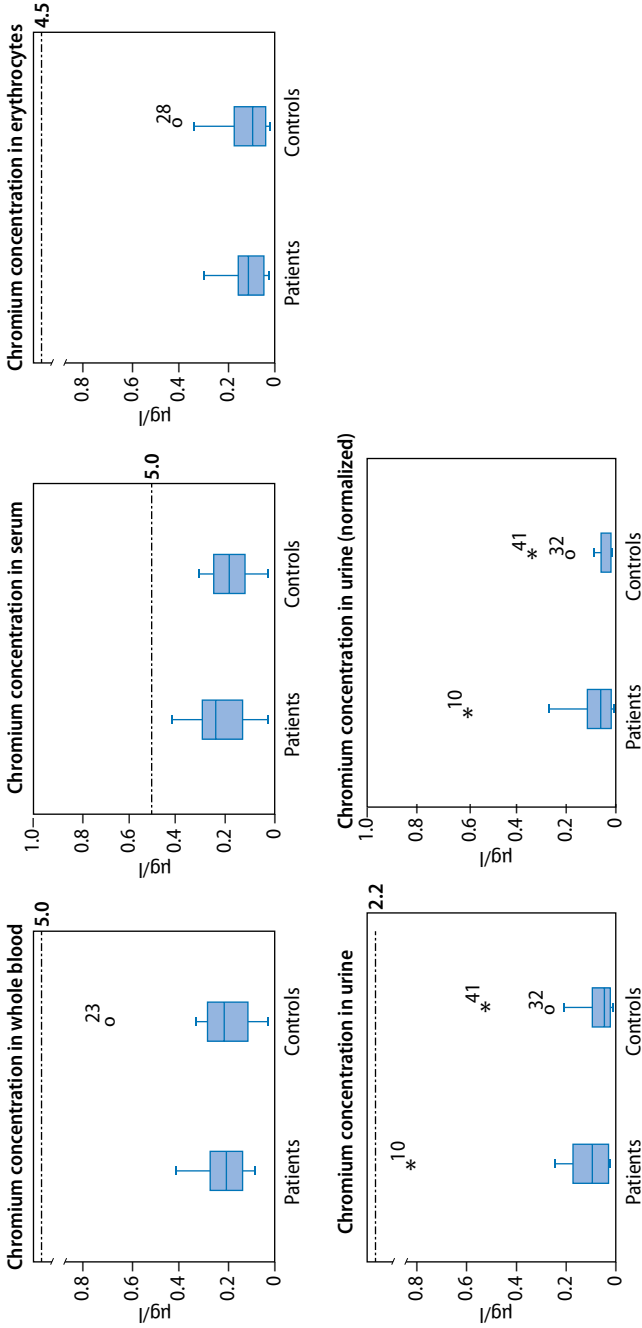


Fig. 8 Boxplot representing the distribution of data collected. Boxes are limited by values of the 25th and 75th percentile. Horizontal line crossing the box represents the median value, while vertical lines extend from minimum to maximum values. The outliers are shown with * or °, depending on the distance from the 25th and 75th percentile (greater than 3 interquartile differences or greater than 1.5) and the number close to the symbol identifies the sample. Dotted lines represent higher reference value. From [49], with friendly permission by Hip International

it can be concluded that no relevant chromium release from Biolox[®]delta couplings was observed. The explanation is that because of the chemical structure of Biolox[®]delta with its strong ionic interatomic bonding a release of chromium ions is unlikely to happen in all four matrices. These results confirm the safety of Biolox[®]delta materials concerning the release of chromium ions and the possibility of using it as an excellent alternative material to metal-based bearing couples.

Take-Home-Message

Ceramic Composite Material (Biolox[®]delta)

- No relevant chromium release
- Safe with regard to chromium ion release
- Excellent alternative material to metal-based bearing couplings

5 Use of Alternative Materials in Patients with Allergy to Implant Material and Adverse Reactions to Metal Debris

Implantable metallic devices have become part of therapeutic routine. In some patients with complications, allergy to implant components (metals, bone cement) can be detected. Thus, concerns regarding the risk of allergy-related implant failure have stimulated the interest in alternative “hypoallergenic” materials. There is growing evidence that in patients with metal sensitivity and proven orthopedic dermatitis, peri-implant inflammation, or adverse reactions to metal debris, good results can be achieved by revision with nonmetallic components. In addition, surface-coated or zirconium and titanium–niobium primary implants are available as alternatives for allergic patients. The hypersensitivity/immune reactions associated with MoM bearings are only partly defined, but it is agreed that they reflect metal intolerance in such patients. Correspondingly, in patients with complications and adverse reactions to metal debris, the treatment and revision including the use of a non-MoM bearing couple (often ceramic on ceramic) led to resolution of symptoms [51]–[77]. In patients with complications after knee arthroplasty, allergy to metals and bone cement components can be found more frequently than in symptom-free individuals [17]. ■ Fig. 9 shows a patient with a knee arthroplasty and local dermatitis associated with nickel sensitization.

It is apparent from the literature, despite the low number of clinical studies, that good results and symptom relief can be obtained by revision with “hypoallergenic” materials. Dietrich et al. reported on a series of metal-allergic knee arthroplasty patients, whose symptoms disappeared upon revision with titanium-based arthroplasty [78]. Thomsen and coauthors describe a chromate-allergic patient, in whom local eczema and pain disappeared when the identical but surface-coated knee arthroplasty was used for revision [79]. Bergschmidt et al. presented a case involving the revision of total knee arthroplasty using a ceramic femoral component. This approach was chosen owing to nickel allergy and concomitant lymphoplasmacellular peri-implant inflammation [80]. Furthermore, in a case of



■ Fig. 9 Patient with knee arthroplasty and local dermatitis associated with nickel sensitization

posttraumatic osteoarthritis, a TKA with a ceramic femoral component was performed successfully. The patient also suffered from arthrofibrosis together with a proven nickel allergy [81].

In another study, the clinical impact of metal allergy on implant performance was assessed by a combined approach of patch testing, peri-implant histology, and periprosthetic cytokine assessment. The connection between metal sensitivity and the outcome of the “hypoallergenic” revision implant could be demonstrated by the patients’ markedly improved WOMAC score [40]. It is to be assumed that as the number of patients with revision using “hypoallergenic” implants increases, it will provide larger series for follow-up studies and enable a better characterization of implant intolerance reactions.

Take-Home-Message

- Good results and symptom relief by revision with “hypoallergenic” materials

6 Conclusion

The umbrella term “adverse reaction” encompasses a series of conditions, of which metal implant allergy represents the hypersensitivity type of immune reaction. The diagnosis of “implant allergy” – after exclusion of other problem elicitors such as infection (■ Fig. 10)



■ Fig. 10 Skin reaction associated with hip arthroplasty: allergy or infection?

– results from the synopsis of several diagnostic steps including medical history, clinical findings, patch testing, analysis of peri-implant tissue, and LTT. Alternatives for metal-sensitive patients include nonmetallic components, surface-coated, or zirconium and titanium–niobium primary implants. The immuno-allergological compatibility of ceramic materials in arthroplasty has been shown by clinical patient data and by *in vitro* and *in vivo* experiments, including safety assessment in terms of chromium ion release.

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Clinical Management of Joint Arthroplasty

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In addition, it also addresses medical practitioners and scientists of adjacent specialist disciplines who are not confronted on a daily basis with problems regarding endoprosthetics but, when required, would like to access important information on a specific topic.

Metal Implant Allergy

The clinical guide is one of a series written for orthopaedic surgeons who seek help in how to proceed when an allergic reaction is suspected to any metal implant component, such as nickel, cobalt, or chromium or to bone cement components. An algorithm is being provided as a laminated insert.



ISBN 978-3-662-47439-6



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