

Metal sensitivity in patients with orthopaedic implants: a prospective study

Elena Frigerio¹, Paolo D. Pigatto¹, Gianpaolo Guzzi² and Gianfranco Altomare¹

¹Department of Technology for Health, Dermatological Clinic, IRCCS Galeazzi Hospital, University of Milan, Milan 20161, Italy and ²Italian Association for Metals and Biocompatibility Research – A.I.R.M.E.B., Milan 20161, Italy

doi:10.1111/j.1600-0536.2011.01886.x

Summary

Background. Sensitization to orthopaedic implant materials is an unpredictable event that might affect implant performance.

Objectives. In candidates for hip or knee joint prosthesis implantation, to evaluate preoperative assessments for identifying patients with metal sensitivity, to determine the percentage of patients who developed metal sensitivity at 1 year after prosthesis implantation, and to examine the clinical relevance of patch tests and lymphocyte transformation tests (LTT-MELISA[®]) for the evaluation of metal sensitization.

Patients and methods. A total of 100 patients referred for total hip or total knee arthroplasty were assessed preoperatively and then at 1 year post-implantation by means of patch tests with the metals present in the implant alloys. In a pilot study, 20 patients also underwent both patch testing and a lymphocyte transformation test (LTT-MELISA[®]) for the same metals.

Results. Only 72 of 100 patients were patch tested both before and after surgery, and 12 of 20 also underwent LTT-MELISA[®] before and after surgery. Of 31/100 patients with an apparent history of nickel sensitivity determined during preoperative assessment of subjects, 12 tested negative on both tests, and 4 with a negative history of nickel sensitivity tested positive. One year post-implantation (72 patients), 5 patients who had initially tested negative for a metal allergy became positive for at least one or more metal constituents of the prosthesis on at least one or the other test.

Conclusions. Given the discrepancies between the information obtained while taking patient histories and test results, preoperative history-taking alone appears to be insufficient for identifying patients with metal sensitivity. Moreover, the increase in the percentage of patients who tested positive for metal sensitivity 1 year post-implantation suggests the possibility of prosthesis-induced sensitization. Therefore, objective determination of metal sensitivity at preoperative assessment should be considered in planning arthroplasty intervention, as it would help the surgeon in selecting the most appropriate prosthesis for the patient and could benefit implant performance.

Key words: arthroplasty/hip replacement; lymphocyte activation; metal hypersensitivity; metals/adverse effects; osteoarthritis; patch testing; prostheses and implants/adverse effects.

Materials used in orthopaedic prostheses generally demonstrate good biocompatibility. Because of long-term

contact with biological tissues and mechanical action, they undergo corrosion, degradation, and wear, which results in the production of wear particles and metallic ions. Wear-debris particles may, in a few cases, lead to a chronic inflammatory reaction in the periprosthetic region, resulting in implant failure caused by macrophage-stimulated aseptic osteolysis. So-called 'debris disease' is the principal biological mechanism underlying prosthesis loosening and failure (1, 2). Metals

Correspondence: Professor Paolo D. Pigatto, Department of Technology for Health, Dermatological Clinic, IRCCS Galeazzi Hospital, University of Milan, Milan 20161, Italy. Tel: +39 (02) 662 141; Fax: +39 (02) 6621 14800. E-mail: paolo.pigatto@unimi.it

Conflicts of interest: The authors have declared no conflicts.

Accepted for publication 15 January 2011

and polymers are the main components of orthopaedic prostheses. Metals as debris or in the form of metal ions can activate the immune system by inducing a delayed-type hypersensitivity reaction (3–8). The response of metal-specific lymphocytes has been linked to poor implant performance. It is thought that the stimulated T-cells generate pro-osteoclastogenic factors that can alter bone homeostasis (7). The most common sensitizing orthopaedic metals are nickel, cobalt, and chromium; even metal immune hypersensitivity to titanium and vanadium has been sometimes reported (9–11). Polymeric biomaterial such as acrylic bone cements are degraded to smaller, water-soluble methacrylates, and immune reactivity to polymethylmethacrylates or other constituents of prostheses has been occasionally reported (12, 13).

Various studies have investigated possible correlations between sensitization to orthopaedic metals and implant failure. It has been reported that the mean prevalence of metal sensitivity in the general population is 10–17% (in recent years, 10% in women and 1% in men) (14, 15), whereas it is 25% in patients with a functioning prosthesis, and 60% in patients with implant failure (about six times higher than in the general population) (16, 17). Although this remains controversial, most investigators have concluded that metal sensitivity can be a contributory factor to implant failure, because of the high proportion of delayed-type hypersensitivity to metals in patients with prosthesis loosening (16, 17), and the shorter lifespan of the implant in patients with a positive patch test reaction to metals (18). This prospective study used preoperative history-taking for the identification of patients with metal sensitivity, as well as *in vivo* patch tests and *in vitro* lymphocyte transformation tests (LTT-MELISA®). We also wanted to study whether some patients developed hypersensitivity to the metals present in the implants 1 year post-implantation, and to validate the clinical relevance of positive reactions to implant materials.

Patients and Methods

Between June 2007 and September 2008, 100 patients (27 men and 73 women; mean age, 68 years; range, 51–84 years) were enrolled in this prospective study. All patients were candidates for the first arthroplasty intervention of total hip or knee joint replacement for osteoarthritis. The study protocol was approved by the local Ethics Committee, and all patients gave written informed consent. The subjects were randomly recruited from patients attending the Department of Orthopaedics for preoperative assessment prior to total hip arthroplasty or total knee arthroplasty. For each patient, a detailed

history was taken, including the following: (i) a history of metal allergy, such as metal-induced contact dermatitis, documented by previous skin tests or known intolerance to earrings, jeans buttons, and other items reported by the patient; (ii) the medical conditions that led to the need for arthroplasty, as well as concomitant illnesses; (iii) the presence of other orthopaedic implants; and (iv) drug therapy.

Of 100 patients, 48 underwent total hip arthroplasty and 52 total knee arthroplasty. The main materials used for implants were: Co–Cr–Mo alloy (Co 60%, Cr 30%, Mo 7%, Ni 1%, and Fe 1%), Ti–Al–V alloy (Ti 90%, Al 6%, and V 4%), ceramic, and polyethylene (Table 1). At the beginning of the study, no subjects presented with skin signs of metal contact allergy. Patients were excluded from the study if the following applied: if they had received an orthopaedic implant previously; and if they had immune disease and/or were under corticosteroid or other immunosuppressant therapy.

Metal allergy was tested before and 1 year after the operation by patch testing, with the following: nickel sulfate, 5% in petrolatum; cobalt chloride, 1% pet; potassium dichromate, 0.5% pet; molybdenum (metal), 5% pet; copper sulfate, 2% pet; tin (metal), 50% pet; titanium (metal), 10% pet; vanadium (metal), 5% pet; silver nitrate, 1% aqua; and palladium chloride, 2% pet. (Chemotechnique Diagnostics, Vellinge, Sweden). All patients were tested according to the guidelines proposed by the Società

Table 1. Clinical characteristics of metal allergy and treatment of patients (n = 100) undergoing orthopaedic surgery

	No. of patients (%)
Sex	
Female	73 (73)
Male	27 (27)
Positive (suggestive) clinical history for metal allergy	31 (31)
Total hip arthroplasty	48
Metal composition of implant	
Acetabular cup/femoral stem	
Co–Cr–Mo alloy	10 (20)
Ti–Al–V alloy	14 (30)
Co–Cr–Mo/Ti–Al–V alloys	24 (50)
Coupling (cup/femoral head):	
Metal-on-metal	12 (25)
Ceramic-on-ceramic	7 (15)
Metal-on-polyethylene	7 (15)
Ceramic-on-polyethylene	22 (45)
Total knee arthroplasty	52
Metal composition of implant	
Femoral/tibial component	
Co–Cr–Mo/Ti–Al–V alloys	33 (70)
Ti–Al–V alloy	9 (10)
Co–Cr–Mo alloy	10 (20)

Italiana di Dermatologia Allergologica Professionale e Ambientale (SIDAPA) and based on international guidelines (19, 20). Readings were made at day 4; an additional reading was, in some cases, made at day 7. Of the total of 100 patients, 20 also underwent LTT-MELISA® to evaluate the memory lymphocyte response to the metal salts. Blood samples for LTT-MELISA® testing were taken from patients during the first medical investigation (before orthopaedic intervention) and 1 year after treatment (follow-up). The reactivity of lymphocytes to metals was assessed by the uptake of tritiated thymidine, as described previously (21–23). The increase in [³H]thymidine incorporation into metal-treated cultures was expressed as a stimulation index (SI), which is calculated as the isotope uptake by lymphocytes in metal-treated cultures divided by the mean isotope uptake in untreated control cultures. Lymphocyte responses induced by metals were characterized by the maximal response obtained with each metal salt. SI ≥ 3 indicated a positive response, and SI > 2 but < 3 indicated a weakly positive response. For morphological evaluation, aliquots were taken from 5-day cultures indicating weakly positive or positive responses by isotope incorporation, as well as from control cultures, and smears were prepared in a cytocentrifuge (Thermo Electron Corporation, Marietta, OH, USA) and stained with a Diff Quick® staining kit. The results were considered to be positive only if increased incorporation of [³H]thymidine was confirmed by the presence of lymphoblasts on cell smears.

Results

The results of the preoperative assessment are summarized in Tables 2 and 3. The percentage of candidates for arthroplasty intervention with metal sensitivity was 23%. Most of the tests were positive for nickel (21 patients), and 8 patients were positive for cobalt, 3 for palladium, 2 for chromium, and 2 for molybdenum. In 16/100 patients,

Table 2. History and results of patch testing in preoperative assessment

History	Patch tests	No. of patients (n = 100)	No. of patients: allergens
Positive	Positive	18	7: Ni 6: Ni, Co 2: Ni, Pd 1: Ni, Cr 1: Ni, Co, Cr, Pd 1: Mo
Negative	Negative	66	—
Positive	Negative	13	MELISA® in 3 patients: 2 negative; 1 positive (Ni SI = 3.5)
Negative	Positive	3	2: Ni 1: Ni, Co and MELISA® (Ni SI = 6.3)

SI, stimulation index.

the findings from the medical history differed from the test results. The results of patch tests and of the LTT-MELISA® test 1 year after orthopaedic surgery are shown in Tables 4 and 5. Of the 72 patients who completed the study (17 men and 55 women), only 12 had undergone both patch testing and LTT-MELISA®. The main reasons for withdrawal from the study were logistic or family problems, and one patient died. The final analysis was conducted on the remaining 72 patients: 16/72 (22%) were noted to have metal sensitivity before surgery and 21/72 (29%) after surgery.

The incidence of new cases of orthopaedic metal sensitization was 6.5%.

Specifically, 5 patients who tested negative before surgery changed to testing positive to at least one metal present in their prosthesis material, as summarized in Table 6. Patient 1 had experienced pain without radiographic evidence of implant loosening. Patient 5, who underwent both patch testing and LTT-MELISA®

Table 3. History-taking and results of patch and MELISA® testing on preoperative assessment

History	Patch tests	MELISA®	No. of patients (%) (n = 20)	No. of patients: allergens
Positive	Positive	Positive	3 (15)	1: Ni, Co and MELISA® Ni SI = 12 1: Ni and MELISA® Ni SI = 3.9 1: Ni, Cr and MELISA® Ni SI = 7.1
Negative	Negative	Negative	9 (45)	—
Positive	Positive	Negative	3 (15)	2: Ni 1: Ni, Co, Pd, Cr Ni SI = 3.5 Mo SI = 7.4
Positive	Negative	Positive	1 (5)	—
Negative	Negative	Positive	1 (5)	—
Positive	Negative	Negative	2 (10)	—
Negative	Positive	Positive	1 (5)	Ni, Co and MELISA® Ni SI = 6.3

SI, stimulation index.

Table 4. Comparison between history-taking and patch testing in preoperative and postoperative assessments at 1 year (n = 72 patients who completed the study)

History	Patch tests	No. of patients (%) before surgery (n = 72)	No. of patients (%) after surgery (n = 72)	Comments
Positive	Positive	15 (21)	14 (19)	1 patient who was Ni-positive converted to negative status
Negative	Negative	50 (70)	46 (64)	—
Positive	Negative	6 (8)	7 (10)	—
Negative	Positive	1 (1)	5 (7)	—

testing, had a positive history of metal sensitivity. This 61-year-old woman had developed allergic contact dermatitis from wearing earrings many years earlier, but, in recent years, she had not experienced problems with wearing metal jewellery. On preoperative assessment, both patch testing and LTT-MELISA® were negative; on postoperative examination, the patch test was still negative but LTT-MELISA® showed positive reactions to nickel (SI 3.5) and molybdenum (SI 12.7). To date, none of the patients has developed cutaneous signs attributable to metal sensitization, or experienced implant loosening after total hip arthroplasty or total knee arthroplasty.

Discussion

The results of this study show that, in some patients, the information obtained by taking a preoperative medical history of metal sensitivity differed from the data obtained by patch testing and *in vitro* LTT-MELISA® testing. Comparison of the findings from history-taking and those

from patch testing demonstrated that history-taking was far less reliable (85.5% sensitivity; 83.5% specificity) than patch testing for ascertaining metal sensitivity. Our results are in accordance with other studies showing that the validity of self-reported nickel allergy is low (24). The LTT-MELISA® test for metal sensitivity seems to give additional information, but the number of patients tested was too small, and a much larger study is necessary to answer the questions about the predictive value of this *in vitro* test for metal sensitivity in the orthopaedic setting.

On preoperative assessment, 23% of our patients showed metal sensitivity, nearly double the rate in the general population (15). This difference most likely results from the fact that 73% of the patients studied were elderly women, in whom the percentage appears to be higher (14). Most of our patients tested positive for nickel (21%), followed, in descending order, by cobalt (8%), palladium (3%), chromium (2%), and molybdenum (2%). Positivity for cobalt, chromium and palladium was always associated with a positive reaction to nickel, probably because of cross-reactivity. Among patients who completed the study, the percentage testing positive to metals 1 year after surgery increased only from 22% to 29%, indicating a possible but not statistically significant involvement of the implant in inducing sensitization (*p* = 0.34). These findings are in accord with previous studies reported by other investigators (17, 25, 26).

The 5 patients who developed post-intervention metal sensitivity had been implanted with a prosthesis with at least one component of Co–Cr–Mo alloy (Co 60%, Cr 30%, Mo 7%, Ni 1%, and Fe 1%), and 4 patients became positive for nickel and one for cobalt. None of our patients tested positive for titanium or vanadium, either before or after the surgical procedure, but, as the frequency of immunological sensitivity to titanium is low (9–11), this might be attributable to the relatively low number

Table 5. Relationship between history-taking, patch testing and LTT-MELISA® in preoperative and postoperative assessments at 1 year (N = 12 patients who completed the study)

History	Patch tests	MELISA®	No. of patients before surgery (n = 12)		No. of patients after surgery (n = 12)	
				No. of patients: allergens		No. of patients: allergens
Positive	Positive	Positive	3	—	3	1: MELISA® Ni SI = 3.9 before, then negative after surgery
Negative	Negative	Negative	6	—	5	—
Positive	Positive	Negative	2	1: Ni, Co, Cr 1: Ni	2	1: MELISA® negative before, then Ni SI = 7.2 1: remained negative on MELISA®
Positive	Negative	Positive	0	—	1	1: MELISA® Ni SI = 3.5, Mo SI = 12.7
Positive	Negative	Negative	1	—	0	—
Negative	Negative	Positive	0	—	1	1: MELISA® Ni SI = 3.3

SI, stimulation index.

Table 6. Characteristics of 5 patients becoming positive to tests after surgery

Patients/age (years)	History	Patch test before surgery	MELISA® before surgery	Type and materials of implant	Patch test after surgery	MELISA® after surgery
1. M.B./70	Negative	Negative	—	Total knee arthroplasty: Femoral: Co–Cr–Mo alloy Tibial: Co–Cr–Mo alloy	Ni ++	—
2. M.M./71	Negative	Negative	—	Total hip arthroplasty: Stem: Ti–Al–V alloy Cup: Co–Cr–Mo alloy Coupling: metal on polyethylene	Co ++	—
3. MA.R./70	Negative	Negative	—	Total knee arthroplasty: Femoral: Co–Cr–Mo alloy Tibial: Ti–Al–V alloy	Ni ++	—
4. B.P./56	Negative	Negative	—	Total hip arthroplasty: Stem: Co–Cr–Mo alloy Cup: Co–Cr–Mo alloy Coupling: metal on metal	Ni ++	—
5. MG.R/61	Positive	Negative	Negative	Total hip arthroplasty: Stem: Ti–Al–V alloy Cup: Co–Cr–Mo alloy Coupling: metal on metal	Negative	Ni (SI = 3.5) Mo (SI = 12.71)

SI, stimulation index.

Couplings on metal are Co–Cr–Mo alloy.

of patients studied. Sensitization to implant materials is an unpredictable event, and is usually recognized by cutaneous manifestations. The first report dates back to 1966 (27), and this was followed by a number of case reports describing localized forms involving the skin over the implant (eczema and pruritus) and generalized forms (widespread pruritus, eczema, urticaria, and vasculitis) (28–30). Thus, it can be concluded from the published data that, despite the higher prevalence of metal sensitization after prosthesis implantation, symptoms presenting as cutaneous complications are relatively rare. This has also been confirmed in our patient group, where none of the patients studied exhibited cutaneous manifestations. Cell-mediated hypersensitivity appears to play a key role in influencing implant performance. Although not all authors agree with this view (31), data from various studies have underlined its importance in the onset or acceleration of events that lead to implant failure (16–18). A local immune response may induce or accelerate inflammatory processes involved in implant failure. Sensitization to at least one metal component of an implant, as well as a clinical history of allergic contact dermatitis caused by metals, seems to have a negative impact on implant lifespan.

For example, although a total hip arthroplasty prosthesis usually has a mean lifespan of about 120 months, the implant lifespan is reduced to 78 months in patients testing positive and/or with a history of allergic contact

dermatitis caused by metals (18). A shorter implant lifespan of a total hip arthroplasty prosthesis in patients with metal allergy emphasizes the relevant role of metal-induced delayed-type hypersensitivity in implant failure. The debate is still open on which type of test (*in vivo* or *in vitro*) is better able to detect sensitization to orthopaedic implant metals. The frequency of positive patch test reactions reported by Granchi et al. (25) was similar to that obtained with *in vitro* LTT testing by Hallab et al. (32). Owing to funding limitations, we were able to perform both tests on only 20 patients, and only 12 patients completed the study. Therefore, comparison of those two test methods has to be the subject of future studies. Patch testing has certain advantages over *in vitro* testing: it is less expensive and there is no need for specialist laboratory services, although it requires skilled and trained personnel. For clinical purposes, this makes patch testing more suited for preoperative screening of candidates for prosthesis implantation. Unfortunately, the *in vivo* application of nickel might potentiate nickel-specific allergy in already sensitized individuals, and thus might be contraindicated in certain subgroups. Furthermore, patch testing might be less suitable for titanium allergy, as titanium dioxide salts and the titanium metal used in this study are not soluble, and are therefore not able to penetrate the skin under the conditions of patch testing (23).

In vitro testing might be more sensitive in this respect, as demonstrated by several authors (9, 11, 23). For example, Müller et al. (11) reported on 56 patients who

developed health problems after receiving titanium-based implants. In the LTT-MELISA® test, more than half responded with increased proliferation in response to titanium dioxide, although they were all patch test-negative. Clinical symptoms disappeared or improved rapidly after implant replacement. We would also like to point out that the use of different metal preparations in patch testing and *in vitro* LTT testing makes comparison of the two methods difficult. For example, in this study, molybdenum, vanadium and titanium were used in the form of metals in patch testing, whereas metal salts were used for LTT testing. In the absence of any data on the actual release of metal ions under the conditions of patch testing, it is difficult to draw any conclusions about the clinical relevance of such testing. *In vitro* LTT uses metals in the form of water-soluble salts, with the exception of titanium dioxide, which is water-insoluble. Nevertheless, titanium dioxide particles are engulfed by monocytes and macrophages, and are thus clearly accessible to immunocompetent cells (22).

Although complications in metal-allergic patients appear to be generally rare (31), implantation of a prosthesis containing metals to which the patient is sensitized (perhaps resulting from a prior implant) could trigger early events leading to implant failure or a shorter implant lifespan, as also recently described by Summer et al. (33).

In light of these considerations, and based on our results, despite some important limitations of our study, such as small sample size and a short-term follow-up period, we believe that testing both with *in vivo* and *in vitro* methods should be performed in the planning phase of arthroplasty interventions, as it allows the surgeon to select the best prosthesis for the patient.

Acknowledgements

We would like to thank Dr Cristian Ricci for assistance with statistical analysis.

References

- Hallab N J, Jacobs J J. Biologic effects of implant debris. *Bull NYU Hosp Jt Dis* 2009; **67**: 182–188.
- Pioletti D P, Leoni L, Genini D, Takei H, Du P, Corbeil J. Gene expression analysis of osteoblastic cells contacted by orthopedic implant particles. *J Biomed Mater Res* 2002; **61**: 408–420.
- Merritt K, Rodrigo J J. Immune response to synthetic materials: sensitization of patients receiving orthopaedic implants. *Clin Orthop Relat Res* 1996; **326**: 71–79.
- Wooley P H, Petersen S, Song Z, Nasser S. Cellular immune responses to orthopaedic implant materials following cemented total joint replacement. *J Orthop Res* 1997; **15**: 874–880.
- Yang J, Black J. Competitive binding of chromium, cobalt and nickel to serum proteins. *Biomaterials* 1994; **15**: 262–268.
- Yang J, Merritt K. Production of monoclonal antibodies to study corrosion products of CO-CR biomaterials. *J Biomed Mater Res* 1996; **31**: 71–80.
- Purdue P E, Koulouvaris P, Potter H G, Nestor B J, Sculco T P. The cellular and molecular biology of periprosthetic osteolysis. *Clin Orthop Relat Res* 2007; **454**: 251–261.
- Gamerding K, Moulon C, Karp D R et al. A new type of metal recognition by human T cells: contact residues for peptide-independent bridging of T cell receptor and major histocompatibility complex by nickel. *J Exp Med* 2003; **197**: 1345–1353.
- Lalor P A, Revell P A, Gray A B, Wright S, Railton G T, Freeman M A. Sensitivity to titanium. A cause of implant failure? *J Bone Joint Surg Br* 1991; **73**: 25–28.
- Sicilia A, Cuesta S, Coma G et al. Titanium allergy in dental implant patients: a clinical study on 1500 consecutive patients. *Clin Oral Implants Res* 2008; **19**: 823–835.
- Müller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence. *Neuro Endocrinol Lett* 2006; **27**: 31–35.
- Haddad F S, Cobb A G, Bentley G, Levell N J, Dowd P M. Hypersensitivity in aseptic loosening of total hip replacements: the role of constituents of bone cement. *J Bone Joint Surg Br* 1996; **78**: 546–549.
- Gil-Albarova J, Laclériga A, Barrios C, Cañadell J. Lymphocyte response to polymethylmethacrylate in loose total hip prostheses. *J Bone Joint Surg Br* 1992; **74**: 825–830.
- Thyssen J P, Linneberg A, Menné T, Johansen J D. The epidemiology of contact allergy in the general population – prevalence and main finding. *Contact Dermatitis* 2007; **57**: 287–299.
- Thyssen J P, Linneberg A, Menné T et al. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. *Br J Dermatol* 2009; **161**: 1124–1129.
- Hallab N, Merritt K, Jacobs J J. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001; **83-A**: 428–436.
- Jacobs J J, Goodman S B, Sumner D R, Hallab N J. Biologic response to orthopaedic implants. In: *Orthopaedic Basic Science: Biology and Biomechanics of the Musculoskeletal System*, Buckwalter J A, Einhorn T A, Simon S R (eds): Rosemont, American Academy of Orthopaedic Surgeons, 2001: pp. 401–426.
- Granchi D, Cenni E, Trisolino G, Giunti A, Baldini N. Sensitivity to implant materials in patients undergoing total hip replacement. *J Biomed Mater Res B Appl Biomater* 2006; **77**: 257–264.
- Bourke J, Coulson I, English J. British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of contact dermatitis: an update. *Br J Dermatol* 2009; **160**: 946–954.
- Bourke J, Coulson I, English J. British Association of Dermatologists. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001; **145**: 877–885.
- Stejskal V, Cederbrandt K, Lindvall A, Forsbeck M. MELISA – an *in vitro* tool for the study of metal allergy. *Toxicol In Vitro* 1994; **8**: 991–1000.
- Stejskal V, Hudecek R, Stejskal J, Sterzl I. Diagnosis and treatment of metal-induced side-effects. *Neuro Endocrinol Lett* 2006; **27**: 7–16.

- 23 Valentine-Thon E, Müller K, Guzzi G, Kreisel S, Ohnsorge P, Sandkamp M. LTT-MELISA is clinically relevant for detecting and monitoring metal sensitivity. *Neuro Endocrinol Lett* 2006; **27**: 17–24.
- 24 Josefson A, Färm G, Meding B. Validity of self-reported nickel allergy. *Contact Dermatitis* 2010; **62**: 289–293.
- 25 Granchi D, Cenni E, Tigani D, Trisolino G, Baldini N, Giunti A. Sensitivity to implant materials in patients with total knee arthroplasties. *Biomaterials* 2008; **29**: 1494–1500.
- 26 Willert HG, Buchhorn GH, Fayyazi A et al. Metal on metal bearings and hypersensitivity in patients with artificial hip joints: a clinical and histomorphological study. *J Bone Joint Surg Am* 2005; **87**: 28–36.
- 27 Foussereau J, Laugier P. Allergic eczemas from metallic foreign bodies. *Trans St Johns Hosp Dermatol Soc* 1966; **52**: 220–225.
- 28 Rostoker G, Robin J, Binet O et al. Dermatitis due to orthopaedic implants: a review of the literature and report of three cases. *J Bone Joint Surg Am* 1987; **69**: 1408–1412.
- 29 Balato N, Costa L, Lembo G et al. Allergic contact dermatitis from orthopaedic devices. *Contact Dermatitis* 1995; **32**: 314–315.
- 30 Kubba R, Taylor J S, Marks K E. Cutaneous complications of orthopedic implants: a two-year prospective study. *Arch Dermatol* 1981; **117**: 554–560.
- 31 Thyssen J P, Jakobsen S S, Engkilde K et al. The association between metal allergy, total hip arthroplasty, and revision. *Acta Orthop* 2009; **80**: 646–652.
- 32 Hallab N J, Anderson S, Stafford T, Glant T, Jacobs J J. Lymphocyte responses in patients with total hip arthroplasty. *J Orthop Res* 2005; **23**: 384–391.
- 33 Summer B, Paul C, Mazoochian F et al. Nickel (Ni) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni. *Contact Dermatitis* 2010; **63**: 15–22.