International Orthopaedics (SICOT) (2014) 38:2231–2236
DOI 10.1007/s00264-014-2367-1

ORIGINAL PAPER

A prospective study concerning the relationship between metal allergy and post-operative pain following total hip and knee arthroplasty

Yirong Zeng · Wenjun Feng · Jie Li · Lu Lu · Chuntao Ma · Jianchun Zeng · Feilong Li · Xinyu Qi · Yueguang Fan

Received: 13 April 2014 / Accepted: 22 April 2014 / Published online: 10 June 2014

Abstract
Purpose A prospective study was conducted to detect whether a relationship exists between metal allergy and post-operative pain in total hip and knee arthroplasty patients. We postulated that to some extent a relationship does exist between them.
Materials and methods Patients who had undergone total hip and knee arthroplasty surgery because of hip and knee disease were included. The exclusion criteria were patients who were treated with immunosuppressor two weeks pre-operatively, skin conditions around the patch testing site, and other uncontrollable factors. Each patient agreed to patch testing for three days before surgery. Photographic images before patch testing, two and three days after patch testing were obtained to evaluate the final incidence of metal allergy. The patch tests contained 12 metal elements; chromium, cobalt, nickel, molybdenum, titanium, aluminium, vanadium, iron, manganese, tin, zirconium, and copper. Two independent observers evaluated the images. The results were divided into a non-metal allergy group and a metal allergy group. Pre-operative and postoperative VAS score, lymphocyte transforming test, and X-rays were collected to detect the relationship between metal allergy and post-operative pain following total hip and knee arthroplasty.
Results There were 96 patients who underwent pre-operative patch testing. The overall metal allergy rate was 51.1 % (49/96) in our study. Nickel, cobalt, manganese, and tin were the most common allergic metal elements in our study. Nine inappropriate cases were excluded, and 87 patients were finally included in our study. There were 36 metal allergy and 26 non-metal allergy patients in the THA group, while 11 metal allergy and 14 non-metal allergy patients were found in the TKA group. We found no relationship existed between metal allergy and post-surgery pain in total hip and knee arthroplasty.
Conclusion Pain caused by metal allergy usually presents as persistent and recurrent pain. The white cell count, C-reactive protein, erythrocyte sedimentation rate and postoperative radiographs were not affected. Currently, patch testing and lymphocyte transforming tests are used for metal allergy diagnosis. We deemed that a relationship between post-surgery pain and metal allergy in total hip and knee patients may exist to some extent. Larger samples and longer follow-up time are essential for further study.

Keywords Metal allergy · Patch testing · Lymphocyte transforming test · Post-surgery pain · Total hip arthroplasty · Total knee arthroplasty

Background

Patients who suffer from diseases, such as osteoarthritis, rheumatoid arthritis, osteonecrosis, etc. have benefited from total joint arthroplasty (TJA refers to total hip arthroplasty and total knee arthroplasty regardless of any

Yirong Zeng and Wenjun Feng contributed equally to this article.

Y. Zeng (✉) · W. Feng · J. Li · L. Lu · C. Ma · J. Zeng · F. Li · X. Qi · Y. Fan
Orthopadic Department of The First Affiliated Hospital, Guangzhou University of Traditional Chinese Medicine, Guangzhou, China
e-mail: 13711456292@163.com

W. Feng
e-mail: foreverarsene@126.com

other replacement surgery) have been frequently treated in our clinical practice [1–3]. From the introduction of the first generation of artificial joints, there has been a great of advancement in the design and materials leading to low wear rates, and thus longevity of use.

Currently, there are a multiplicity of prostheses available, including metal-on-metal, metal-on-polyethylene, ceramic-on-polyethylene, and ceramic-on-ceramic implants for total hip arthroplasty (THA), while only the metal-on-polyethylene prosthesis is available for total knee arthroplasty (TKA). All these prostheses are divided according to their bearing surfaces. Not only THA prostheses but also TKA prostheses have some metallic parts apart from the bearing surfaces which may lead to metal allergy reactions [4]. Hans Georg Willert et al. [5] reported that histological analysis of the periprosthetic tissues from revision surgeries in patients who underwent primary metal-on-metal THA revealed vasculitis with perivascular, postcapillary venules infiltrated by intramural lymphocytes, recurrent localised bleeding, and necrosis, which was defined as delayed type-IV hypersensitivity mediated by T-lymphocyte cells [6–9]. Innocenti et al. [10] found that approximately 16.6 % of metal hypersensitivity incidence existed in patients who underwent TKA, though the number was small.

As to the symptoms of metal allergy, presentation varies. Some patients complained of skin manifestations, such as contact dermatitis, localised eczema, bullous eruption, and other undefined cutaneous lesions [11–13]. Localised recurrent pain, swelling, tenderness, and failure of implants were also reported [14–16]. It is hard to differentiate metal allergy from periprosthetic infection because both clinical symptoms and radiological findings are to some extent alike [17]. The patch testing procedures of the potential allergen are wildly used to detect metal allergy reactions because of their high specificity and sensitivity [18–20]. Our study was aimed at detecting whether or not there was a correlation between metal allergy and post-surgery pain following TJA through the patch testing results.

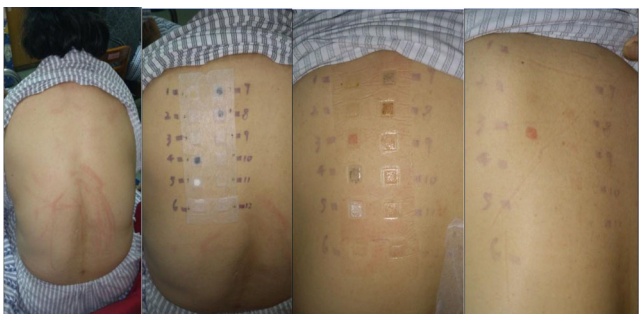
Methods and materials

Before the study was commenced, we registered at the site http://www.chictr.org and received the registry number ChiCTR-ONRC-12002425. Thereafter, we presented our program to the ethnics committee of our hospital and received approval after serious review. Patients who suffered serious hip and knee joint dysfunction and needed to undergo total joint arthroplasty in our orthopaedic department from August, 2012 to August, 2013 provided the cases of our study. All patients were informed of the relevant benefits and risks, and written consent was obtained.

Patients who had made the decision to undergo total joint arthroplasty, as one of the treatment options, following the standard guidelines were included in our study. The exclusion criteria were as follows. First, patients that were administered an immunosuppressor because of diseases such as rheumatoid arthritis, nephrotic syndrome, systemic lupus erythematosus, etc., two weeks before surgery were excluded. Second, those with skin impairments (mainly left side of upper back) which appeared on the patch testing site, and third, patients who showed bad compliance and removed the patch reagents without informing us were also excluded.

The procedures were performed by the same surgeon (Professor Yirong Zeng) and all the patients were informed that the selected hip and knee prostheses were LINK (made in Germany) prostheses. We confirm that the study accepted no financial sponsorship and there were no conflicts of interests with any other prosthesis companies. We selected 12 metal elements for our patch testing according to the main contents of the LINK prostheses provided. The metallic elements were chromium, cobalt, nickel, molybdenum, titanium, aluminium, vanadium, iron, manganese, tin, zirconium, and copper. The left side of upper back was selected as the patch testing site owing to its flat surface and sufficiently large area (Fig. 1). Photographs of the entire patch sites were taken pre-testing. We attached the patch reagents and numbered each metal element parallel to the side after the patients had taken showers on the night before surgery. After 48 hours, the patch reagents were removed and the remaining metal elements were wiped out. We touched each chamber for primary evaluation of the patch testing results and took localised and integral pictures thereafter.

The final results were obtained when re-assessing the 12 chambers after 72 hours of patch testing and pictures were taken as mentioned above for further identification. The recommended standard interpretation of the test results were: irritant reaction (IR), referring to discrete patchy erythema without infiltration;



Pre-patch testing Time of patch testing 48 hours later 72 hours later

Fig. 1 Exact procedures of patch testing

doubtful reaction (?+), referring to faint macular, no infiltration, and homogeneous erythema; weak positive reaction ("+"), referring to erythema, papules, and infiltration; strong positive reaction ("++"), referring to erythema, papules, infiltration, and discrete vesicle; and extreme positive reaction ("+++"), referring to coalescing vesicles, bullous or ulcerative reaction (Fig. 2). We defined the irritant reaction and doubtful reaction as negative results. All evaluation results of the patch testing was completed by two independent observers. The overall incidence of metal allergy reaction was determined, and we divided those patients into metal allergy groups and non-metal allergy groups for both THA and TKA patients. We detected the relationship between metal allergy and post-operative pain following THA and TKA, respectively.

Other values were also needed to strengthen and confirm our findings. VAS scores, lymphocyte transforming test, anteroposterior and lateral X-rays of both hips and anteroposterior and lateral X-rays of the operated knee were obtained pre-operatively. We defined our observation time as three months. The lymphocyte transforming test, VAS scores, and X-rays, erythrocyte sedimentation rate (ESR), C-reaction protein (CRP) and blood analysis were added to exclude periprosthesis infection.

Results

A total of 96 patients who had undergone total hip and knee arthroplasty participated in our study. There were 30 osteoarthritis (OA) patients, 26 osteonecrosis of femoral head (ONFH) patients, two rheumatoid arthritis (RA) patients, three ankylosing spondylitis (AS) patients, and six patients who suffered other diseases in the THA group (Table 1). Fifty-three patients underwent bilateral THAs and 14 patients underwent unilateral THAs.

The mean age was 48.28±14.87 years (range 22–76 years), mean weight was 59.63±10.04 kg (range 42–75 kg), mean height was 1.62±0.08 m (range 1.48–1.75 m), and mean BMI was 22.68±3.26. While there were 29 patients (four men and 25 women) in the TKA group, there were 25 OA patients, two RA patients, and two other undiagnosed disease patients. Among them, 19 patients underwent bilateral TKAs and the remaining ten patients underwent unilateral TKAs. The mean age was 65.07±9.16 years (range 45–79 years), mean weight was 59.17±10.17 kg (range 51–102 kg), mean height was 1.56±0.07 m (range 1.48–1.71 m), and mean BMI was 24.09±3.59 (Table 2).

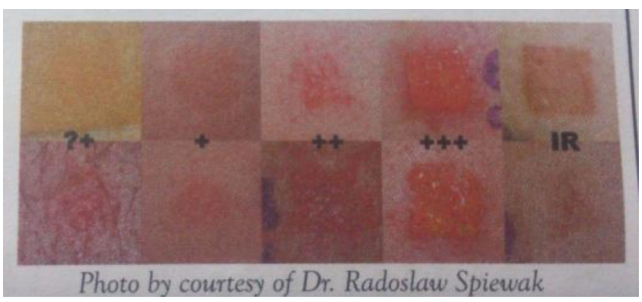


Fig. 2 Interpretation of the patch testing results

Table 1 Preoperative diagnosis in the study groups

Diagnosis	Hip disease	Knee disease
Osteoarthritis (cases)	30	25
Osteonecrosis of femoral head (cases)	26	
Rheumatoid arthritis (cases)	2	2
Ankylosing spondylitis (cases)	3	
Other diseases (cases)	6	2

In the THA group, 46 patients received ceramic-on-ceramic prostheses, 13 patients received ceramic-on-polyethylene prostheses, five patients received metal-on-polyethylene prostheses, and the remaining three patients received other kinds of prostheses. While in the TKA groups, 25 patients received Gemini MKII PS prostheses, and four patients received other kinds of prostheses. The overall metal allergy rate was 51.1 % (49/96) in our study. Nickel, cobalt, manganese, and tin were the most common allergic metal elements in our study (Table 3).

In the THA and TKA groups, we excluded seven patients from our study which aimed at detecting the relationship between metal allergy and post-surgery pain following THA and TKA because non-LINK prostheses were implanted. One patient died of high fever due to a serious and uncontrollable infection which was confirmed to not be a THA complication. Another patient was lost to follow-up contact. Consequently, 87 patients were finally included in our study. There were 36 metal allergy and 26 non-metal allergy patients in the THA group, while 11 metal allergy and 14 non-metal allergy patients were in the TKA group. For THA patients, the mean age, mean BMI index, mean VAS score (we defined VAS score here as deference value of pre-operative VAS score minus postoperative

Table 2 Demographic data in THA and TKA groups

Characteristic	THA group	TKA group
Gender (cases)		
Male	35	4
Female	32	25
Age (years)	48.28±14.87	65.07±9.16
Height (metres)	1.62±0.08	1.56±0.07
Weight (kg)	59.63±10.04	59.17±10.17
BMI index	22.68±3.26	24.09±3.59
Bilateral (cases)	54	19
Unilateral (cases)	13	10

Table 3 Rates of metal allergy in THA and TKA groups

Metal	THA group	TKA group
Chromium (%)	1.03	3.03
Cobalt (%)	11.2	3.03
Nickel (%)	15.5	7.22
Molybdenum (%)	0	0
Titanium (%)	1.04	0
Aluminium (%)	0	0
Vanadium (%)	0	0
Iron (%)	0	0
Manganese (%)	8.24	4.12
Tin (%)	18.6	3.09
Zirconium (%)	3.08	1.03
Copper (%)	5.13	1.03

pain), and mean lymphocyte transforming test in the metal allergy group were 48.33±14.74 years, 23.18±3.26, 3.75± 1.02 points, and 76.28 %±2.92 %, respectively. For patients in the non-metal allergy groups, the mean age was 48.54± 16.24 years, the mean BMI index was 22.16±3.35, mean VAS score was 3.88±1.45, and points, mean lymphocyte transforming test was 71.76 %±3.24 %. Both the demographic data (years and BMI index) and VAS score between the two groups were of no statistical significance ($p>0.05$). For TKA patients, the mean age, mean BMI index, mean VAS score, and mean lymphocyte transforming test in the metal allergy group were 67.36±7.19 years, 23.17±1.66, 4.09±0.70 points, and 78.52 %±2.64 %, respectively. For patients in the non-metal allergy groups, the mean age was 62.57±7.38 years, the mean BMI index was 24.04±1.41, mean VAS score was 3.86±1.83 points, and mean lymphocyte transforming test was 76.52 %± 2.74 %. Not only mean years, BMI index, and VAS score but also lymphocyte transforming test revealed no statistical significance between the two groups ($p>0.05$, Table 4). No patient suffered infection because of the negative results of postoperative X-rays of anteroposterior and lateral bilateral hips and anteroposterior and lateral X-rays of the operated knee, blood analysis, CRP, and ESR. We concluded that post-surgery pain in our study was not due to infection.

Discussion

There are many causes of chronic pain following total hip and knee arthroplasty. Septic prostheses loosening, aseptic prostheses loosening, malposition of implanted prostheses, mechanical stress, pre-operative pain level and functional impairment have accounted for post-surgery pain according to some documented studies [21–26]. In some recent studies, metal allergies were described as another potential factor resulting in post-operative pain and subsequent prostheses failure in THA and TKA patients [27]. When our patients complain of surgical site pain three months postoperatively or more, what can we do to cope with the condition? Postoperative infection may be the first consideration; however, when radiological (when metal artifact can be decreased, magnetic resonance image is highly recommended) and serological (blood analysis, ESR, CRP, intra-articular aspiration, bacterial culture, and so on) evidence reveals no signs of infection, other reasons must be taken into consideration though low titre infection cannot be totally ruled out. When aseptic prostheses failure, prostheses malposition, and above mentioned other reasons are excluded, we should consider metal allergy. Metal allergy and infection have a lot in common. The differential diagnosis of metal allergy and infection is of great importance because subsequent treatment is definitely different. When infection is confirmed, a two-stage revision procedure is essential, while metal allergy accompanied with serious and recurrent pain can be an indication for one-stage revision surgery [28, 29].

Unlike periprosthetic infection, metal allergy patients show negative results on blood analysis, CRP, ESR, and X-Ray findings. Patch testing and serological lymphocyte transforming testing are the main diagnostic methods in our

Table 4 Detailed results in THA and TKA groups

Parameter	THA group		TKA group	
	P	N	P	N
Cases	36	26	11	14
Mean age (years)	48.33±14.74	48.54±16.24	67.36±7.19	62.57±7.38
Mean BMI index	23.18±3.26	22.16±3.35	23.17±1.66	24.04±1.41
Mean pre VAS score (points)	4.14±0.99	4.27±1.54	5.00±0.45	4.71±2.02
Mean post VAS score (points)	0.39±0.80	0.38±0.57	0.90±0.54	0.86±0.66
Mean difference VAS score (points)	3.75±1.02	3.88±1.45	4.09±0.70	3.86±1.83
Lymphocyte transforming test (pre,%)	75.42±3.83	72.27±4.21	77.81±2.92	76.54±3.12
Lymphocyte transforming test (post,%)	76.28±2.92	71.76±3.24	78.52±2.64	76.52±2.74

P positive, metal allergy; *N* negative, non-metal allergy

clinical practice [30–34]. With regard to the mechanism of metal allergy, this is still not fully understood. Some studies suggest that the implanted prostheses has direct contact with the serum mediator systems and tissues, which may stimulate the prostheses to release metal wear particles. The released particles may lead to T-lymphocyte mediated delayed type-IV hypersensitivity, which may arouse localised inflammation eliciting tissue damage and bone degradation and subsequent prostheses loosening [35–38].

Our study aimed at finding out whether or not a relationship existed between metal allergy and post-surgery pain following TJA mainly through patch testing results. Most implanted prostheses contain metal elements which were commonly seen as contact allergens, such as nickel, cobalt, and chromium [7]. Sensitisation to nickel, cobalt, and chromium are known to cause metal allergy[39–42]. Potential metal allergies can be identified commonly from the patch testing results though the accuracy is not well understood [27]. Some other studies have described patch testing as a standardised, and in vivo diagnostic test for evaluation of metal allergy [43]. Besides, lymphocyte transforming tests in metal allergy patients were higher than the reference values. Patients were tested for 12 metal elements on the basis of the constituent parts of the implanted prostheses in our study. During our follow-up period, we showed a high suspicion of metal allergy in one THA patient. The female patient was 71 years old and underwent left side THA surgery with a ceramic-on-ceramic LINK prostheses because she suffered dysfunction and pain from bilateral osteronecrosis of the femoral head. The patient had no previous medical history apart from hypertension, which reached up to 175/110 mmHg, for one year, and responded oral Nifedipine controlled released tablet. She complained of recurrent serious pain six months postoperatively. She described the feeling as “rupture pain” in the groin area. Physical examination, radiological and serological results revealed no signs of infection. We prescribed oral analgesia (Celexib, one pill once a day) combined with oral calcium tablets (Caltrate, one pill once a day), and Rocaltrol (one pill once a day) for the prevention of osteoporosis. However, she was still so obsessed with pain that she could not walk freely and laid on the bed for most of the day. The pre-operative patch testing results showed weak positive reaction to cobalt, tin, zirconium, and copper, which drew our attention to metal allergy in the patient, though the lymphocyte transforming test was negative. The patient felt gradual pain relief after oral glucocorticoid was administered.

There were several limitations in our study which may prevent widespread recognition. First, the numbers were relatively small. The patch testing results obtained from the 96 patients cannot explain the real endemic rates of metal allergy in China. Consequently, the reported rates of each metal element had some limitation. Second, the interpretation of the patch testing results had the potential bias of observation because to some extent this is subjective. Third, there were still other possible risks of allergy reactions, such as polyethylene liner and ceramic parts, which may lead to post-surgery pain. Fourth, false negative results may exist if patients had no previous contact history of the included 12 metal elements.

Conclusion

There are several causes of thigh pain in THA patients and recurrent knee swelling in TKA patients. Aseptic and septic prosthesis loosening, surgical techniques, metal allergy and other unknown reasons may lead to those symptoms. Pain caused by metal allergy usually manifests as persistent and recurrent pain. The results of white blood cell and neutrophil, C-reactive protein, erythrocyte sedimentation rate tests and postoperative plain X-rays are negative. Currently, patch testing and the lymphocyte conversion test are used for metal allergy diagnosis. We concluded that metal allergy may form to some extent a relationship with thigh pain in THA patients and recurrent knee swelling in TKA patients. Large samples and long follow-up time are essentially needed for further study.

Acknowledgments We show much thanks to the Department of Orthopaedics of the First Affiliated Hospital of Traditional Chinese Medicine of Guangzhou University. And the study received financial support from the National Nature Science Fund of the People’s Republic of China (Grant number is 81273784).

Conflict of interest The authors claim that there exist no conflicts of interest.

References

1. Shan L, Shan B, Graham D et al (2014) Total hip replacement: a systematic review and meta-analysis on mid-term quality of life. Osteoarthr Cartil 22(3):389–406
2. Abram SG, Nicol F, Hullin MG et al (2013) The long-term outcome of uncemented low contact stress total knee replacement in patients with rheumatoid arthritis: results at a mean of 22 years. Bone Joint J 95-B(11):1497–1499
3. Rahman WA, Garbuz DS, Masri BA (2013) Total hip arthroplasty in steroid-induced osteonecrosis: early functional and radiological outcomes. Can J Surg 56(1):41–46
4. Merritt K, Rodrigo JJ (1996) Immune response to synthetic materials: sensitization of patients receiving orthopedic implants. Clin Orthop Relat Res 326:71–79
5. Willert HG, Buchhorn GH, Dipl-Ing et al (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints: a clinical and histomorphological study. J Bone Joint Surg Am 87:28–36
6. Evans EM, Freeman MAR, Miller AJ, Vernon-Roberts B (1974) Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. J Bone Joint Surg (Br) 56:626–642

7. Hallab N, Merritt K, Jacobs JJ (2001) Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 83:428–436
8. Abbas AK, Lichtman AH, Pober JS (2000) Cellular and molecular immunology, 4th edn. Saunders, Philadelphia, pp 34–36
9. Vernon-Roberts B, Freeman MAR (1976) Morphological and analytical studies of the tissues adjacent to joint prostheses: investigations into the causes of loosening of prostheses. Springer, New York, pp 148–186
10. Innocenti M, Carulli C, Matassi F et al (2014) Total knee arthroplasty in patients with hypersensitivity to metals. Int Orthop 38(2):329–333
11. Kubba R, Taylor JS, Marks KF (1981) Cutaneous complications of orthopedic implants: A two-year prospective study. Arch Dermatol 117:554–560
12. Thyssen JP, Menné T, Schalock PC et al (2011) Pragmatic approach to the clinical work-up of patients with putative allergic disease to metallic orthopaedic implants before and after surgery. Br J Dermatol 164:473–478
13. Bazex A, Parant M, Bazex J et al (1978) Dermatosis caused by bone graft material(author's transl). Ann Dermatol Venereol 105:9–15
14. Kubba R, Champion RH (1975) Nickel sensitivity resembling bullous pemphigoid. Br J Dermatol 93(suppl 11):41–43
15. Lammintausta K, Pitkänen OP, Kalimo K et al (1985) Interrelationship of nickel and cobalt-contact sensitization. Contact Dermatitis 13:148–152
16. Mayor MB, Merritt K, Brown SA (1980) Metal allergy and the surgical patient. Am J Surg 139:477–479
17. Zeng Y, Feng W (2013) Metal allergy in patients with total hip replacement: A review. JIMR 41(2):247–252
18. Mesinkovska NA, Tellez A, Molina L et al (2012) The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants. Arch Dermatol E1-E7
19. Nonaka H, Nakada T, Iijima M et al (2011) Metal patch test results from 1990-2009. J Dermatol 38:267–271
20. Warshaw EM, Raju SI, Fowler JF et al (2012) Positive patch test reactions in older individuals: Retrospective analysis from the North American Contact dermatitis group, 1994-2008. J Am Acad Dermatol 229–240
21. Piscitelli P, Iolascon G, Innocenti M et al (2013) Painful prosthesis: approaching the patient with persistent pain following total hip and knee arthroplasty. Clin Cases Miner Bone Metab 10(2):97–110
22. Boettner F, Cross MB, Nam D et al (2011) Functional and emotional results differ after aseptic verse septic revision hip arthroplasty. HSS J 7(3):235–238
23. Yagdi S, Kazimoglu C, Dirim B et al (2011) Retroperitoneal migration of a septically loose femoral component. J Arthroplasty 26(6): 977.e17-20
24. Szczesny G, Babiak I, Kowalewski M (2005) Septic loosing of hip and knee prosthesis. Chir Narzadow Ruchu Ortop Pol 70(3):179–184
25. Rajgopal A, Vasdev A, Gupta H (2013) Revision total knee arthroplasty for septic versus aseptic failure. J Orthop Surg (Hong Kong) 21(3):285–289
26. Duff RE, Razzoog ME (2006) Management of a partially edentulous patient with malpositioned implants, using all-ceramic abutments and all-ceramic restorations: A clinical report. J Prosthet Dent 96(5):309–312
27. Thyssen JP, Jakobsen SS, Engkilde K et al (2009) The association between metal allergy, total hip arthroplasty, and revision: A case–control study. Acta Orthop 80(6):646–652
28. Niki Y, Matsumoto M, Otani T et al (2005) Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 26:1019–1026
29. Parvizi J, Adeli B, Zmistowski B et al (2012) Management of periprosthetic joint infection: the current knowledge. AAOS exhibit selection. J Bone Joint Surg Am 94:e104
30. Brown GC, Lockshin MD, Salvati EA et al (1997) Sensitivity to metals as a possible cause of sterile loosening after cobalt-chromium total hip replacement. J Bone Joint Surg 59:164–168
31. Yoshihisa Y, Himizu TS (2012) Metal allergy and systemic contact dermatitis: An overview. Dermatol Res Pract 749561:1–5
32. Zug KA, Warshaw EM, Fowler JF Jr et al (2009) Patch-test results of the North American Contact Dermatitis Group 2005-2006. Dermatitis 20(3):149–160
33. Reed KB, Davis MD, Nakamura K, Hanson L, Richardson DM (2008) Retrospective evaluation of patch testing before or after metal device implantation. Arch Dermatol 144(8):999–1007
34. Rushing GD, Goretsky MJ, Gustin T, Morales M, Kelly RE Jr, Nuss D (2007) When it is not an infection: metal allergy after the Nuss procedure for repair of pectus excavatum. J Pediatr Surg 42(1):93–97
35. Thomsen M, Rozak M, Thomas P (2011) Pain in a chromium-allergic patient with total knee arthroplasty: disappearance of symptoms after revision with a special surface-coated TKA-a case report. Acta Orthop 82(3):386–388
36. Hallab NJ, Merrit K, Jacobs JJ (2011) Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 83:428–436
37. Schuh A, Lill C, Hönle W, Effenberger H (2008) Prevalence of allergic reactions to implant materials in total hip and knee arthroplasty. Zentralbl Chir 133(3):292–296
38. Doorn PF, Mirra JM, Campbell PA, Amstutz HC (1996) Tissue reaction to metal on metal total hip prostheses. Clin Orthop 329(Suppl):S187–S205
39. Brasch J, Geier J (1997) Patch test results in schoolchildren. Results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). Contact Dermatitis 37:286–293
40. Schnuch A, Uter W, Geier J, Gefeller O, IVDK Study Group (2002) Epidemiology of contact allergy: an estimation of morbidity employing the clinical epidemiology and drug-utilization research (CE-DUR) approach. Contact Dermatitis 47:32–39
41. Vamnes JS, Lygre GB, Gronningsaeter AG, Gjerdet NR (2004) Four years of clinical experience with an adverse reaction unit for dental biomaterials. Commun Dent Oral Epidemiol 32:150–157
42. Hegewald J, Uter W, Pfahlberg A, Geier J, Schnuch A (2005) IVDK: a multifactorial analysis of concurrent patch-test reactions to nickel, cobalt, and chromate. Allergy 60:372–378
43. White JML (2011) Patch testing: what allergists should know. Clin Exp Allergy 42:180–185