

Prevalence of metal hypersensitivity in total knee replacement

Mohan M. Desai^a, Kunal Ajitkumar Shah^{a,*}, Anuradha Mohapatra^b, Digen C. Patel^a

^a Department of Orthopaedics, Seth G S Medical College & KEM Hospital, Parel, Mumbai, India

^b Department of Community Medicine, Seth G S Medical College & KEM Hospital, Parel, Mumbai, India

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ABSTRACT

Background: Cutaneous and local reactions to metals used in orthopaedic implants have been well documented. The prevalence of metal sensitivity in general population is 10%–15%. Nickel, Cobalt and Chromium are the most common allergen. The association between cutaneous reactions and implants has been less understood. Hence, this study was taken up with the aim to assess the prevalence of metal hypersensitivity in Total Knee Replacement (TKR) patients and find the most prevalent allergen.

Materials & methods: Longitudinal study conducted during January–December 2017. We enrolled 233 subjects who were at least three months postoperative. Radiological assessment was done. CREDISOL® kit was used for patch test. Results were recorded using ICDRG grading at 48 hours and five days.

Results: Mean age was 59.59 years; 12.01% were symptomatic. Pain followed by loss of function were the most common symptoms. However, loss of function and patient dissatisfaction towards procedure were significantly associated with metal hypersensitivity (χ^2 value > 3.84; p value < 0.05). In 66% subjects, pre-operative diagnosis was severe osteoarthritis, followed by rheumatoid arthritis (23%). None of the subjects had evidence of loosening on X-ray. Prevalence of Metal Hypersensitivity was found to be 15.87% (patch test positive). Chromium (11.58%) was found to be most common allergen followed by Nickel (8.58%) and then Cobalt (6.43%).

Conclusions: Significant prevalence of metal hypersensitivity was found. Therefore, we recommend pre-operative patch test for detecting allergic reactions to implants. Alternatives like Titanium or Zirconium can be used to avoid complications.

1. Introduction

Metallic knee arthroplasty components are being used by orthopaedic surgeons for over 60 years. There has been an increase in incidence of cutaneous reactions to metals in these implants. The prevalence of metal sensitivity in the general population is 10%–15%¹ and in poorly functioning joint is 60%.² Metals undergo some degree of corrosion and metal ions released from components intra-articularly form complexes with native proteins. These metal-protein complexes act as antigens and cause an immunologic response in the body and synovial joint.¹ Nickel, Cobalt and Chromium sensitivities have been often cited as cause of knee implant revisions.³ Metal hypersensitivity presents with pain, swelling, epi-cutaneous rash, patient dissatisfaction and loss of function. Patch testing involves the application of metallic material by an adhesive tape to the skin for 48 h, after which it is removed and the reaction is recorded.^{1,4}

The association between cutaneous reactions and reaction to

implants has been less understood. This study was conducted to assess the prevalence of metal hypersensitivity in patients with TKR. Specific objectives were to study the demographic profile, assess the most prevalent allergen (out of Ni, Co, and Cr) and assess the symptoms associated with metal hypersensitivity in study participants.

2. Materials and methods

2.1. Study period

This longitudinal study was conducted during Jan 2017 to Dec 2017 in an Orthopaedic outpatient department (OPD) of a tertiary care center in a metropolitan city after obtaining ethical clearance from the institutional ethics committee.

* Corresponding author. Department of Orthopaedics, 6th Floor, New building, K.E.M Hospital, Parel, Mumbai, 400012, India.

E-mail addresses: md1964@gmail.com (M.M. Desai), kunalajitshah@gmail.com (K.A. Shah), anuradha.moha@gmail.com (A. Mohapatra), digenpatel8@icloud.com (D.C. Patel).

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2.2. Inclusion criteria

All patients with TKR who followed up in orthopaedics OPD of the study center during the study period with time duration of minimum of three months post TKR.

2.3. Exclusion criteria

Post TKR patients who were not willing to participate in study and those post TKR patients with less than three months since surgery.

2.4. Sample size

Complete enumeration method was used to determine sample size. A total of 241 patients fulfilled our inclusion criteria out of which eight refused to participate. Hence, 233 subjects were enrolled.

2.5. Materials

CREDISOL® (Nickel, Cobalt, Chromium patch kit.) was procured from Creative Diagnostic Medicare Pvt Ltd. Nickel sulphate 5%, Cobalt sulphate 5%, Potassium bi-chromate 0.1% were used as allergen in the study.

2.6. Procedure

On first visit, initial history taking, clinical examination and radiological assessment of the joint was done by x-rays. Aseptic loosening of implants/osteolysis was looked for. Further, they were subjected to patch testing. Patch testing involved the incorporation of a metallic material into plastic chambers and applied by an adhesive tape to the skin for 48 h, at which point it was removed and the reaction was recorded. The delayed reaction was recorded on day five. The study was totally non-invasive and was done after obtaining written informed consent taken from the participants. They were explained about rare chances of local allergic reactions. If any reactions on skin, further dermatology opinion was taken on priority basis at no extra cost to the participants. Two follow-up visits were done to assess results of patch test, one at 48 h and another at five days. Results of patch test were analysed by International Contact Dermatitis Research Group (ICDRG) grading.⁵ (Table 1)

3. Results

Participants with TKR, all being more than 3 months post-operative were included in study (N = 233). All were subjected to patch test after clinical and radiological evaluation. Mean age of study population was 59.59 years (range 30–78 years). Highest number of subjects were from the age group 60–70 years (42.06%) followed by 50–60 years (37.76%), 70–80 years (10.3%), 40–50 years (6.43%) and 30–40 years (3.43%). Out of 233, 149 (64%) were females and 84 (36%) were males. Comorbidities associated with the study subjects were Hypertension in 109 subjects (55%), Rheumatoid Arthritis in 44 (22%), Diabetes Mellitus in 30 (15%), haematological diseases in 6 (3%), Asthma in 5(3%), gout in 1(1%), Ankylosing spondylitis in 1 (1%) and Breast

Table 1
International contact dermatitis research group (ICDRG) grading.

GRADE	REACTION
Negative	No reaction
Doubtful	Faint erythema
Irritant	Discrete or patchy with no infiltration
1+ (weakly positive)	Erythema, infiltration, and possible papules
2+ (strong positive)	Erythema, infiltration, papules and vesicles
3+ (extreme positive)	Bullous reaction

cancer in 1 (1%).

None of the subjects had any history of allergic reactions before being subjected to patch test. 28 out of 233 (12.01%) were symptomatic, of which 21 (75%) cases presented with pain followed by loss of function in 12(42.85%) cases, patient dissatisfaction in 7(25%) cases, swelling in 4(14.28%) cases, percutaneous rash in 1(3.57%) case. However, loss of function and patient dissatisfaction towards the procedure were the only two symptoms significantly associated with patch test positive patients. ($p < 0.05$) (Table 2).

Pre-operative diagnosis of 155 out of 233 subjects (66%) was severe osteoarthritis, 53 (23%) was rheumatoid arthritis, 19 (8%) was post-traumatic, 5 (2%) was haemophilic arthropathy, gout in 1(0.33%), ankylosing spondylitis in 1(0.33%) and septic arthritis in 1(0.33%). Subject with septic arthritis had undergone two stage TKR.

ESR and CRP values of all subjects were noted at the time of first visit. Out of 233 subjects, 228 (97.8%) had ESR values more than 30 and only 5 (2.14%) subjects had less than 30. Out of 233, 197 (84.5%) subjects had CRP values more than 10 and 36 (15.4%) subjects had values less than 10. None of the patients had evidence of loosening of implants on X-ray.

Patch testing results were interpreted using ICDRG grading. Out of 233, 196 (84.1%) subjects tested negative and 37 (15.8%) were positive. Out of 37 subjects who tested positive, 21 (56.75%) were positive for grade 1 + and 16 (43.24%) were positive for grade 2 + reaction. None of subjects showed 3 + reaction (Figs. 1 and 2).

Prevalence of Metal Hypersensitivity in patients of TKR is found to be 15.87%. Chromium is found to be most common allergen followed by nickel and cobalt. Chromium hypersensitivity was found in 27 patients (11.58%), Nickel in 20 patients (8.58%) and Cobalt in 15 patients (6.43%). Isolated Chromium hypersensitivity was found in 17 subjects (7.29%) and isolated Nickel hypersensitivity in 5 subjects (2.14%). None of them reported isolated Cobalt hypersensitivity. Combined Nickel and Cobalt hypersensitivity were found in 5 subjects (2.14%) and combined Nickel, Cobalt and Chromium hypersensitivity in 10 subjects (4.29%). There were no cases of Cobalt and Chromium, Nickel and Chromium (Fig. 3). No complications were recorded during the study.

4. Discussion

This longitudinal study was conducted during Jan 2017 to Dec 2017 in an Orthopaedic outpatient department (OPD) of a tertiary care center with the aim to find the prevalence of metal hypersensitivity and the most common allergen. We found chromium to be the most common allergen and overall prevalence of metal hypersensitivity as 15.87%. Hallab et al in their meta-analysis, noted a relationship demonstrating a higher incidence of allergy to Nickel, Cobalt and Chromium among patients with poorly functioning implants than in patients with well performing implants. Prevalence of metal hypersensitivity was 10% in general population, 25% in patients of well-functioning implants and 60% in patients poorly functioning implants.¹ In our study we found the prevalence in patients of TKR to be 15.87%. Benson et al reported to have prevalence of 28% while Elves et al reported prevalence of 38%.^{6,7}

A prospective study of 92 patients performed by Niki et al, consisted of 75 females and 17 males with mean age of 68.9 years. Similarly, our study also had majority population of females (64%) and mean age 59.9 years. Also both the studies had maximum subjects with pre-operative diagnosis of severe osteoarthritis.⁸ Webley et al in a case control study had a mean age of 66 years with 32% patients being patch test positive.⁹

We found symptoms such as pain, swelling, cutaneous rash, loss of function, patient dissatisfaction for procedure present in total 28 (12.01%) patients. Loss of function and patient dissatisfaction for procedure were found to be significantly associated with the patch test positive patients. However, we couldn't find other studies supporting

Table 2
Frequency of occurrence of symptoms in total knee replacement patients (N = 233).

Symptoms	Frequency of occurrence in Patch test positive patients [n = 37 (100%)]	Frequency of occurrence in Patch test negative patients [n = 196(100%)]	Corrected χ^2	p value
Pain	6(16.21%)	15(7.65%)	1.83	0.17
Swelling	0(0%)	4(2.04%)	0.03	1.0
Rash	0(0%)	1(0.51%)	0	1.0
Loss of function	5(13.51%)	7(3.57%)	4.42	0.03
Patient Dissatisfaction	5(13.51%)	2(1.02%)	12.65	0.01

*Table value of $\chi^2 = 3.84$ at $p = 0.05$.

† χ^2 value > 3.84 are significant.

this association. **Jauregui et al** reported symptoms for metal allergy as chronic eczema, joint effusions, joint pain, and limited range of motion during a study of revision joint arthroplasty.¹⁰ **Amini et al** reported half of patients presented with pain and swelling, while only one-third presented with cutaneous symptoms.¹¹ In contrast to our findings, **Krecisz et al** in a study done for patch testing, revealed that patients who had Co Cr implants became sensitized to the component metals but had no symptoms of metal hypersensitivity.¹² Similarly, **Carlson et al** reported in a study of 18 patients whose preoperative skin tests were positive for metal allergies. None was found to have dermatologic or joint related symptoms at an average of 6.3 years postoperatively.¹³ There was no evidence of loosening on X-ray in any of the cases in our study that were patch test positive. **Webley et al** in a case control study did patch testing on 50 patients with hinge knee prosthesis keeping 33 controls. Only one patient had aseptic loosening out of seven patch test positive patients showing no correlation between metal sensitivity and loosening.⁹ Similarly, **Granchi et al** in a case control study of 94 patients reported higher incidence of patch test positive in TKR patients irrespective of stable or loosened implants.⁵ **Brown et al** also found no correlation with loosening.¹⁴ In contrast, **Elves et al and Benson et al** found strong correlation between patch testing and aseptic loosening.^{6,7}

We are of the opinion that patch test could be dependable method to diagnose metal hypersensitivity in the patients of TKR. Other methods like lymphocyte transformation test, modified lymphocyte stimulation test (mLST), periprosthetic cytokine assessment (IFN-gamma expression) by histopathology have also been proven to be useful by some studies but were not be used due to its high cost.^{8,15–17} We are of the opinion that, patch testing could be the cheaper and dependable method. Some studies have concluded no certain value of pre-implant patch testing. Thus, its use in detecting metal hypersensitivity is controversial.^{1,2,22}

Mihalko et al (North American Skin Patch testing group) in 2009 reported the results of patch testing in almost 5000 patients and found that nickel (Ni) was the most common allergen (21%) and cobalt and chrome 8% each.¹⁸ **Atanaskova and Mesinkovska N et al** in a study of 31 patients with preoperative history of hypersensitivity found 21 were patch positive and all did well with “allergen-free” implants. In another study by same author, 41 subjects suspected of hypersensitivity with TKR, 10 were patch test positive. 6 out of these 10 had resolution of symptoms with allergen free implant.¹⁹ **Krecisz B et al** did patch testing in a study of 14 patients with poor functioning implants, among which 8 were patch positive (7 for Ni, 6 for Cr), 3 underwent revision and improved.¹² **Carossino Anna Maria et al** in 2016 reported that combined use of the patch test and lymphocyte transformation test, along with cytokine detection in selected patients, provides a useful tool for prevention of hypersensitivity in patients undergoing primary joint arthroplasty, and for monitoring the onset of a metal sensitization in patients with implanted devices.²⁰ **Niki Y et al** in 2005 did a prospective study of 92 patients undergoing total knee replacement. In this study 24 of 92 patients of TKA were mLST (modified lymphocyte stimulation test) positive pre-operative and among 24 patients, 5 developed eczema. Chromium allergy was positive in eczema patients. When the type of sensitive metals were compared significant association between presence of Cr-sensitivity and development of eczema ($P < 0.05$) was identified. Author has advised routine preoperative screening for metal hypersensitivity especially for chromium.⁸ **Adrien Lons et al** in 2017 studied on release of metallic ions and found significant blood elevation of Cr, Co levels one year after implantation exceeding the normal values which leads to numerous effects such as allergy, hypersensitivity etc.²¹

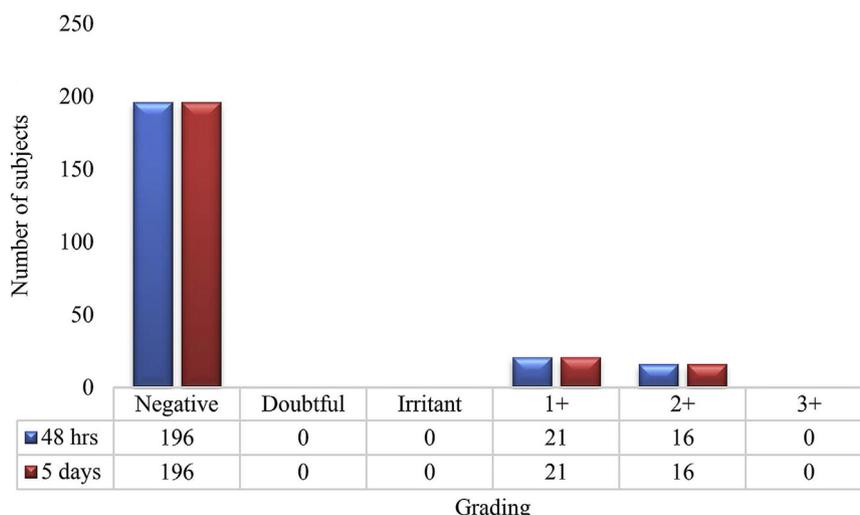


Fig. 1. Results of patch test according to ICDRG grading.



Fig. 2. Clinical picture of patch test (day 0, day 2 and day 5).

5. Conclusion

We found prevalence of metal hypersensitivity 15.87% with chromium being most common allergen (11.58%). We also found no cases of aseptic loosening in patch test positive patients. We therefore, recommend patch test on all pre-operative patients undergoing total knee replacement in view of avoiding complications of metal hypersensitivity in patients hypersensitive to Ni, Co, Cr. In patients with idiopathic pain post TKR, after ruling out all possibilities of infection if pain still persists, we recommend patch test to rule out metal hypersensitivity. As there is no consensus regarding best method to diagnose metal hypersensitivity, patch test remains cheap and reliable method. Combining allergy diagnostics with histopathology and peri-prosthetic cytokine assessment (IFN -gamma expression) will allow us to design better diagnostic strategies for metal hypersensitivity but at higher cost.

There is no irrefutable data on prevalence of metal hypersensitivity in TKR but, our study has shown significant prevalence of metal hypersensitivity (15.87%) in recruited TKR patients. We are of the opinion that, if patient has metal hypersensitivity (Nickel/cobalt/chromium) one can avoid cobalt–chromium implants during revision surgery and use titanium, zirconium or polyethylene mono-block tibial component to avoid future metal hypersensitivity and its related complications. Multicentric studies with adequate sample size would be needed for generalizing results for patients undergoing TKR. It is also recommended that in future studies patch test be performed pre and post

TKR.

Patient declaration statement

“The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.”

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NIL.

Conflicting interest

None declared.

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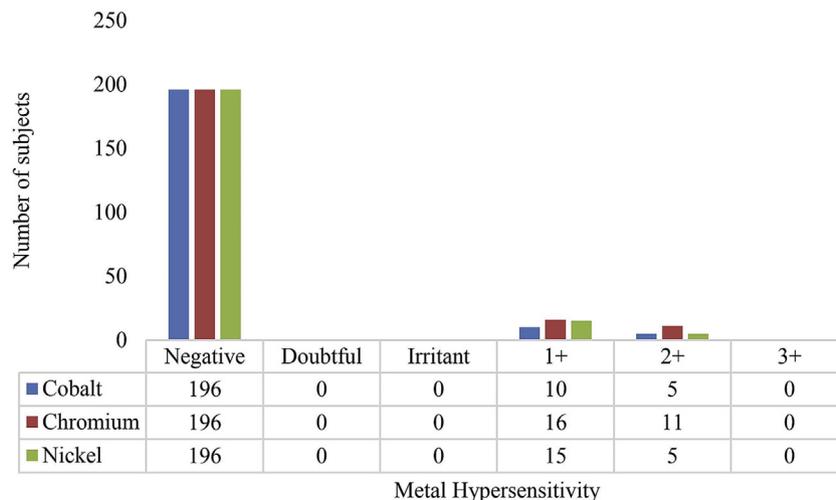


Fig. 3. Prevalence of Metal Hypersensitivity for individual metals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jor.2019.05.005>.

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