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Metal sensitivity in patients before and after total knee arthroplasty (TKA): comparison between ceramic surfaced oxidized zirconium and cobalt-chromium implants

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Abstract

Backgrounds: The purpose of this study was to investigate clinical relevance of preoperative screening for metal sensitivity (MS), and to assess whether there is any difference in the MS after total knee arthroplasty (TKA) between oxidized zirconium (OxZr) and cobalt-chrome (Co-Cr) implants.

Methods: A total of 48 subjects referred for TKA were enrolled the study with no history of metal allergy. After preoperative screening, we prospectively evaluated subjects, who were received either of 2 components, by comparing values of skin patch test, lymphocyte stimulation test (LST), and serum ion sampling.

Results: Preoperatively, positive rates to Co, Ni, Cr were 2.1, 6.3, 0 (%, patch test), and were 6.3, 29.2, 16.7 (%, lymphocyte stimulation test (LST)), respectively. Postoperatively, 1 subject (4%) newly tested positive to Va in the Co-Cr group, and positive rates of LST to Co, Ni, and Cr were higher in the Co-Cr group. As the result of serum ion sampling, there was a slight increase of Co and Ni levels in the Co-Cr group. However, none of the subjects has developed cutaneous signs attributable to metal sensitization, and no evidence of the implant loosening was confirmed at the latest examination.

Conclusions: The finding of our study suggested that the past history alone was insufficient for identifying subjects with MS, and preoperative screening might be useful for subjects with no history of allergy. However, we could not conclude the benefit of the OxZr implant during short post-operative period.

Keywords: Metal sensitivity, total knee arthroplasty, oxidized zirconium, allergy

Introduction

Implant-related metal sensitivity has been reported mainly in case studies and metal sensitivity (MS) develops in 20-25% of patients who have undergone total knee arthroplasty (TKA) using cobalt-chrome (Co-Cr) alloy femoral components [1,2]. Metal ions can activate the immune system by inducing a delayed type IV hypersensitivity reaction, in which antigens activate T lymphocytes. Through this cascade, CD4 and CD8 cells are activated, releasing a multitude of cytokines including interferon gamma, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) alpha, and the response of metal-specific lymphocytes has been linked to poor implant performance.

Although only a few highly susceptible (<1%) patients exhibit symptoms such as eczema or erythema, there has been a prospective report indicating that patients with failed implants have a higher incidence of metal allergy [3]. In the general population, the mean prevalence of MS was reported be 10-17% [4,5], and the clinical relevance of preoperative screening remains controversial because there currently is little information concerning the preoperative prevalence of MS in candidates for TKA with no history of metal allergy, and the detail of the relation to postoperative allergic reaction is unknown. In case the patient has high reactivity to a prominent implant metal such as Co or Cr, an implant with an alternative bearing surface of less environmentally prevalent metals may be an option. As one of the options, oxidized zirconium, the metal surface is transformed into a ceramic layer, is increasingly being used to reduce ion release into periprosthetic tissue. It forms a thick enough ceramic layer to be more wear resistant than typical Co-Cr alloy TKA femoral components [6,7]. However, there is little evidence of the prognostic value of the oxidized zirconium (OxZr) component compared standard Co-Cr component for subjects with no past history of metal allergy.

The purpose of this study was to investigate clinical relevance of preoperative screening for MS by comparing values of *in vivo* patch test and *in vitro* LST. In addition, a secondary purpose of the study was to assess whether there is any significant difference in the metal sensitization after TKAs between ceramic surfaced OxZr and Co-Cr femoral implants.

Materials and methods

Consecutive patients were recruited among individuals who were admitted to the authors' institution from July 2009 to May 2011. Among candidates for primary TKA, subjects who

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suffered from advanced osteoarthritis with no history of metal hypersensitivity were enrolled the study. After approval by the institutional review board, all participants were provided informed consent and detail of the personal history was collected by a standard questionnaire, including symptoms related to metal-induced contact dermatitis, documented by previous skin test or intolerance to metal items. Exclusion criteria were subjects with any previous history of implantations of the metal-containing devices or history of metal related contact dermatitis. In addition, subjects who suffered from rheumatoid arthritis, or those who were using corticosteroid or other immunosuppressive drugs were also excluded from the study.

A total of 48 individuals referred for TKA were enrolled the study, consisted of 6 males and 42 females with a median age of 75 years (range 6 4-89). MS was accessed by means of patch testing using the following haptens: 2% cobalt chloride (Co), 5% nickel sulphate (Ni), 2% chromium trichloride (Cr), 2% aluminium chloride (Al) (Torii Pharmaceutical Co., Tokyo, Japan), 5% vanadium trichoride (Va), 10% titanium dioxide (Ti), and 5% molybdenum chloride (Mo) (Chemotechnique Diagnostics, Vellinge, Sweden). A drop of each hapten was applied to the back of the patient using chambers (Finn Chambers on Scanpor, Epitest Ltd Oy, Tuusula, Finland). Readngs were made after 48 hour, and additional reading was made after 72 hour in 34 of all cases. Skin reactions were graded according to the International Contact Dermatitis Research Group guidelines [8]. Skin reactions were classified as (1) weak positive reaction: homogeneous redness throughout the entire test area, non vesicular reaction (+), (2) moderate positive reaction: homogeneous redness throughout the entire test area, oedematous or vesicular reaction (++), (3) severe positive reaction: intense homogeneous redness throughout the entire test area, bullous or ulcerative reaction (+++), and (4) negative reaction: an irritant reaction, doubtful or negative reading.

For *in vitro* testing, blood samples were taken from each subject using a standard technique to minimize the risk of contamination for lymphocyte stimulation test (LST) to 3 haptens: Co, Ni, and Cr. Briefly, the reactivity of lymphocytes to metals was assessed by the uptake of tritiated thymidine, and increase in [3H] thymidine incorporation into metal-treated cultures was expressed as a stimulatory index (S.I.), and over 200% is considered positive. In addition, blood samples were also taken with a plastic syringe and placed in lithium heparin tubes for metal ion sampling of 3 metals, Co, Ni, and Cr. Serum ion levels were measured using inductively coupled plasma mass spectrometry. LST and metal ion sampling were conducted at either lab (Mitsubishi Chemical Medience Corporation, Tokyo, Japan) or at lab (Mayo Medical Laboratories, Rochester, Mn).

After preoperative screenings, all surgeries were performed using the same prosthesis design (Genesis II; Smith & Nephew, Memphis, Tennessee) except for subject who were highly suspected of metal allergy, and the subjects were received either an OxZr or a Co-Cr femoral component. Oxidized zirconium (OxZr) is composed of Zr (97.5%) and niobium (2.5%). It is proposed by submitting the alloy to heat in air to greater than 500°C. Thermal oxidation occurs, and as the oxygen diffuses through the alloy, the immediate surface oxidizes into a Zr ceramic approximately 5 μm thick. The alloy immediately underlying the ceramic surface has a high oxygen concentration and this gradually decreases until the alloy is just composed of the two base material. The finish material is a stable monolithic crystalline structure [7,9].

The tibial component is the same for both of the femoral component options, which is modular with a polyethylene insert in a Ti-Al-Va alloy baseplate.

All surgeries were performed by the same surgeon, with the same approach and reproducible techniques for balancing flexion and extension gap and tension of collateral ligaments. The PCL was sacrificed, and the patella was not resurfaced. Both of the femoral and tibial components were cemented in all cases.

During the second 6 months after operation, MS was accessed again by means of skin patch testing, and blood samples were also taken for LST and for metal ion sampling. We performed clinical and radiographic assessments before surgery and at the latest follow-up. The knee Society rating system was used for the clinical evaluation [10]. In addition, subjects attended for clinical review for such parameters as the presence of eczematous dermatitis around operative scar, and itching, and the evidence of joint effusion. We examined follow-up radiographs (antero-posterior weight-bearing and lateral views) of all subjects. The radiolucency results were recorded according to the method recommended by the Knee Society [11]. Radiolucent lines were measured in millimeters in each designated zone for the femoral and tibial prostheses in the coronal and sagittal planes. We added the widths of radiolucent lines for Zone 1 to 7 for each of the components according to this radiographic scoring system of the Knee Society [11].

Statistical analysis

For statistical analysis, we used the paired t-test for the com-parison of pre-and post-operative metal ion sampling. These assessments were performed using software (Dr. SPSS II, developed version of SPSS 11.0; SPSS Inc., Chicago, IL). The comparison and the level of significance was set at $p<0.05$.

Results

Preoperatively, 3 of the 48 subjects showed positive patch testing to Ni, and 1 of the 3 subjects was also positive to Co after 48 hour. The rest of the 2 subjects showed positive only to Ni. No one exhibited positive results on testing to Cr, Al, Ti, Va, and Mo after 48 hour. 34 of the 48 subjects, those who tested negative to all haptens, were evaluated again after 72 hour. However, no subject newly tested positive on patch

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Table 1. Results of preoperative screening.

Positive rates of patch test (%)		Results of LST	
Reading after 48 hour	(n=48)	Positive rates of LST (%)	(n=48)
To any metal	6.3 (n=3)	To any metal	37.5 (n=18)
Co	2.1 (n=1)	Co	6.3 (n=3)
Ni	6.3 (n=3)	Ni	29.2 (n=14)
Cr	0 (n=0)	Cr	16.7 (n=8)
Al, Va, Ti, Mo	0 (n=0)	Al, Va, Ti, Mo	Not tested
Reading after 72 hour	(n=34)		
To any metal	0 (n=0)		

Table 2. Demographic characteristics and post-operative results.

	Co-Cr implant (n=25)	OxZr implant (n=22)
Male: female	4: 21	2: 20
Mean age (year)(range)	75.3 (65 to 89)	75.1 (64 to 85)
Mean follow-up period (month)(range)	24.9 (13 to 36)	24.3 (13 to 37)
Positive rates of patch test (%)		
Ni	0	9.0 (n=2)
Va	4.0 (n=1)	0
Co, Cr, Al, Va, Ti, Mo	0	0
Positive rates of LST (%)		
Co	12.0 (n=3)	0
Ni	24.0 (n=6)	18.2 (n=4)
Cr	8.0 (n=2)	4.5 (n=1)

Table 3. Results of metal ion sampling (Co-Cr implant).

	Ion level (ng/mL)		
Metal (Mean±SD)	**pre-operative**	**post-operative**	**p value**
Co	0.24±0.05	0.29±0.12	0.40
Ni	0.10±0.03	0.18±0.18	0.31
Cr	0.30±0.19	0.33±0.14	0.91
Results of metal ion sampling (OxZr implant)			
	Ion level (ng/mL)		
Metal (Mean±SD)	**pre-operative**	**post-operative**	**p value**
Co	0.24±0.06	0.25±0.10	0.59
Ni	0.11±0.03	0.11±0.10	0.34
Cr	0.25±0.17	0.28±0.09	0.68

testing to all metal haptens. The severity of the positive skin reactions were all (+) weak positive reaction. As the results of LST, positive rates to Ni were highest among 3 haptens, and all subjects who were sensitive on patch testing were also positive on LST to the same hapten. However, among the subjects who had initially tested negative on patch testing to all metal haptens (n=45), 33.3% of subjects showed positive test results on LST at least to 1 hapten. Positive rates of the preoperative screening were summarized in (**Table 1**).

Considering the result of the preoperative screening, one subject, who exhibited positive on both tests to Co, was strongly suspected to Co hypersensitivity. For the reason, she was excluded from the present study, and received a ceramic TKA of the different prosthesis design. 2 subjects, who tested positive on both tests to Ni were not excluded from the study, and were implanted ceramic surfaced OxZr prosthesis. The rest of subjects were tested negative on patch test to all haptens, and were selected either of 2 implants randomizedly. As the results, 22 of 47 knees were received OxZr implants, and 25 subjects were received Co-Cr implants.

Mean follow-up periods reached 24.3 months (OxZr group), and 24.9 months (Co-Cr group), respectively at the time of the last examination, and there was no statistical difference between 2 groups. The demographic characteristics of each group were presented in (**Table 2**).

Postoperatively, in the OxZr group, no subject newly tested positive on patch testing to all metal haptens, except for 2 subjects who had initially positive for Ni. In the Co-Cr group, 1 subject (4%) newly tested positive, (+) weak positive reaction, on patch testing to Va. However, she did not show any symptoms attributable to metal sensitization at the latest examination.

As the results of LST, in the OxZr group, preoperative positive rates to Co, Ni, and Cr were 0, 18.2, 13.6 (%), respectively, and postoperative rates were 0, 18.2, 4.5 (%), respectively, including 2 subjects who tested positive to Ni preoperatively. On the other hand, in the Co-Cr group, preoperative positive rates to Co, Ni, and Cr were 8.0, 36.0, 16.0 (%), respectively, and rates were 12.0, 24.0, 8.0 (%) postoperatively. However, a few subjects who had initially tested positive to Ni or Cr on LST became tested negative postoperatively, and the phenomenon was confirmed in the both groups.

As the result of serum ion sampling, in the Co-Cr group, preoperative positive ion levels to Co, Ni, and Cr were 0.24±0.05, 0.10±0.03, 0.30±0.19 (ng/mL), and postoperative levels were 0.29±0.12, 0.18±0.18, 0.33±0.14 (ng/mL), respectively, which suggested a slight increase of Co and Ni levels during the second 6 months after operation. However, there were no statistically significant differences in levels between pre and post operative values. On the other hand, metal ion levels did not differ between pre and post operative values in the OxZr group during the same period (**Table 3**).

The knee score of the OxZr group improved from an average of 35.0 points (range 15-62) preoperatively to 93.4 points (range 56-100) at the latest follow-up. The score of the Co-Cr group improved from 38.0 points (range 12 - 65) to 91.3 points (range 53-100). The average preoperative functional score of the OxZr group was 42points (range 10-75). It improved to 86.4 points (range 45-95) at the latest follow-up. The score of the Co-Cr group improved from 36.2 points (range 10-70) to 84.6 points (range 40-95), and there were no statistically significant differences between data of 2 groups.

To date, no knee was revised. However, one patient in the Co-Cr group developed eczematous skin reaction and was

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diagnosed as superficial infection by the bacteriological test. As LST showed no increased values and the wound fully healed without complications, the reaction was not thought to be attributed to the allergic reaction. None of the subjects has developed cutaneous signs attributable to metal sensitization, and there was no episode of prolonged joint effusion, or persistent knee pain in the both groups.

As the results of radiological evaluation, there were no radiolucent lines (RLL) at the femoral interface in the the OxZr group. In contrast, RLLs of 1mm were conformed in 2 knees in zone 1 with tibial components. In the Co-Cr group, there were RLLs measuring 1 mm in width in zone 1 of the sagittal view of femoral component in 2 patients, and RLLs of 1mm were also found in 4 knees in zone 1 of the frontal view with tibial components. However, none of the subject exhibited the evidence of the implant loosening at the latest examination in the both groups.

Discussion

In the present study, we investigated the metal sensitivity prior to TKA using both skin patch testing and LST for the subjects with no history of cutaneous metal allergy, and the finding of preoperative testing suggests that past history of cutaneus allergy alone seems to be insufficient for identifying subjects with MS.

In general, individuals who should be screened prior to surgery are those reporting a history of MS, and the retrospective chart review supports the use of patch testing in patients with a clinical history of metal hypersensitivity [12]. Previous report indicated that the surgeons should undertake routine preoperative screening for MS [2]. However, currently, most agree that individuals without a reported history of metal hypersensitivity reactions need not be screened prior to implantations [13-15].

In our results, 6.3% of the subjects with no past history of metal allergy had positive results both on patch test and LST, who might potentially have increased risk of hypersensitivity to metal implants. However, our present data could not provide the evidence that implicates preexisting MS elicits metal allergy after implantation of the component containing metals to which they are reactive preoperatively because it was ethically problematic to select the conventional Co-Cr implant for subjects with highly suspected to MS to Co or Ni. For these reasons, our study results seem to be insufficient to support the clinical relevance of preoperative screening for subjects with no history of MS as a predictive value of metal allergy.

The average prevalence of contact dermatitis was 19.5% in the general population, based on data collected on all age groups and all countries [5]. The North American Skin Patch testing group indicated the results of 4,454 patients to a wide variety of haptens. Nickel (Ni) was the most common reactant (21 percent); reactions to other substances found in orthopaedic implants such as cobalt (Co) (8 percent) and chrome (Cr) (8 percent) were on the rise [16,17]. In Japan, another report of 931 patients showed the metal to which the most patients reacted was Ni (27.2%) [18], and our results also suggested Ni would be the most common sensitizer in the subject with no history of metal allergy. However, previous reports were mostly based on the results of patch test [13] and very few clinical result of LST is available, thus current modalities for metal allergy assessment (patch testing and LST) lack robust clinical validation for either their diagnostic accuracy. The patch test is a cutaneous test, and the test does not recreate the environment in which the metal resides. In addition, mixing metal chlorides used in patch testing has the potential of inducing hypersensitivity by extended dermal contact during patch testing. Therefore, although the use of LST in the assessment of MS is currently less popular than patch testing, several studies indicate that LST may have advantages over dermal patch testing for implant related hypersensitivity [19,20].

Our findings of the discrepancies between 2 testing methods suggested that the LST might be more sensitive than patch test, and could be tested more safely. However, the *in vitro* test seems to lack adequate specificity. Therefore the LST would not be as beneficial for candidates for metal implantations as *in vivo* skin patch test.

Postoperatively, one subject newly tested positive for patch test and the number of subjects who tested positive for LST was increased, which could be caused by sensitization induced by metal implants. In addition, the discrepancy between values of OxZr and Co-Cr also might be attributed to the different bearing surfaces of each component.

The occurrence of metal allergy is particularly uncommon following TKA because there is a polyethylene insert between the femoral and tibial components and no metal-on-metal contact exists, comparing metal-on-metal (MoM) total hip arthroplasty (THA), and there seems to be extremely rare subset of subjects with MS who will develop allergious reactions to implants during short period after operations. In contrast to THA [21-23], there are relatively few publications regarding metal ion exposure after TKA [24], and our investigation suggested a substantial elevation of serum metal ions in the Co-Cr group. There is no traceable Ni in the OxZr, and our data of the OxZr group implied that Co and Cr ion releases also seem to be reduced during short operative period. However, the elevation confirmed in the Co-Cr group was relatively small, comparing the literature of MoM THA, and relation of the metal ion exposure and adverse effect due to MS remains unknown.

The 5-year follow up study showed no adverse events have been observed clinically or radiologically with the same prosthesis design with OxZr [25-27]. Our results also suggested safety for subjects, including those who had the positive patch test to Ni. The phenomenon confirmed in some subjects whose test results of LST became negative postoperatively could be due to false positive reaction or

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immunological tolerance induced by implants, and further studies are needed to investigate diagnostic performance of *in vitro* test.

A larger sample size and longer follow-up period would provide more critical information, which is a major limitation of the present study. In addition, we were not able to access the patch test reaction after 72 hour in those subjects who could not do a outpatient visit repeatedly for various reasons, which is also a limitation of the study.

Conclusions

Preoperative screening might be useful to identify MS in subjects with no history of metal related allergy. However, our results seem to be insufficient to support the clinical relevance of the screening as a predictive value of metal allergy after TKAs.

Although the present study implies that OxZr implant could be a alternative in cases of Ni allergy, we could not conclude the benefit of the specific implants for non allergic subjects during short post-operative period.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	AK	TC	NT	TI
Research concept and design	--	✓	✓	✓
Collection and/or assembly of data	✓	✓	--	--
Data analysis and interpretation	✓	✓	✓	✓
Writing the article	✓	--	--	--
Critical revision of the article	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓
Statistical analysis	✓	--	✓	--

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