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In vivo blood metal ion levels in patients after total shoulder arthroplasty

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Background: Products from metal wear have been identified as a potential cause of adverse local tissue reactions and implant failure in total hip arthroplasty. However, the role of metal ion exposure in patients after total shoulder replacement is unclear. The objective of the present study was to determine in vivo blood metal ion levels of cobalt, chromium, and titanium in patients after anatomic total shoulder arthroplasty (TSA) or reverse TSA.
Methods: A consecutive series of patients after anatomic TSA or reverse TSA was evaluated retrospectively. After exclusion of patients with additional metal implants, 40 patients with unilateral anatomic TSA (n = 20) or reverse TSA (n = 20) were available for whole-blood metal ion analysis at a mean follow-up of 28 ± 9.6 months. Twenty-three healthy individuals without metal implants served as a control group.
Results: Mean cobalt ion concentrations were 0.18 μg/L (range, 0.1-0.66 μg/L), 0.15 μg/L (range, 0.03-0.48 μg/L), and 0.11 μg/L (range, 0.03-0.19 μg/L), mean chromium ion levels were 0.48 μg/L (range, 0.17-2.41 μg/L), 0.31 μg/L (range, 0.09-1.26 μg/L), and 0.14 μg/L (range, 0.04-0.99 μg/L), and mean titanium ion concentrations were 1.31 μg/L (range, 0.75-4.52 μg/L), 0.84 μg/L (range, 0.1-1.64 μg/L), and 0.62 μg/L (range, 0.32-2.14 μg/L) in the reverse TSA group, the anatomic TSA group, and the control group, respectively.
Conclusions: TSA resulted in elevated metal ion levels compared with healthy controls, although overall metal ion concentrations measured in this study were relatively low. The role of local metal ion exposure in patients with total shoulder replacements should be further investigated.
Level of evidence: Basic Science Study; Serology

Keywords: Metal ions; titanium; cobalt; chromium; total shoulder arthroplasty; shoulder replacement; corrosion; metal wear

The Ethikkommission Medizinische Fakultät Heidelberg approved this study (Application No. S-296/2014).

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Total shoulder arthroplasty (TSA) has become a successful treatment option for degenerative shoulder disease. The incidence of primary shoulder arthroplasties has significantly increased in recent decades.[28] To some extent, this increase has been associated with the approval of the reverse shoulder prosthesis in 2003 by the United States Food and

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Drug Administration, which expanded the indications to a broader variety of shoulder pathologies.[35,42] In 2011, reverse TSA accounted for 42% of all primary shoulder replacements in the United States.[26] The rise in primary TSA procedures has been accompanied by a growing burden of revision shoulder arthroplasty; therefore, strategies to improve implant longevity are becoming more important.[2]

Aseptic glenoid component loosening remains one of the major reasons for implant failure, which accounts for up to 24% of all complications in TSA.[8,20,45] Wear particles have been identified as a leading mechanism in implant failure by inducing a chronic inflammatory response that can result in periprosthetic osteolysis and implant loosening.[1,31] Metal ions are able to influence the immune system and bone metabolism through different pathways, thereby contributing to the pathophysiological mechanisms of hypersensitivity reactions and aseptic loosening.[6,7,21]

Modular junctions of metal implants are especially prone to fretting damage and corrosion that can lead to the generation of metal ions.[25] Because mechanical wear and corrosion usually occur simultaneously, the term “tribocorrosion” is also frequently used.[30] Corrosion at taper junctions was first described with metal-on-metal total hip prosthesis but has also been associated with modular metal-on-polyethylene (MoP) hip arthroplasties and total knee replacements.[16,31,39,43] Modularity and large-diameter metal heads are commonly used in total shoulder replacements.

Although initial retrieval studies have found fretting and corrosion also to be present in failed total shoulder prosthesis,[14,40] little is known about the role of metal ion exposure in patients after total shoulder replacement. Therefore, the objective of this study was to determine in vivo blood metal ion levels of cobalt, chromium, and titanium in patients after total shoulder replacement and to compare blood metal ion levels against those in control subjects without metal implants.

Materials and methods

Patients

In this cross-sectional cohort study, we retrospectively evaluated a consecutive series of 254 patients (264 implants) who underwent TSA at our institution with an anatomic or reverse total shoulder replacement between January 2011 and December 2014. Written informed consent was obtained by each patient before inclusion. We excluded 32 patients (42 implants) with bilateral shoulder replacements and 128 patients with other metal implants, such as total hip or knee replacements, to avoid additional sources of metal ion release. From this cohort, 35 patients (14%) were lost to follow-up, and 19 patients (7%) declined to participate in blood metal ion analysis, leaving 40 patients who were included in the present study.

Patients were examined at a mean of 28 months (standard deviation, 9.6; range, 8-52 months) after the primary surgery. At follow-up, demographic data (age, sex, duration of follow-up, implant type, and side of shoulder treated) were documented, and blood metal ion analysis was performed. Implant position was assessed with anteroposterior and lateral radiographs of the shoulder.

We also measured whole blood metal ion levels in a control group of 23 healthy individuals without any metal implants or environmental exposure to metal ions who were recruited at the outpatient clinic of our institution. The study groups and the control group were matched in age and creatinine values. Demographic data of the study cohort and control group are summarized in Table I.

Table I Demographic data of the study groups and the control group, which were matched by age and creatinine value

Demographic variable	TSA group (n = 20)	RSA group (n = 20)	Control group (n = 23)
Implant, No*			—
TESS	11	—	
Simpliciti	6	—	
Aequalis Anatomical	3	—	
Aequalis Reverse	—	20	
Dominant shoulder treated, No. (%)	10 (47.6)	7 (35)	—
Side treated, No.			
Right	12	10	
Left	8	10	—
Sex			
Male	12	6	10
Female	8	14	13
Age at time of follow-up, yr	67 (49-76)	72.5 (47- 93)	68 (56-81)
Duration of follow-up, mo	29.5 (8-52)	25.7 (19-37)	—
Creatinine, mg/dL	0.93 (0.6-1.5)	0.99 (0.68-1.6)	0.93 (0.7-1.4)

TSA, anatomic total shoulder arthroplasty; *RSA*, reverse total shoulder arthroplasty.
Categorical data are presented as number (%) or number and continuous data as mean (range).
* TESS (The Total Evolutive Shoulder System; Biomet, Inc., Warsaw, IN, USA), Simpliciti (Tornier, Bloomington, MN, USA), Aequalis Anatomical (Tornier), Aequalis Reversed Shoulder Prosthesis (Tornier).

Implants

In the study cohort, 4 different implants were used (Table I). The Total Evolutive Shoulder System (TESS; Biomet, Inc., Warsaw, IN, USA) consists of an uncemented metaphyseal fixation by a 6-armed corolla made of cobalt chrome with a porous titanium and hydroxyapatite coating. It was used with a cemented all-polyethylene glenoid component and an anatomic head made of cobalt-chromium alloy that is locked on the corolla with a taper (Fig. 1, *A*).

The Simpliciti shoulder system (Tornier, Bloomington, MN, USA) consists of an uncemented metaphyseal humeral component made of titanium alloy with a titanium bead coating that is combined with a humeral head made of cobalt-chromium alloy and a cemented all-polyethylene glenoid component (Fig. 1, *B*).

The Aequalis Anatomical Shoulder System (Tornier) has a cemented titanium alloy stem and a cobalt-chromium anatomic head. A cemented all-polyethylene glenoid component was used for this implant (Fig. 1, *C*).

The Aequalis Reversed Shoulder Prosthesis (Tornier) is intended to be used in patients with shoulder arthropathy and a massive or nonrepairable cuff tear. For this modular shoulder system, 2 humeral components are available with a cemented and an uncemented stem version. In this cohort, a cemented stem was used in all patients (Fig. 1, *D*). The stem is combined with a metaphyseal component and can be augmented with a lateralized spacer, if necessary. Aside from the polyethylene insert, all humeral components are made of cobalt-chromium alloy. The glenoid component consists of an uncemented titanium baseplate with a central peg and hydroxyapatite coating. It is impacted press-fit into the glenoid bone and secured by 4 self-tapping screws. The glenoid sphere is made of cobalt-chrome alloy and fixed on the baseplate with a Morse taper and a locking screw.

Operative technique

Indications for surgery were primary osteoarthritis (n = 17), fracture sequelae (n = 16), cuff-tear arthropathy (n = 4), and revision arthroplasty (n = 3). An internal fixation device, such as an osteosynthesis plate or intramedullary nailing system, was removed in 50% (n = 8) of patients who were treated for fracture sequelae during the total shoulder replacement procedure. A deltopectoral approach was used in all patients. The humeral and glenoid components were implanted according to the manufacturers' surgical instructions.

Radiographs of the shoulder were taken postoperatively to document correct implant position. Physical therapy was started on the first day after surgery with passive motion exercises. External rotation and motion above 90° of shoulder abduction and forward flexion were not recommended for 6 weeks after surgery.

Metal ion analysis

Blood samples were collected using a specific blood collection system suitable for trace metal ion analysis (Sarstedt, Nuembrecht, Germany; Refs. 58.1162.600 and 01.1604.400). We discarded the first 5 mL and stored the blood samples at −20°C until analysis. Whole-blood metal ion concentrations for cobalt, chromium, and titanium were analyzed using high-resolution inductively coupled plasma-mass spectrometry (Element 2; Thermo Fisher Scientific, Bremen, Germany). Before analysis, blood samples were digested with high-purity nitric acid (HNO_3) and hydrogen peroxide (H_2O_2) under clean-room conditions in a high-pressure microwave autoclave (UltraClave II; Milestone, Bergamo, Italy).[30,36]

To minimize calibration error of the spectrometer, all blood samples were analyzed at the same time. Metal ion measurements were repeated 3 times in every sample, and mean values of metal ion concentrations for each sample were calculated. Detection limits were calculated by analyzing 6 independent blank solutions considering the usual 3 (sigma) criterion. Detection limits of 0.005 µg/L for cobalt, 0.02 µg/L for chromium, and 0.06 µg/L for titanium were established.[30] Because metal ion levels in the blood depend on the renal capacity of metal ion excretion, we also measured serum creatinine values for each patient to rule out severe renal insufficiency (Table I).

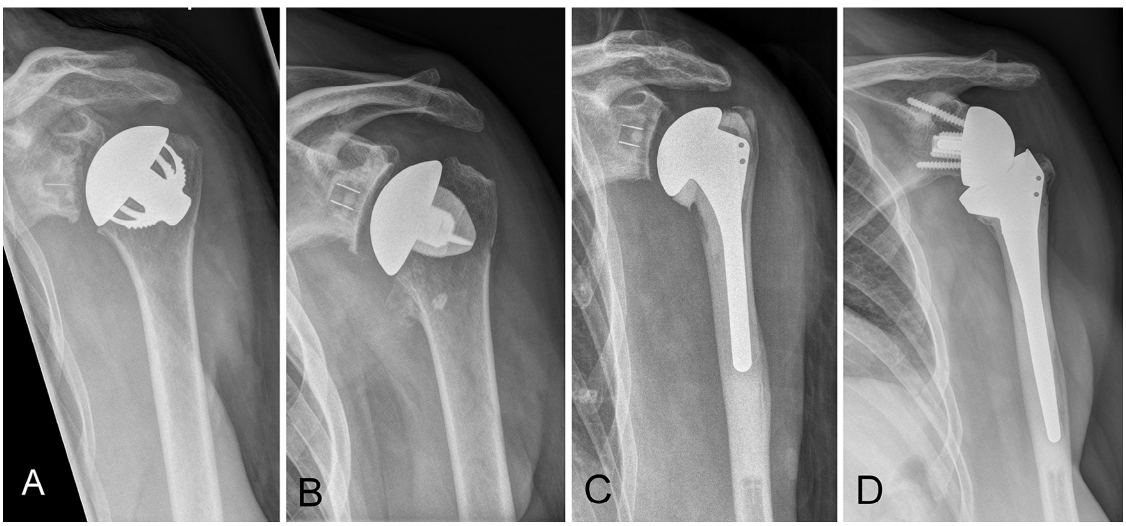

Figure 1 Anteroposterior radiographs of the shoulder of 4 different patients demonstrating the total shoulder prosthesis used in this study: (**A**) The Total Evolutive Shoulder System (TESS; Biomet, Inc., Warsaw, IN, USA), (**B**) the Simpliciti shoulder system (Tornier, Bloomington, MN, USA), (**C**) the Aequalis Anatomical Shoulder System (Tornier), and (**D**) the Aequalis Reversed Shoulder Prosthesis (Tornier).

Table II Results of blood metal ion analysis for patients with anatomic total shoulder arthroplasty, reverse total shoulder arthroplasty, and for control subjects without metal implants

Group	No.	Cobalt level (μg/L)	Chromium level (μg/L)	Titanium level (μg/L)
RSA	20	0.18 (0.1-0.66)	0.48 (0.17-2.41)	1.31 (0.75-4.52)
TSA	20	0.15 (0.03-0.48)	0.31 (0.09-1.26)	0.84 (0.1-1.64)
Control	23	0.11 (0.03-0.19)	0.14 (0.04-0.99)	0.62 (0.32-2.14)
		P value	*P* value	*P* value
RSA vs. control		<.001*	<.001*	<.001*
TSA vs. control		.064	.002*	.041*
TSA vs. RSA		.105	.058	<.001*

RSA, reverse total shoulder arthroplasty; *TSA*, anatomic total shoulder arthroplasty.
Data are shown as the mean (range).
* Statistically significant differences ($P < .05$).

Statistical methods

Statistical analysis was performed using SPSS 22.0 software (IBM, Armonk, NY, USA). Data were evaluated descriptively as arithmetic mean, median, minimum, and maximum. Because metal ion concentrations were not normally distributed, nonparametric tests were used for comparison of median metal ion levels between the groups. The Kruskal-Wallis test was used as a global test, and a stepwise analysis was done with the Mann-Whitney *U* test to compare median blood metal ion concentrations between the groups. To investigate correlations between blood metal ion levels and clinical parameters (such as body mass index, patient age, time of follow-up, and creatinine values), the Spearman rank correlation coefficient and multiple linear regression analysis was used. Correlation was defined as poor (0.00 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), good (0.61 to 0.80), or excellent (0.81 to 1.00). All tests were 2-sided, and $P < .05$ was considered significant.

Results

Metal ion levels were elevated in patients with total shoulder replacements compared with healthy controls. Median whole-blood metal ion concentrations of cobalt, chromium, and titanium were higher in the anatomic TSA and reverse TSA groups than in the control group. Except for the difference in cobalt ion concentration between the TSA and the control groups, all differences were statistically significant (Table II; Figs. 2-4). Median metal ion levels in patients with reverse TSA were higher compared with the anatomic TSA group; however, only the difference in titanium ion levels between the 2 groups was statistically significant ($P < .001$; Table II). Intragroup analysis revealed no significant difference between the 3 prosthesis designs of the anatomic TSA group for metal ion levels of cobalt ($P = .789$), chromium ($P = .296$), and titanium ($P = .591$). No patient demonstrated cobalt ion levels higher than 1 μg/L. Two patients with reverse total shoulder replacement and 1 patient with anatomic total shoulder replacement showed chromium ion levels above 1 μg/L. In these patients, there was no evidence of impingement, component malposition, or other signs of mechanical failure on plain radiographs. Spearman coefficient revealed fair correlation between the cobalt ion concentrations and time of follow-up ($\rho = 0.386$, $P = .015$). However, neither of the tested variables showed any correlation with blood metal ion levels in multivariate regression analysis.

Discussion

Our data suggest that there is an increase of circulating chromium, cobalt, and titanium ion levels after total shoulder replacement. The metal ion levels observed in the present study are relatively low compared with blood metal ion levels reported for patients with metal-on-metal total hip arthroplasty (THA)[23,24] but compare well with those reported in the literature for modular MoP THA.[5,19,38] Briggs et al[5] investigated whole-blood metal ion levels in patients with MoP total hip replacements using inductively coupled plasma-mass spectrometry and reported mean cobalt and chromium ion concentrations of 0.34 μg/L (range, 0.1-1.3 μg/L) and 0.75 μg/L (range, 0.4-1.4 μg/L) 5 years after surgery. Gofton et al[19] investigated metal ion concentrations in patients after MoP THA with a cementless titanium stem and a modular neck system 2 years after surgery. They reported median cobalt, chromium, and titanium ion levels of 0.26 μg/L, 0.28 μg/L, and 2.70 μg/L, respectively. Elevated serum metal ion levels in patients with well-functioning total knee arthroplasties compared with patients without metal implants have also been reported,[33] and increased local metal ion exposure due to abrasive wear and corrosion in total knee arthroplasty was shown in an experimental study.[31]

Metal ions originate from corrosion at the surface of a joint replacement or from corrosive degradation of abrasive metal wear products. Mechanical wear can occur at the articulating surfaces of joint replacements or at nonarticulating surfaces, for example, at taper junctions of modular components.[27,32] In hip arthroplasty, corrosion and fretting damage at the femoral head-neck taper interface have been identified as a cause for implant failure.[34] The local accumulation of metal

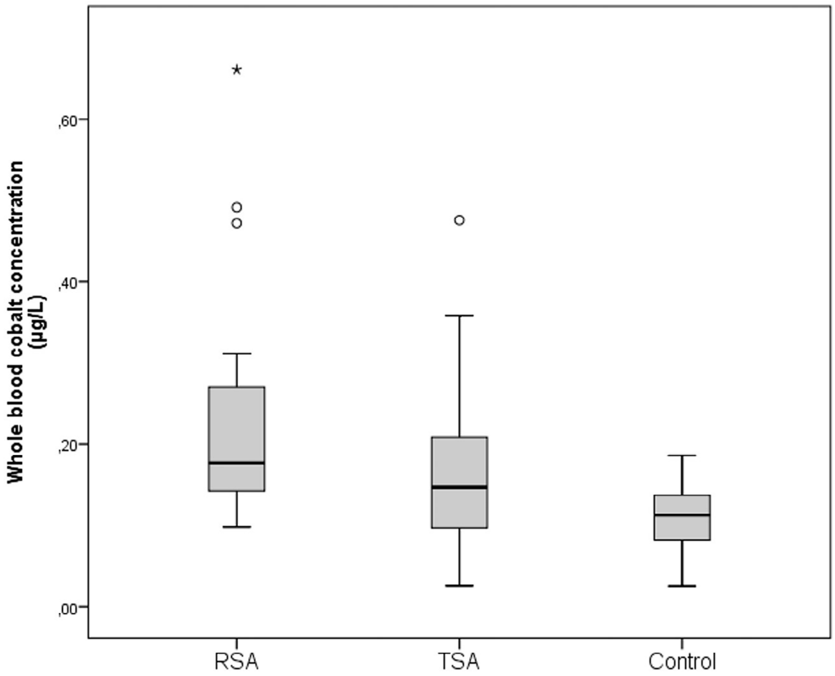

Figure 2 Box-and-whisker plots show whole-blood cobalt ion concentrations of the study groups and the control group. Mean cobalt ion concentrations were 0.18 µg/L (range, 0.1-0.66 µg/L) in the reverse total shoulder arthroplasty (*RSA*) group, 0.15 µg/L (range, 0.03-0.48 µg/L) in the anatomic total shoulder arthroplasty (*TSA*) group, and 0.11 µg/L (range, 0.03-0.19 µg/L) in the control group. The *box* marks the range between first and third quartile, the *band* inside the box indicates the median, and *whiskers* indicate minimum and maximum data, respectively. The *circles* and the *asterisk* indicate outliers.

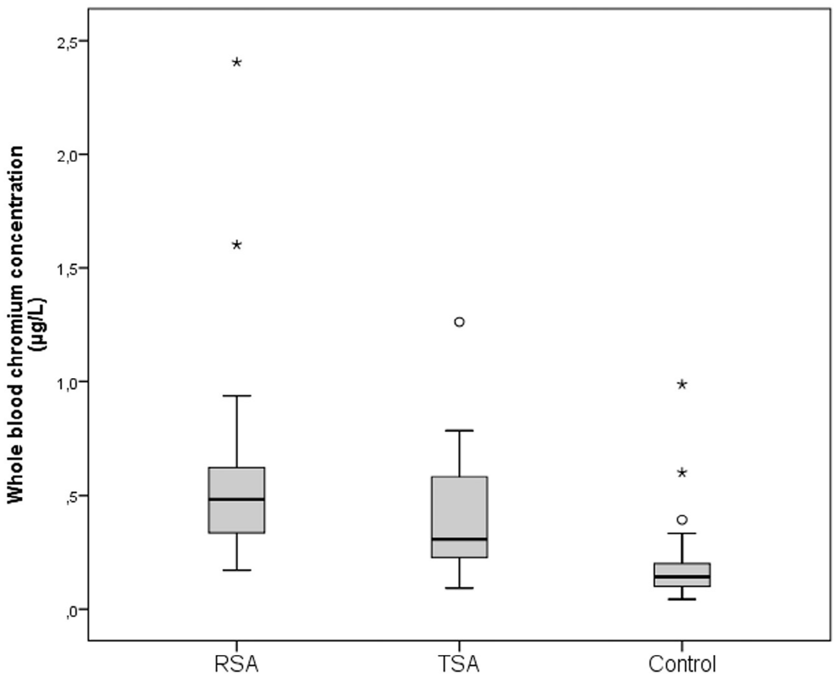

Figure 3 Box-and-whisker plots show whole-blood chromium ion concentrations of the study groups and the control group. Mean chromium ion concentrations were 0.48 µg/L (range, 0.17-2.41 µg/L) in the reverse total shoulder arthroplasty (*RSA*) group, 0.31 µg/L (range, 0.09-1.26 µg/L) in the anatomic total shoulder arthroplasty (*TSA*) group, and 0.14 (range, 0.04-0.99 µg/L) in the control group. The *box* marks the range between first and third quartile, the *band* inside the box indicates the median, and the *whiskers* indicate minimum and maximum data, respectively. The *circles* and the *asterisk* indicate outliers.

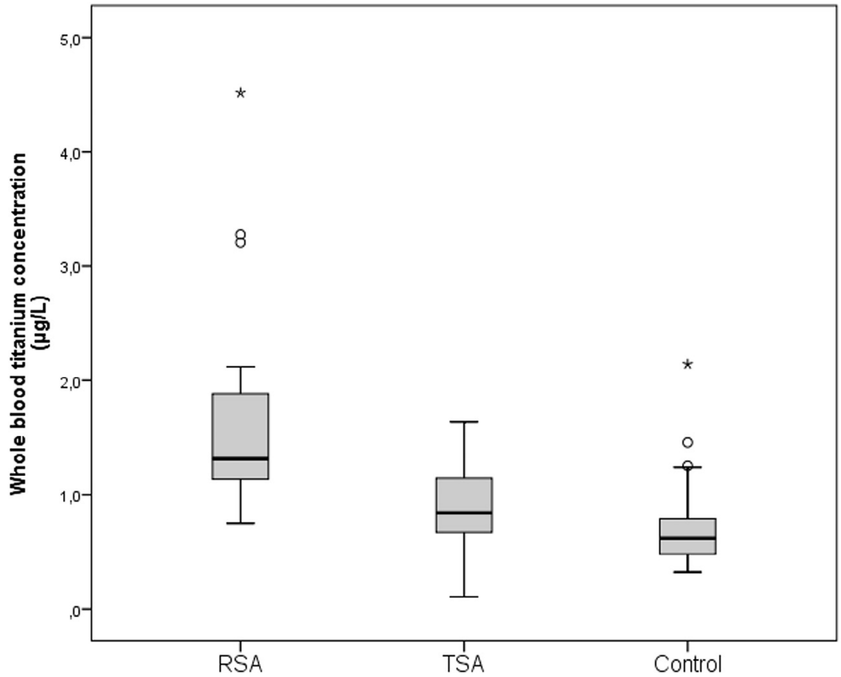

Figure 4 Box-and-whisker plots show whole-blood titanium ion concentrations of the study groups and the control group. Mean titanium ion concentrations were 1.31 µg/L (range, 0.75-4.52 µg/L) in the reverse total shoulder arthroplasty (*RSA*) group, 0.84 µg/L (range, 0.1-1.64 µg/L) in the anatomic total shoulder arthroplasty (*TSA*) group, and 0.62 µg/L (range, 0.32-2.14 µg/L) in the control group. The *box* marks the range between first and third quartile, the *band* inside the box indicates the median, and the *whiskers* indicate minimum and maximum data, respectively. The *circles* and the *asterisk* indicate outliers.

wear products and metal ions can trigger adverse local tissue reactions, such as pseudotumor formation and periprosthetic osteolysis, which can ultimately result in implant loosening.[11,37]

Retrieval studies of TSA have shown that tribocorrosion also frequently occurs at modular connections of total shoulder replacements.[12,14,40] Teeter et al[40] evaluated 28 retrieved anatomic total shoulder replacements with a mean follow-up duration of 6.2 years and found corrosion was present in 38% of the stems and in 32% of the heads. Another study reported corrosion in 81% of the stems and in 75% of the heads of retrieved anatomic total shoulder replacements.[14] The authors noticed a higher prevalence of corrosion in stemmed total shoulder replacements composed of mixed metal alloys; however, moderate and severe corrosion was only found in 16%. The authors concluded that higher torsional moments at the modular junctions of stemmed prosthesis compared with stemless humeral components might result in increased micromotions at the modular interface, thereby facilitating fretting damage and metal ion release.[14] In our cohort, we did not find a significant difference in systemic metal ion exposure between stemmed and stemless prosthesis designs in anatomic shoulder implants, taking into account that the number of stemmed TSAs was limited in the present study.

Taper junctions of mixed metal components are prone to tribocorrosion due to the potential for additional galvanic corrosion.[10,17] Galvanic corrosion arises if metals of different electrochemical potentials are combined. In the presence of an electrolyte, the 2 dissimilar metals act as anode and cathode, which ultimately results in ion migration and corrosion.[29] In our cohort, there was no evidence that patients after anatomic TSA with mixed metal components (Simpliciti; cobalt-chromium head combined with a titanium alloy metaphyseal component) had significantly higher blood metal ion levels compared with patients with implants of similar metal alloys (TESS; both humeral head and metaphyseal component made of cobalt-chromium alloy). However, titanium ion levels were significantly higher in the reverse TSA group than in the anatomic TSA group. In this implant, a mixed metal combination is present with the cobalt-chromium glenosphere and the titanium alloy baseplate, which could potentially give rise to galvanic corrosion. Also, 4 titanium screws are used to secure the baseplate, which might be an additional source for titanium ion release.

Furthermore, the semiconstrained biomechanical concept of the reverse shoulder replacement design, which allows for the treatment of irreparable cuff tear arthropathy and increases friction and shear forces at the glenoid-baseplate and the glenosphere as well as at the polyethylene locking mechanism. Increased micromotion at the modular connections might cause localized loss of protective surface oxide layers and facilitate fretting and corrosion damage resulting in higher blood metal ion concentrations in these patients.[11,18] Interestingly, Cusick et al[12] reported limited evidence of corrosive wear on the taper interface of 5 retrieved glenosphere components. However, further retrieval studies on tribocorrosion of reversed shoulder prosthesis are missing.

The clinical effects of elevated blood metal ion levels in the context of TSA remain unclear. Local adverse tissue reactions as well as systemic effects of increased metal ion concentrations have been described for metal-on-metal hip arthroplasties.[4,9,13,22,41,44] Periarticular, metal debris and corrosion products can trigger an immune response that might result in pseudotumor formation and periprosthetic osteolysis.[3] Reports of systemic effects of cobalt metal ion toxicity in association with the use of cobalt-chromium alloys in joint replacements are rare. Neurologic, cardiac, and thyroid effects have been observed most commonly, and in most of these cases, serum cobalt ion concentrations of more than 100 μg/L were reported.[46] Considering the relatively low cobalt ion levels measured in this study, systemic adverse effects of metal ions exposure after TSA seem very unlikely. To our knowledge, no case of adverse reaction to metal debris or pseudotumor manifestation in association with total shoulder replacements has been reported so far.

This study has some limitations. First, the study is limited by the number of patients that could be included and because a sample size calculation was not performed. However, the 2 study groups and the control group compare well regarding relevant demographic parameters. No statistically significant difference was found between the groups in age ($P = .130$), duration of follow-up ($P = .325$), or creatinine values ($P = .871$).

Secondly, 3 different implant designs of anatomic TSAs were included. However, intragroup analysis revealed no significant difference regarding metal ion levels between the different prosthesis designs.

Thirdly, the environmental ingestion of metal ions by variable doses in drinking water and food is difficult to assess and may have biased our results.[15,36] Due to high standardized trace metal ion analysis, we intended to keep the methodologic confounding variables as small as possible.

Finally, intraindividual follow-up of the patients is missing because of the cross-sectional character of the study. A prospective and longitudinal study design would be helpful to investigate postoperative changes in blood metal ion concentrations over time.

Conclusion

The results of our study suggest that the metal ion release of total shoulder replacements leads to a measurable increase in circulating blood metal ion levels of cobalt, chromium, and titanium. Further studies are necessary to investigate the effects of these metal ions on the clinical outcome of total shoulder arthroplasties.

Disclaimer

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