Metal hypersensitivity and metal ion levels in patients with coated or uncoated total knee arthroplasty: a randomised controlled study

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Abstract

Purpose Metal ion release by orthopaedic implants may cause local and systemic effects and induce hypersensitivity reactions. Coated implants have been developed to prevent or reduce these effects. This study was initiated to investigate the safety of a novel coating for total knee arthroplasty (TKA) implants.

Methods A total of 120 patients undergoing primary TKA with no history of hypersensitivity and no other metal implant were randomised to receive either a coated or uncoated implant. Chromium (Cr), cobalt (Co), molybdenum (Mb) and nickel (Ni) hypersensitivity patch testing and plasma ion concentrations were evaluated pre-operatively and one year post-operatively.

Results At the one year follow-up both groups demonstrated significant improvement in knee function and quality of life. One new weakly positive reaction to Co in the TKA group with coated implant and two doubtful skin reactions to Ni

(one in each group) were noted. Even with sensitisation to implant materials no skin reactions were observed. Plasma metal ion concentrations did not increase and were not elevated at the one year follow-up in either group.

Conclusions Sensitisation after TKA was rare and had no influence on clinical results. TKA with coated implant and standard TKA demonstrated no plasma metal ion elevation.

Introduction

Total knee arthroplasty (TKA) is an established treatment option for advanced osteoarthritis of the knee with an increasing number of implantations. Although patients obviously benefit from joint replacement in terms of mobility and quality of life, implant-specific local and systemic adverse effects, due to corrosion and wear, still constitute a matter of concern [3, 27]. Every metal implant in a biological environment corrodes, depending on the exposed surface area and the composition of the alloy [15]. As they contain large metallic surfaces, TKA implants are subject to corrosion. This process results in the release of metal ions. These metal ions may trigger local and systemic toxic effects, activate the immune system [32], induce a delayed-type hypersensitivity reaction [1, 12, 20] and may even contribute to the pathophysiological mechanism of aseptic loosening [3].

Adverse reactions to metal debris (ARMD) [18] are of concern in metal-on-metal (MoM) total hip arthroplasty (THA) and led finally to a decreased use of these implants [25]. Elevated metal ion concentrations were also detected in patients after TKA compared to patients without metal implants [19] and increased rates of metal hypersensitivities after TKA have been reported [7, 11, 12]. However, the influence of these findings on outcome after TKA is still unclear.

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According to guidelines [28] patients with hypersensitivity to implant materials usually receive hypoallergenic implants. Ceramic femoral components can be used [2], but these implants are expensive, their application is more demanding [17] and ceramic tibial components are not available. Therefore, reduction of metal ion release by coating of a standard implant is a common solution. In vitro biomechanical tests demonstrated a reduction of metal ion release and superior tribological characteristics of these coated TKA implants and thus less polyethylene wear particles [5, 21, 26, 29]. However, it is unknown whether these costly implants add a patient-relevant benefit in vivo with regard to hypersensitivity reactions, metal ion release and improved long-term results by reduced wear. There have even been reports about less favourable clinical results [9, 13] and blistering of the coating caused by differences in stiffness between implant and coating [8]. A novel seven-layer coating system has been developed to solve these problems by a gradient change in stiffness between the implant body and the final coating layer [21]. This study was initiated to investigate the safety of this novel coating system. We hypothesised that the coating would prevent metal ion release resulting in lower plasma metal ion concentrations and less hypersensitivity reactions to implant materials.

Methods

The study protocol was approved by the local independent Ethics Committee. Sample size calculation was done using data from a cross-sectional study of patients who underwent TKA with a CoCrMo alloy implant in comparison to patients without implants [19]. To detect a difference in metal ion levels of 0.67 µg/l with a significance level of 5 % and test strength of 80 % a minimum of 36 patients per group was required.

Patients

Between April 2009 and November 2011 all 628 patients who were admitted to our Orthopaedic Department for a primary unconstrained TKA were screened (Fig. 1). Exclusion criteria included existing orthopaedic metal implants, a history of hypersensitivity to metals or bone cement particles, malignancies, renal insufficiency and other severe illnesses that would impair participation in this study. After informed consent 126 patients were randomised to receive either a coated or uncoated TKA implant using a randomisation list. During preoperative patch testing four patients demonstrated a previously unknown hypersensitivity to cobalt, chromium or nickel. According to local guidelines [28] all four patients received a coated implant, although two were randomised to receive an

Fig. 1 CONSORT flow chart of patients eligible for the study

uncoated implant. In six patients an intra-operative decision was made to use a higher constraint implant, and these patients were excluded.

Both groups were not different at pre-operative baseline values for gender, age, body mass index (BMI), American Society of Anesthesiologists (ASA) grade and deformity (Table 1). After one year four patients were lost to follow-up: One patient died and three patients ceased to participate in the study and refused to complete follow-up.

In all patients metal ion analysis and patch testing were done for cobalt, chromium, molybdenum and nickel preoperatively and at the one year follow-up. Patient's activity [University of California Los Angeles (UCLA) Activity Score], knee function (Knee Society Score) and quality of life (Oxford Knee Score, Short Form 36) was assessed pre-operatively and at the three month and one year follow-ups by a trained study nurse. Further data were taken from the patient's hospital records (age, gender, BMI, ASA grade, operative time, adverse events).

Implant

The Columbus Knee System (Aesculap, Tuttlingen, Germany, Fig. 2) is a CE-certified TKA implant and consists of a CoCrMo alloy (ISO 5832-4) containing cobalt (58.65–64.65 %), chromium (26.5–30.0 %), molybdenum (4.5–7.0 %) and less than 1.0 % nickel. To reduce ion release, a multilayer coating system (Advanced Surface, AS) was developed consisting of a thin adhesive chromium layer, five alternating intermediate layers out of chromium nitride-chromium carbonitride (CrN-CrCN) and a final shielding layer of zirconium nitride (ZrN). The seven-layer coating system was applied on the CoCrMo knee implants using a physical vapour deposition (PVD) method with a total thickness of about 4 μm .

Operative procedure

In all patients unconstrained cemented TKA was performed using a coated or uncoated implant with a fixed polyethylene insert without patellar resurfacing. All operations were

Fig. 2 Coated TKA implant (AS Columbus, *left*) and uncoated TKA implant (Columbus Standard) used in this study

performed with a tourniquet after a single dose of antibiotics (1.5 g cefuroxime), using a medial parapatellar approach and a conventional measured resection technique. Post-operatively full weight-bearing was allowed, and mobilisation started from the first post-operative day.

Patch testing

Hypersensitivity to metals was tested before surgery and at the one year follow-up using the following haptens: cobalt chloride 1 %, potassium dichromate 0.5 %, molybdenum(V) chloride 0.5 % and nickel sulphate 5 % in Vaseline (Almirall Hermal GmbH, Reinbek, Germany; HAL Allergie GmbH, Düsseldorf, Germany). Each hapten was applied to the patient's back using a standardised patch test procedure [24]. Preoperative patch testing was evaluated by a trained study nurse and, in the case of a reaction, confirmed by a dermatologist. Patch testing at the one year follow-up was done by a dermatologist, blinded to the randomisation of the implant. Skin reactions were read at 72 hours and graded as negative (no reaction), doubtful (weak erythema only), irritative (e.g. follicular reactions) or positive (erythema with oedema, papules or vesicles graded as +, ++ or +++).

Table 1 Pre-operative patient characteristics: per cent for categorical values and mean (standard deviation) for continuous values

	Coated TKA implant, <i>n</i> =61	Standard TKA, <i>n</i> =59	<i>p</i>
Female gender	54.1 %	57.6 %	0.717
Age at surgery (years)	65.6 (9.1)	68.1 (8.2)	0.118
BMI (kg/m ²)	31.3 (5.2)	30.2 (5.1)	0.297
ASA grade			
1 and 2	39 (63.9 %)	36 (61.0 %)	0.511
3	22 (36.1 %)	23 (39.0 %)	
Valgus deformity	18.0 %	20.3 %	0.819
Deformity > 10°	29.5 %	32.2 %	0.871

Metal ion analysis

Blood samples were collected in 7.5-ml S-Monovette® tubes (for trace metal analysis, Sarstedt AG, Nümbrecht, Germany) using a specific steel needle for trace metal analysis (Sarstedt AG, Nümbrecht, Germany). Within one hour, plasma was separated by centrifugation at 2,500 *g* for ten minutes. Samples were stored at −20 °C before being analysed for chromium, cobalt, molybdenum and nickel content using a graphite furnace atomic absorption spectrometer Z-8270 with Polarised Zeeman Absorption (Hitachi Ltd., Tokyo, Japan). The accuracy and precision of the method is validated to <10 % using the control materials Seronorm™ Trace Elements Serum (SERO AS, Billingstad, Norway). The detection limit of the method is estimated at 0.5 µg/l for chromium, cobalt and molybdenum and 1.0 µg/l for nickel (mean+3 standard deviations from buffer). All probes having ion levels below the detection limit were adjusted to 0.25 µg/l for chromium, cobalt and molybdenum and 0.5 µg/l for nickel.

Statistical analysis

All analyses were performed with SPSS (release 19 for Windows). Data are described as mean and standard deviation (SD) for continuous values and absolute/relative frequencies for categorical values. Comparison between groups was done non-parametrically by a two-sample Wilcoxon test for continuous values and a pairwise Fisher's test for categorical values. The results of these significance tests were summarised by *p* values in which *p*<0.05 indicates locally significant differences.

Results

Adverse events

One death occurred two months post-operatively. No autopsy has been performed. In four patients a revision without exchange of the implant was necessary: two patients developed a large haematoma and revision was necessary, one with pre-existing thrombocytopenia and one receiving anticoagulation therapy due to cardiac atrial fibrillation; another patient had a fall resulting in wound dehiscence which had to be revised. One patient demonstrated an acute deep infection seven months post-operatively and was treated with open revision and a polyethylene insert exchange. At the one year follow-up there were no signs of persisting infection. In seven patients mobilisation under anaesthesia followed by intensive physiotherapy was necessary due to restricted range of motion. Further medical adverse events were recorded (*n*=47), including distal deep venous thrombosis (*n*=15).

Clinical results

Short-term results demonstrated considerable functional improvement and improved quality of life in both groups. Increase in activity using the UCLA Activity Score demonstrated only a minor increase as is usual in this age group (Table 2).

Metal hypersensitivity

There was one newly diagnosed hypersensitivity (graded as weak reaction, +) to cobalt in the TKA group with coated implant at the one year follow-up and two doubtful skin reactions to nickel (one in each group). In one patient in the TKA group with coated implant, a weakly positive reaction to chromium pre-operatively could not be reproduced at the one year follow-up. In all other patients patch testing for cobalt, chromium, molybdenum and nickel was negative.

Metal ion concentrations

Of note, no increases in plasma metal ion concentrations of cobalt, chromium, molybdenum or nickel were detected one year after insertion of a coated or uncoated TKA implant (Table 3).

Discussion

Short-term results demonstrated functional improvement in both groups comparable to results reported in the literature and no implant-related adverse events. The number of adverse events was as expected in this age group undergoing a high-risk surgery if standardised assessment is performed [16]. It is, however, relatively high compared to many other studies in which adverse events are often not defined and not assessed in a standardised manner [10].

Metal hypersensitivities are frequent in our population with up to 20.4 % to nickel and 3.4 % to cobalt [23]. Studies demonstrated more frequent positive skin reactions to metals in patients with total joint replacements (up to 44 % with stable TKA [12]) in comparison to patients without implants [4, 12, 31]. Therefore sensitisation of patients through metal implants has been discussed [11]. However, these studies did not conduct pre-operative testing and patients with a positive history were included. In our study, patch testing revealed in only 3.2 % (four of 126 patients) a previously unknown hypersensitivity to one or more of the tested metals. This is consistent with the findings of another prospective study in which 3 % of patients with a negative history of metal hypersensitivity had a positive patch test, most frequently for nickel [7]. The rate of newly discovered metal hypersensitivity reactions after TKA in our patients by patch testing

Table 2 Clinical results pre-operatively and at three month and one year follow-ups and improvement given as mean (standard deviation)

	Coated TKA implant	Standard TKA	<i>p</i>
Knee Society Score (max. 200 points)			
Pre-operative	96.6 (18.2)	93.0 (24.0)	0.533
3 months	140.3 (32.8)	140.9 (24.0)	0.586
1 year	161.1 (26.7)	155.9 (20.7)	0.224
Knee Score (max. 100 points)			
Pre-operative	44.5 (13.4)	42.7 (16.5)	0.772
3 months	76.4 (16.3)	77.7 (14.8)	0.820
1 year	84.3 (11.6)	82.9 (13.3)	0.698
Function Score (max. 100 points)			
Preoperative	52.0 (12.3)	50.5 (12.4)	0.431
3 months	63.8 (21.2)	63.7 (16.8)	0.912
1 year	75.9 (18.3)	72.5 (15.3)	0.299
Oxford Knee Score (max. 48 points)			
Preoperative	21.4 (6.3)	21.8 (7.4)	0.838
3 months	33.6 (8.3)	32.0 (6.7)	0.949
1 year	37.5 (7.8)	37.5 (7.8)	0.951
SF-36 physical scale			
Preoperative	36.2 (14.2)	38.4 (18.3)	0.577
3 months	55.0 (21.5)	55.1 (17.0)	0.816
1 year	61.7 (21.4)	61.6 (20.9)	0.867
SF-36 psychological scale			
Preoperative	68.3 (20.7)	68.2 (24.8)	0.677
3 months	73.0 (22.0)	73.1 (22.0)	0.953
1 year	76.4 (19.2)	74.3 (20.7)	0.681
UCLA Activity Score			
Preoperative	4.0 (1.5)	3.9 (1.7)	0.674
3 months	4.5 (1.5)	4.4 (1.4)	0.853
1 year	5.2 (1.4)	4.8 (1.5)	0.089

Table 3 Plasma metal ion concentrations pre-operatively and at the one year follow-up given as mean (standard deviation). Detection limit was 0.5 µg/l for cobalt, chromium and molybdenum and 1.0 µg/l for nickel. Values below detection limit were set to 0.25 µg/l for cobalt, chromium and molybdenum and to 0.5 µg/l for nickel

	Coated TKA implant	Standard TKA	<i>p</i>
Cobalt			
Pre-operative	0.53 (0.33)	0.67 (0.54)	0.493
1 year	0.45 (0.37)	0.50 (0.44)	0.714
Chromium			
Pre-operative	0.54 (0.60)	0.50 (0.42)	0.519
1 year	0.31 (0.15)	0.35 (0.31)	0.561
Molybdenum			
Pre-operative	1.29 (1.78)	1.21 (0.74)	0.111
1 year	0.90 (0.85)	0.97 (1.09)	0.742
Nickel			
Pre-operative	0.69 (0.42)	0.88 (0.66)	0.087
1 year	0.78 (0.66)	0.62 (0.32)	0.321

was very low, with only two doubtful reactions to nickel and one weak reaction to cobalt. The metal ion levels of these three patients at follow-up were all below detection limit. This is consistent with a prospective study in which testing was performed pre- and post-operatively (21 vs 26 % positive patch tests) [7]. However, our post-operative results demonstrate considerably lower hypersensitivity rates than described in previous, cross-sectional studies without longitudinal follow-up. Reasons for that finding might include the strict patient selection in our study (all patients with a history of hypersensitivity to implant materials were excluded) and the pre-operative testing of all included patients. This suggests that the majority of metal hypersensitivities might already exist pre-operatively and most of them can be detected by patient questioning.

The fact that the new hypersensitivity reaction to cobalt was noted in the TKA group with coated implant indicates that factors other than the implant (surgical instruments, environmental conditions) might also have an impact. Even

the sensitisation of a previously insensitive patient by patch testing is possible [14, 20]. None of these patients with a doubtful or positive patch test had any skin reaction around the implant or had relevant problems with the operated knee, which is consistent with the results of Frigerio et al. [7] and emphasises the questionable relationship between epicutaneous skin test and deep tissue hypersensitivity reaction.

The lymphocyte stimulation test (LST) has been described as more reliable in diagnosing a systemic metal hypersensitivity but is currently not applicable to large-scale testing due to costs and availability [12, 20]. Patients assessed by the LST before total joint arthroplasty demonstrated up to 30 % positive results for implant materials [7, 20]. However, the results of the LST did not comply with the results of the patch test [7] and the relevance of a positive LST on outcome is a subject of debate in the literature. While Niki et al. [20] observed that 15 % (4 of 26) of their patients with a positive LST before TKA developed eczema around the implant for more than 1 year post-operatively, Frigerio et al. [7] did not find any cutaneous signs after TKA or THA. Therefore despite its disadvantages epicutaneous patch testing currently remains the standard method to detect metal hypersensitivities [11].

Plasma metal ion concentrations did not change during the first year after insertion of a coated or uncoated TKA implant. This is in contrast to a cross-sectional study 5–7 years after insertion of a CoCrMo alloy TKA implant in which elevated cobalt and chromium concentrations were measured with the same methods as in our study [19]. The process of ion release in TKA is different to MoM bearings in THA. An increase of metal ion concentrations in the first few months after implantation and decrease thereafter, the so-called running-in phenomenon [30] which is a major source of metal ion release in MoM bearings, does not seem to play a role in TKA with a metal-on-polyethylene bearing. However, the surface area as a source of metal ion release by corrosion seems to be relevant as higher metal ion levels have been observed in megaprotheses with a large metallic surface area [6]. It may therefore take more time and longer follow-up to measure a difference, which has been demonstrated in vitro [22] and in vivo [19].

Limitations of this study include the exclusion of patients with a history of metal hypersensitivity and the short follow-up. According to guidelines and local standard of care, patients with a history of metal hypersensitivity receive a coated implant and could therefore not be randomised. While the short follow-up may be relevant for plasma metal ion levels it is not for hypersensitivity reactions. This time is sufficient for the development of a sensitisation to implant material and reduces the influence of environmental conditions.

In conclusion, we observed no problems with the novel coating during short-term follow-up. Rates of previously

unknown hypersensitivities to implant materials were low and sensitisation after TKA was rare. Even with sensitisation to implant materials no skin reactions were noted. TKA with coated implant and standard TKA demonstrated no plasma metal ion elevation. Longer follow-up will be needed to further assess clinical results and metal ion levels.

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Conflict of interest The authors declare that some of them have received speakers honoraria from different companies including the sponsor of this study.

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