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Preclinical Evaluation of Coated Knee Implants for Allergic Patients

Background and Problem

For patients with a metal allergy, a knee implant's coating should not only reduce the allergy risk by minimising ion release, but must also fulfil other requirements. Therefore, it should not have any harmful side effects (e. g. higher wear) and adhere to the implant in such a way as to prevent it from flaking off during service. In a preclinical setting, we tested a new ceramic coating system against these requirements.

Over the last decades, total knee replacement (TKR) has become a well-established surgical procedure with good clinical and long-term radiological results [2, 16, 18]. In general, the implant materials are highly biocompatible. [19, 26, 27]. Complications are caused not only by infections or biomechanical dysfunctions, but also by allergic reactions [19, 26, 27, 29]. They are associated with wound healing disorders, pain, swelling, urticaria, eczema, fistula, impaired bone healing and even aseptic loosening [8,10, 13, 24, 26, 27, 33].

Implant allergies are mostly triggered by metals such as nickel, cobalt, or chromium, but also in rare cases by components of the bone cement [8, 10, 23, 25, 28, 29]. Compared with the skin allergies [7, 22], they seem to be rare [4, 5, 21], but large epidemiological studies are still lacking [27]. In a review of several articles from the 1970's to the 1990's on "metal sensitivity", Hallab et al. [10] reported a prevalence of 10% in the general population. Among patients with well functioning implants, they found an average rate of 25% (3%-43%) and, among patients with poorly functioning implants, a higher rate of 60% (13% - 71%). Here, they measured "metal sensitivity" by different in vitro lymphocyte stimulation assays and in vivo allergy tests. Using patch tests, a study on a general population in South Germany found the contact allergy rates to be in average 13% for nickel, 2% for cobalt and ca. 1% for chrome [22]. But it is still unknown under which conditions a metal allergy will cause periprosthetic hypersensitivity [27,29].

To reduce ion release in the periprosthetic tissue, CoCrMo or titanium alloy femoral and tibial components with a PVD (physical vapour deposition) coating consisting of titanium nitride or of titanium niobium nitride (surface cover; [1, 11, 31]), are increasingly being implanted in patients with a metal allergy. These ceramic coatings exhibit a high degree of hardness and excellent wear resistance, but in rare cases, they may flake off the softer base material [17, 30]. To further reduce the risk of fatigue due to a large difference in hardness and residual stress gradients, a new approach consists of applying a multilayer PVD coating system to the CoCrMo implants that has a smaller difference in hardness at each layer interface and also lower tensile stresses in the layer.

The preclinical tests presented here investigated the potential failure mechanisms of this new coating system, such as insufficient bond strength, wear behaviour in articulation with polyethylene, layer fatigue through the third-body effect and inadequate barrier function against ion release, in comparison with uncoated CoCrMo implants.

Material and Method

To reduce ion release from knee implants made out of a $CoCr_{29}Mo_6$ alloy, a new coating system has been developed consisting of a thin adhesive chromium layer, five alternating intermediate layers out of chromium nitride, (CrN-)/ chromium carbonitride (-CrCN) and a final zirconium nitride (ZrN) shielding layer (**Fig. 1**).

The 7-layer , 3.5 to 5 µm thick, coating system is applied to the CoCrMo knee implants using the physical vapour deposition (PVD) method. The gradiently applied CrN-CrCN layers bridge the differences in hardness and residual stress between the softer base material, CoCrMo, and

Abstract

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Preclinical evaluation of coated knee implants for allergic patients

Abstract

Background. 10–15% of the population show allergic reactions against skin contact to metals as nickel, cobalt or chromium and have thus a risk of not tolerating implants containing those materials. The relationship between periimplantary hypersensivity reaction and given cutaneous contact allergy is currently unknown. A new developed multilayer coating system is supposed to prevent long-term allergic reactions that may result from uncoated implants.

Methods. Stability and function (concerning bonding durability, wear and ion release to the serum) of the multilayer coating system has been examined in a test series.

Results. The specific architecture of the multilayer coating system evidences a very good bonding durability. The results of the test in the simulator show a reduction of wear of approximately 60% compared to the uncoated implants. Ion concentrations within the serum of the wear tests were by magnitudes lower than those measured in reference tests on uncoated components.

Conclusion. The results of the preclinical evaluation prove that the durability and function of the multilayer coating system are as intended.

Keywords

Knee arthroplasty · Implant for allergic patients · Metal ion hypersensitivity · Ceramic coating · Ion concentration

Präklinische Ergebnisse beschichteter Knieimplantate für Allergiker

Zusammenfassung

Hintergrund. Etwa 10–15% der Bevölkerung weisen eine Metallkontaktallergie gegenüber Nickel, Kobalt oder Chrom auf mit dem potentiellen Risiko einer Unverträglichkeit entsprechender Implantatmaterialien. Bislang ist unbekannt, welche Konstellationen eine periimplantäre Überempfindlichkeitsreaktion bei bestehender kutaner Allergie auslösen. Ein neu entwickeltes mehrlagiges Schichtsystem soll langfristig allergische Reaktionen verhindern, die bei unbeschichteten Implantaten auftreten können.

Methoden. In einer präklinischen Versuchsreihe (Schichthaftung, Verschleiß, Ionenabgabe ins Serum) wurde die Beschichtung auf ihre Stabilität und ihre Funktionalität hin überprüft.

Ergebnisse. Der spezifische 7-lagige Aufbau des Beschichtungssystems gewährleistet eine sehr gute Haftfestigkeit. Im Verschleißsimulator wurde eine Reduktion des Abriebs gegenüber dem unbeschichteten Implantat um ca. 60% gemessen. Die Ionenkonzentrationen im Serum des Verschleißversuchs lagen um Größenordnungen unter den Referenzwerten der unbeschichteten Komponenten.

Schlussfolgerung. In der präklinischen Testung konnte die Stabilität und Funktionalität des Schichtsystems nachgewiesen werden.

Schlüsselwörter

Knieendoprothetik · Allergikerimplantat · Metallionenhypersensitivität · Keramische Beschichtung · Ionenkonzentration

the very hard shielding layer, ZrN, and thus ensure the system's mechanical integrity. The interfaces between the layers constitute an additional diffusion barrier against ions from the base material. Highly biocompatible, the final ceramic ZrN layer seals the system.

The VDI-3198 indentation test was conducted to evaluate the coating's bond strength. In analogy to a hardness test, a Rockwell C (HRC) test was performed to determine the bond strength of the layers on the CoCrMo implants and qualitatively assess the likelihood of a failure. A diamond cone with an apex angle of 120° was used as an indenter. To eliminate surface effects, it was applied with a preliminary load of 10 N. Then, it penetrated into the layer system with a maximum load of 1471 N. Deviating from the standard method, the interface between the layer surface and the conical penetrating crater was not examined for flaking or cracking by 100x magnified light microscopy, but with a scanning electron microscope (SEM) with a magnification of 25x.

To determine the abrasive properties, a wear simulation was conducted in vitro in accordance with ISO 14243-1:2002 (E), directly comparing the coated and the uncoated knee implants. As prescribed by this protocol, level walking was simulated with a flexion of 0-58° on a servo-hydraulic 4-station simulator (Endolab GmbH, Thansau/Rosenheim). In the stance phase of the gait cycle, a maximal axial load of 2600 N was exerted with a flexion of 15° distally with a medial offset of 7 %. To emulate the design-specific tibiofemoral kinematics, the tests were conducted with an A/P load of +110 N (anterior) and -265 N (posterior) and with an I/E rotation of +6 Nm (internal) and -1 Nm (external). To simulate the surrounding tendon and tissue structures, a system of springs arranged in pairs with a stiffness of 30 N/mm in the A/P motion and with 0.6 Nm/° in the I/E rotation pulled in the opposite direction.

For the implant configuration of the Columbus© CR Knee System (Aesculap AG, Tuttlingen), 4 uncoated (samples U_0-U_3) and 4 coated (samples C_0-C_3) knee prostheses were mounted on the simulator with epoxin resin. They were tested over 5 million cycles with a frequency of 1 Hz. To avoid errors in the gravimetric wear

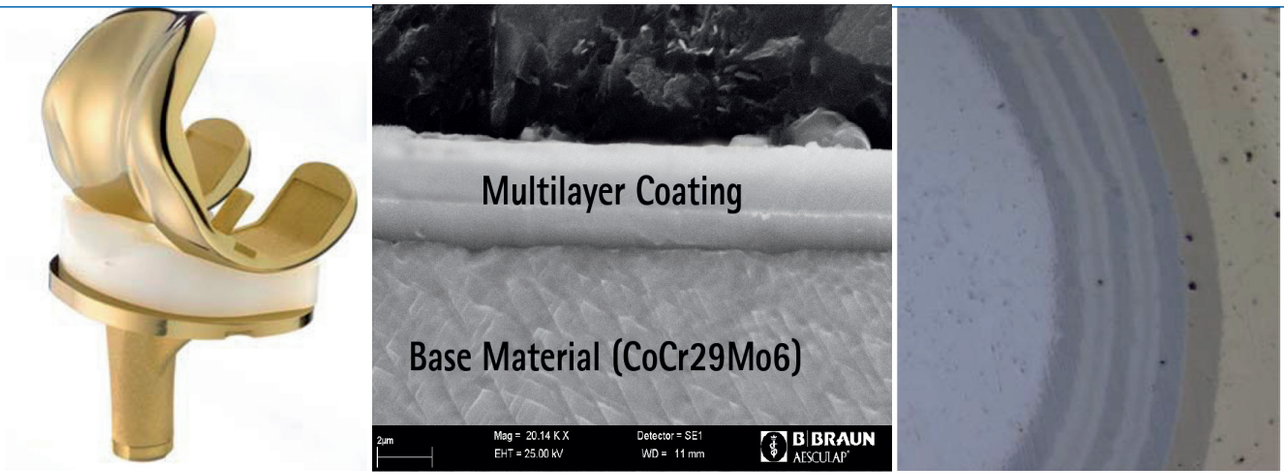

Fig. 1 ▲ Zirconium nitride coated knee implants (**left**) and structure of the multilayer coating system in an image from a scanning electron microscope (**middle**) and part of a dome-shaped section (**right**) in which the individual layers can be seen **Implant material ($CoCr_{29}Mo_6$)**

measurement due to absorption of the synovial fluid replacement, the gliding surfaces were soaked in a serum-based medium (state of saturation). To approximately simulate the lubricant environment after artificial joint replacement, a test medium was used, consisting of calf serum and deionized water with a defined protein content of 30 g/l. The medium was maintained at 37°, pH-stabilized by EDTA and replaced at intervals of 0.5 million cycles. At each measurement interval (0.5, 1, 2, 3, 4, 5 million cycles), the wear amount was measured gravimetrically once the gliding surfaces were cleaned using a standardized procedure [ISO 14243-2:2002 (E)].

After completion of the ISO test (5 million cycles), to create extreme test conditions, the chambers of the samples were massively contaminated with cortical bone splinters and bone cement particles (Palacos^R, Heraeus Medical, Wehrheim) (**Fig. 2**) and submitted to additional 500,000 cycles. In particular, the hard ceramic particles of the X-ray contrast medium contained in the cement (zirconium dioxide) can lead in vivo to deep scratches on the polished CoCrMo surfaces of knee implants and hip cups [3, 12].

To measure the metal ion concentration in the serum, test medium was collected at each measurement interval. The individual samples from the simulator stations U_1-U_3 (uncoated) and C_1-C_3 (coated) were poured together to form the serum samples $IC_{U1\text{-}3}$ and $IC_{C1\text{-}3}$. Using inductively coupled plasma atom emission spectrometry (ICPAES), the ion concentrations of

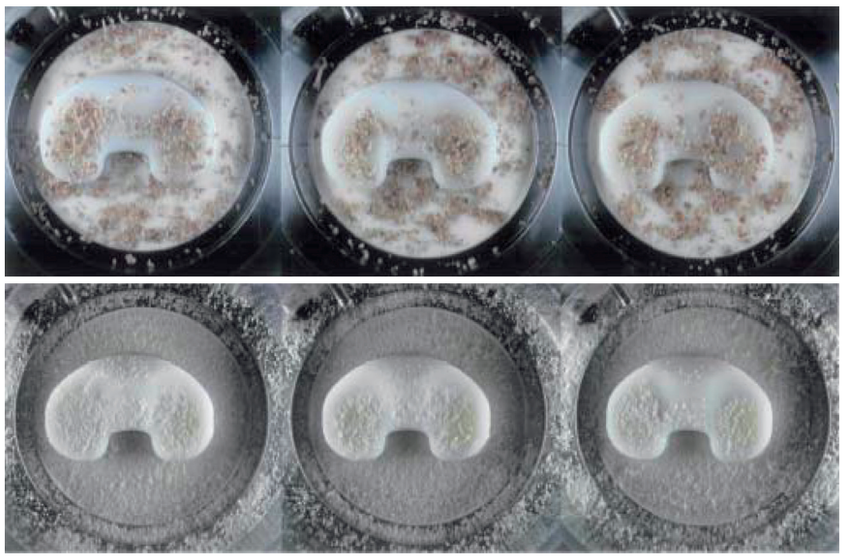

Fig. 2 ▲ Sample chamber heavily contaminated with cortical bone (**above**) and bone cement (**below**) to simulate wear on the multilayer system under extreme wear conditions

molybdenum (Mo), nickel (Ni), cobalt (Co) and chromium (Σ Cr^{III}+Cr^{VI}) were measured in the serum samples $IC_{U1\text{-}3}$ and $IC_{C1\text{-}3}$ in accordance with ISO 11885, with a detection limit of 1 µg/l (1 ppb). Taken from the stations U_0 and C_0, the serum analyses of the only axially loaded reference samples, without relative motion of the tibio-femoral articulation (IC_{U0}, IC_{C0}), serve as a comparison basis.

Results

In the indentation test, the qualitative evaluation of the bonding strength did not reveal any flaking or cracking at the interface between the surface layer and the conical penetrating crater (**Fig. 3**). Thus, the multilayer coating system exhibits an excellent bond strength on the implant components out of a CoCrMo alloy.

The wear test according to ISO 14243–1:2002(E) yielded an average wear rate of 8.8 ±2.85 mg/million cycles for the polyethylene gliding surfaces in articulation with uncoated femoral and tibial components (U_1-U_3). In contrast, with 3.5 ±0.18 mg/million cycles (**Fig. 4**), the ZrN coating on the knee implants (C_1-C_3) achieved a significant wear reduction. In particular, the slight variations in the coated knee prostheses is a clear indication of

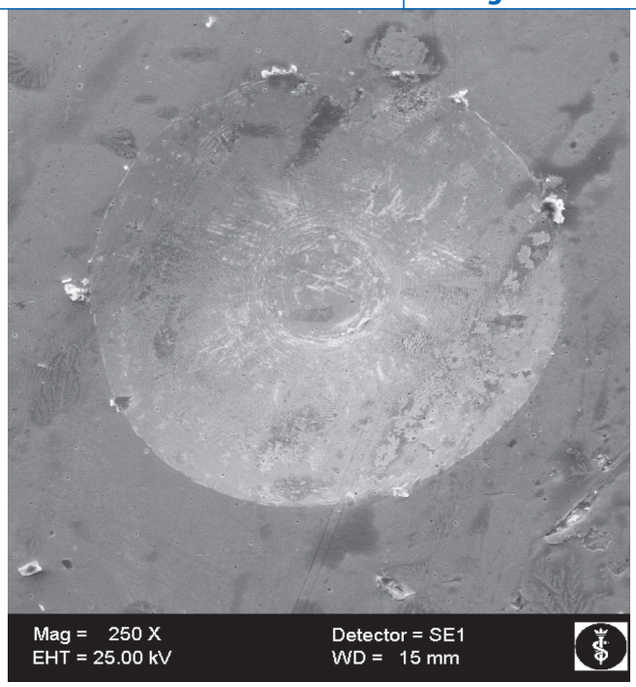

Fig. 3 ◀ Indentation by test indenter with 250x magnification. On the rim of the crater, no flakes or cracks can be seen; a proof of excellent bond strength. The isolated white particles are simply dust particles that could not be eliminated completely.

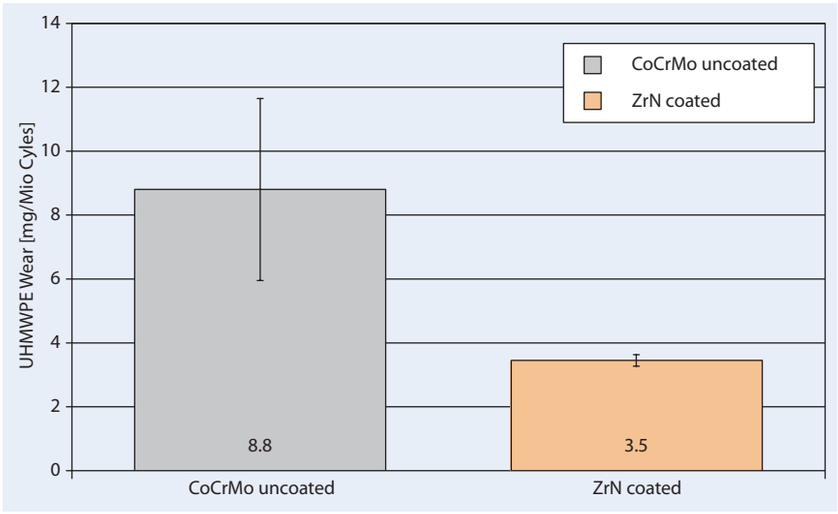

Fig. 4 ▲ Wear rate of the polyethylene gliding surfaces of the uncoated (U_1-U_3) and the coated (C_1-C_3) knee systems according to ISO 14243-1:2002 (E)

the high surface quality and high resistance against scratches of this coating. In both groups, the polyethylene gliding surfaces exhibit generally comparable wear patterns consisting of polished areas with slight scratches, faded and uneven surfaces, and corrugated spots. After 5 million cycles, the surfaces of the ZrN coated femoral components were not significantly altered from their original condition. The light brightening observed on the articulating condylar areas simply indicates more polishing of the ZrN coating (**Fig. 5**).

The optical analysis of the ZrN coated femoral components reveals a comparable layer structure in the areas outside of the articulation with the UHMWPE (region A) and of the articulating condylar surfaces (regions B, C and D). Adding cortical bone splinters (5.0–5.5 million cycles) and bone cement particles (5.5–6.0 million cycles) did not lead to any visible scratches or layer breakages (**Fig. 6**).

These results highlight the high mechanical integrity of the multilayer coating system even under extremely severe tribological test conditions.

In the serum of the coated implants, the concentrations of nickel and molybdenum ions remained in the range of the detection limit (1 µg/l, or 1 ppb), but were 20 and 10 times higher, respectively, in the uncoated components out of $CoCr_{29}Mo_6$ (**Fig. 7**).

In the ZrN coated knee implants (samples B_1-B_3), the serum concentrations of cobalt and chrome ions (Σ Cr^{III}+Cr^{VI}) were slightly beyond the detection limit whereas, in the uncoated implants, these concentrations were almost two orders of magnitude higher. The ion concentrations in the serum of the ZrN coated reference sample loaded only axially were practically on the same level as in the serums of the ZrN coated knee components. These results confirm that, even under extreme wear stress, the multilayer coating system constitutes a secure barrier against diffusion of metal ions out of the CoCrMo base material.

Discussion

For patients with suspected periprosthetic metal ion hypersensitivity, a new ceramic multilayer coating system has been developed for knee implants with the purpose of minimizing the release of nickel, cobalt, molybdenum and chromium ions in the periprosthetic surrounding tissue. The basic idea was to combine the advantages of the conventional metal knee implants out of CoCrMo, such as fracture toughness, with the advantages of ceramics, such as high hardness, scratch resistance and good wettability. Shielded by a last, highly biocompatible, ceramic inert ZrN layer, this multilayer coating system prevents allergic reactions by providing a barrier in each layer against diffusion of metal ions out of the base material.

In a preclinical test, the present study investigated the potential failure mechanisms of this new coating system, such as insufficient bond strength, wear behaviour in articulation with polyethylene, layer fatigue through the third-body effect and inadequate barrier function against ion release, in comparison with uncoated implants out of CoCrMo.

A VDI-3198 indentation test was conducted to determine the coating's bond strength. It confirmed the excellent bond strength with results of class HF_1, the highest. This excellent bond strength is clearly revealed in the images of the scanning

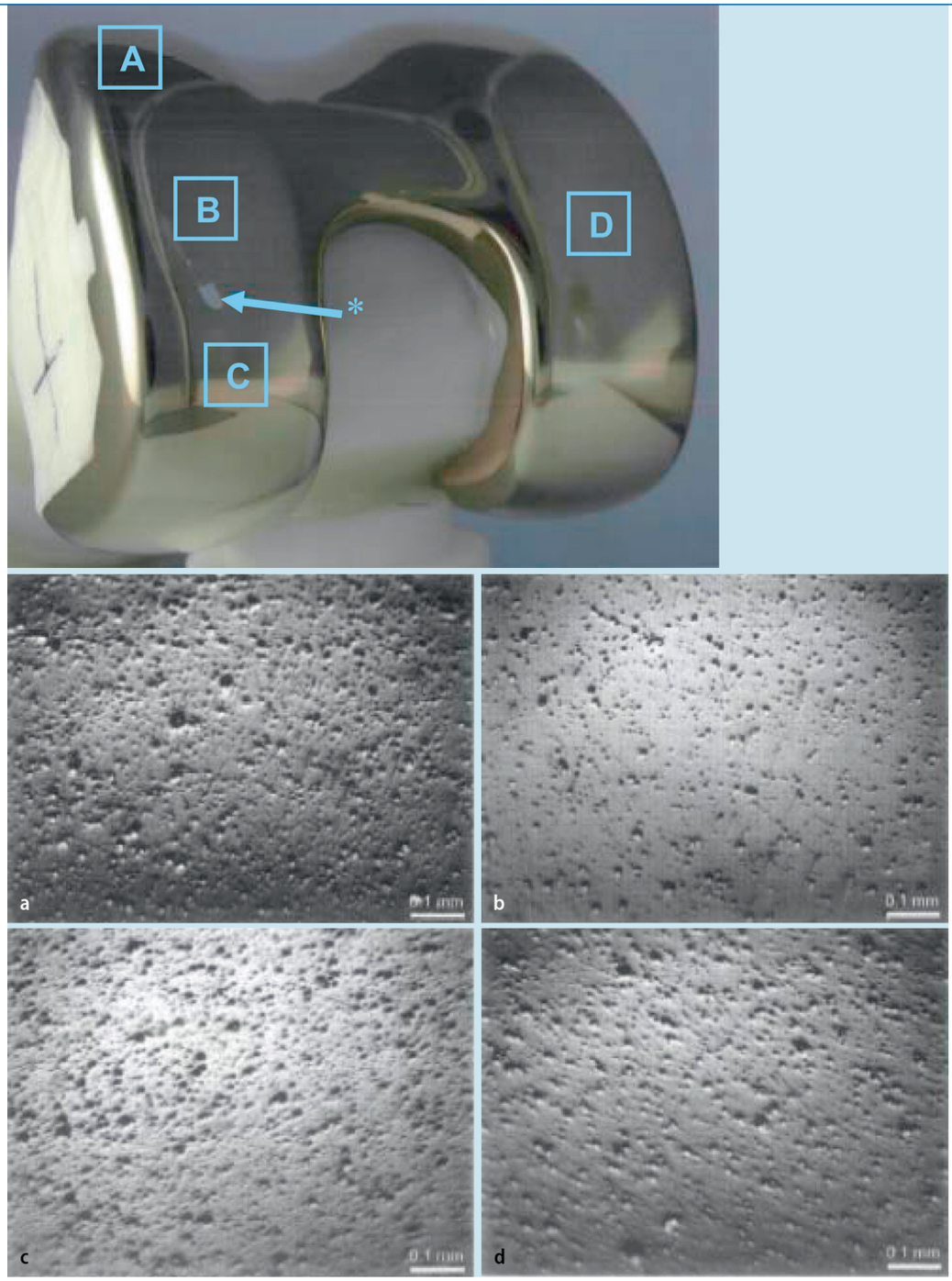

Fig. 5 ▶ Surface analysis of the ZrN coated femoral components (C2) with the microscope after 5 million cycles in 4 different condylar areas (A B, C, D). * The white spot is caused by the lighting used to obtain the image

electron microscope at the interface of the crater created by the diamond cone in the indentation test which is completely free of flaking or cracking. This means that, in vivo also, a failure of the coating system is not to be expected on the long-term. Thus, the risk of flaking associated with conventional monolayer coating [17, 30] due to initial damage (e. g. during the implantation) or to long-term fatigue of the thin and very hard covering layer (shell of a boiled egg) is practically excluded with this multilayer coating system.

The evaluation of the abrasive properties yielded an average wear rate of 8.8±2.85 mg/million cycles for the polyethylene gliding surfaces of the uncoated implants, but a rate of 3.5±0.18 mg/million cycles for those of the coated implants. These results match those of comparable wear tests on different knee implants reported in the literature. For conventional polyethylene, an average of 15.4 (3.1–38.3) mg/million cycles was reported and of 8.2 (2.8–12.1) mg/million cycles for highly crosslinked polyethylene [9]. The multilayer ZrN coated knee implants have been found to reduce wear by approximately 60 % compared to CoCrMo. This wear reduction also distinguishes the ZrN coated knee implants from "allergy solutions" made out of titanium or titanium alloy with very high wear rates [14, 15].

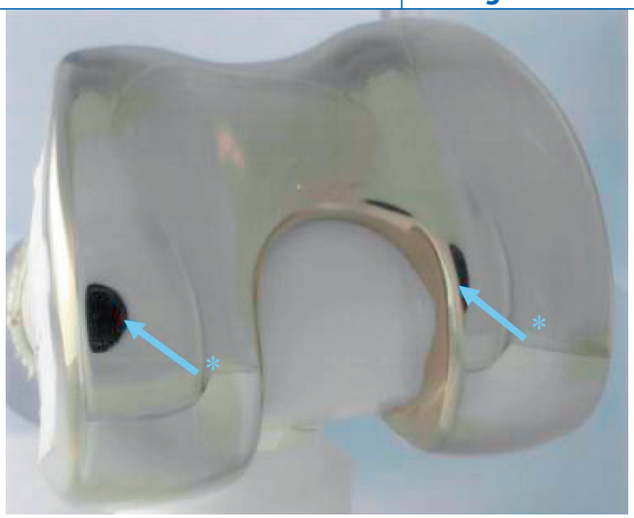

Fig. 6 ◀ Surface analysis of the ZrN coated femoral components (C3) with the microscope after adding cortical bone splinters and bone cement particles (6 million cycles). * The black spots are caused by the lighting used to obtain the image

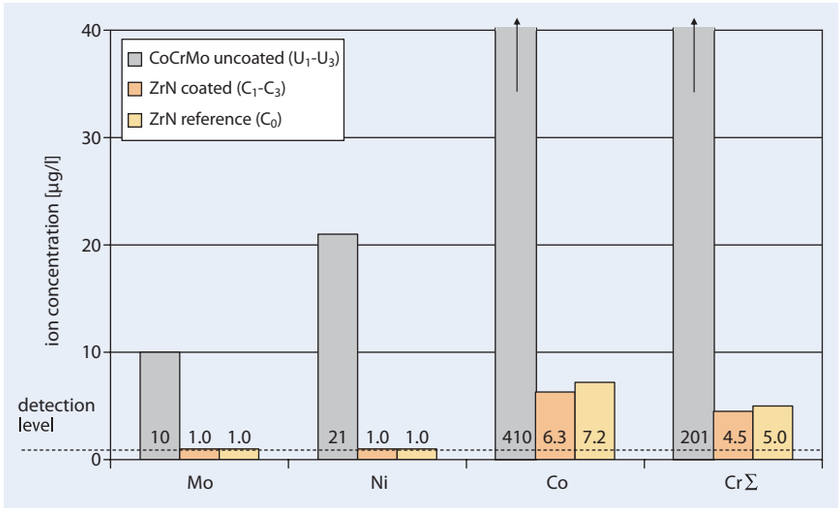

Fig. 7 ▲ Molybdenum, nickel, cobalt and chromium ion concentrations in the uncoated (U1-U3) and coated (C1-C3) knee systems at the end of the running-in phase of the wear simulation (1 million cycles). The concentrations in the axially loaded sample serve as reference

For forged implants made out of a zirconium niobium alloy with a ceramic surface (ZrO_2) created by oxidation, White et al. [32] demonstrated, compared to the same implants made out of CoCrMo, a clearly lower polyethylene wear rate which they attribute to better wettability (reduction of adhesion) and higher hardness (higher resistance against scratches) of the ceramic surface. In a more recent study using a wear simulator, these results were confirmed by Ezzet et al. [6] who found a wear reduction of 42% of the ZrO_2 implants compared to the CoCrMo.

Under more severe wear conditions, Ries et al. [20] tested the wear properties of CoCrMo and ZrO_2 implants in direct comparison. They found that the higher resistance of the ZrO_2 implants against roughening or scratching by hard particles clearly increases the benefit of reduced polyethylene wear.

In the present tests of the ZrN coated knee implants, even after adding cortical bone splinters and bone cement particles, no damage of any kind (scratches, flakes, etc.) was seen on the condylar surfaces. This highlights the excellent wear resistance and durability of this multilayer coating system.

In the serum of the wear tests, the nickel and molybdenum ion release from the ZrN coated implants is reduced so much that traces of these elements appear only in the range of the detection limit. Minimal amounts of cobalt and chromium were found in the serum, but orders of magnitudes smaller than those from the uncoated implants out of CoCrMo. Here, it cannot be excluded that these minimal amounts could be due to contamination in the serum caused by the metal containers used in the production, storage or handling of the serum. The fact that approximately the same cobalt and chrome concentration was found in the serum of the unloaded reference sample B_0 (◘ **Fig. 7**) seems to confirm this hypothesis. If this is the case, the ZrN coated articulated implants would not have release any additional cobalt or chromium ions.

The absolute ion concentration which can trigger a periprosthetic hypersensitivity against metal ions has not yet been clearly determined. Presumably, it can be very different from one patient to another. Thus, the purpose of the new multilayer coating system was to minimize the release of possibly allergy-inducing ions to the detection limit, the only way to reduce to an absolute minimum the risk of an allergy reaction against ZrN coated implants.

The results of the tests performed show that the multilayer coating system presented here completely fulfils, in a preclinical setting, the requirements in terms of bond strength, wear reduction on the polyethylene gliding surfaces, continuous resistance to abrasive damage and ion barrier function. It remains for clinical studies to show whether these good preclinical results can also be confirmed in clinical practice on a long-term basis.

Summary for the Practice

For patients with the risk of a metal allergy-induced hypersensitivity to a knee prosthesis made out of CoCrMo, it would seem appropriate to use a special "implant for allergic patients". First-generation problems, such as higher wear rates of the titanium alloys implants and fatigue damage to the ceramic monolayer, have been overcome by this new multilayer coating system.
A series of preclinical tests have demonstrated its high fatigue resistance, favourable wear behaviour and ion barrier effect. Now, its long-term clinical effectiveness must be studied.

Conflict of interest. Some authors are members of research and development of the company Aesculap AG. Despite the possible conflict of interest the contribution is independent and product neutral.

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Literature

1. Bader R, Bergschmidt P, Fritsche A et al (2008) Alternative Werkstoffe und Lösungen in der Knieendoprothetik für Patienten mit Metallallergie. Orthopade 37:136–142
2. Buechel FF (2004) Mobile-bearing knee arthroplasty. Rotation is our salvation. J Arthroplasty 19:27–30
3. Caravia L, Dowson D, Fisher J, Jobbins B (1990) The influence of bone and bone cement debris on counterface roughness in sliding wear tests of ultrahigh molecular weight polyethylene on stainless steel. Proc Inst Mech Eng 204(1):65–70
4. Carlsson A, Möller H (1989) Implantation of orthopaedic devices in patients with metal sensitivity. Acta Derm Venereol 69:62–66
5. Duchna HW, Nowack U, Merget R et al (1998) Prospektive Untersuchung zur Bedeutung der Kontaktsensibilisierung durch Metallimplantate. Zentralbl Chir 123:1271–1276
6. Ezzet KA, Hermida JC, Colwell CW Jr, D'Lima DD (2004) Oxidized zirconium femoral components reduce polyethylene wear in a knee wear simulator. Clin Orthop Relat Res 428:120–124
7. Goh CL (1985) Prevalence of contact allergy by sex, race and age. Contact Derm 14:237–240
8. Granchi D, Cenni E, Tigani D et al (2008) Sensitivity to implant materials in patients with total knee arthroplasties. Biomaterials 29:1494–1500
9. Grupp TM, Stulberg D, Kaddick C et al (2009) Fixed bearing knee congruency – influence on contact mechanics, abrasive wear and kinematics. Int J Artif Organs 32:213–223
10. Hallab N, Merrit K, Jacobs JJ (2001) Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg Am 83:428–436
11. Hendry JA, Pilliar RM (2001) The fretting corrosion resistance of PVD surface-modified orthopaedic implant alloys. J Biomed Mater Res 58:156–166
12. Isaac GH, Wroblewski BM, Atkinson JR, Dowson D (1992) A tribological study of retrieved hip prostheses. Clin Orthop Relat Res 276:115–125
13. Kubba R, Taylor JS, Marks KE (1981) Cutaneous complications of orthopaedic implants. Arch Dermatol 117:554–560
14. Peterson CD, Hillberry BM, Heck DA (1988) Component wear of total knee prosthesis using Ti-6Al-4 V, titanium nitride coated Ti6Al4V and cobalt-chromium-molybdenum femoral components. J Bone Miner Res 22:887–903
15. Plitz W (2000) Knieendoprothetik – Werkstoffauswahl und -anforderungen. Orthopade 29:727–731
16. Pradhan NR, Gambhir A, Porter ML (2006) Survivorship analysis of 3234 primary knee arthroplasties implanted over a 26-year period. A study of eight different implant designs. Knee 13:7–11
17. Raimondi MT, Pietrabissa R (2000) The in-vivo wear performance of prosthetic femoral heads with titanium nitride coating. Biomaterials 21:907–913
18. Ranawat CS, Flynn WF, Saddler S et al (1993) Long-term results of the total condylar knee arthroplasty. A 15-year survivorship study. Clin Orthop Relat Res 286:94–102
19. Rau C, Thomas P, Thomsen M (2008) Metallallergie bei Patienten vor bzw. nach endoprothetischem Gelenkersatz. Orthopäde 37:102–110
20. Ries MD, Salehi A, Widding K, Hunter G (2002) Polyethylene wear performance of oxidized zirconium and cobalt-chromium knee components under abrasive conditions. J Bone Joint Surg Am 84(Suppl 2):129–135
21. Rooker GD, Wilkinson JD (1980) Metal sensitivity in patients undergoing hip replacement. A prospective study. J Bone Joint Surg Br 62:502–505
22. Schäfer T, Böhler E, Ruhdorfer S et al (2001) Epidemiology of contact allergy in adults. Allergy 56:1192–1196
23. Schuh A, Thomas P, Reinhold R et al (2006) Allergie auf Knochenzementbestandteile nach Knieendoprothesenimplantation. Zentralbl Chir 131:429–431
24. Schuh A, Thomas P, Kachler W et al (2005) Das Allergiepotenzial von Implantatwerkstoffen auf Titanbasis. Orthopade 34:327–333
25. Summer B, Fink U, Zeller R et al (2007) Patch test reactivity to a cobalt-chromium-molybdenum alloy and stainless steel in metal-allergic patients in correlation to the metal ion release. Contact Dermatitis 57:35–39
26. Thomas P (2003) Allergien durch Implantatwerkstoffe. Orthopade 32:60–64
27. Thomas P, Schuh A, Ring J, Thomsen M (2008) Orthopädisch-chirurgische Implantate und Allergien. Orthopade 37:75–88
28. Thomas P, Schuh A, Eben R, Thomsen M (2008) Allergie auf Knochenzementbestandteile. Orthopade 37:117–120
29. Thomas P, Thomsen M (2008) Allergiediagnostik bei Metallimplantatunverträglichkeit. Orthopade 37:131–135
30. Thull R (2003) Oberflächenmodifikationen zur Verbesserung von Biokompatibilität und mechanischen Eigenschaften von orthopädischen Implantaten. Orthopade 32:51–59
31. Thull R, Handke KD, Karle EJ (1995) Tierexperimentelle Prüfung von Titan mit Oberflächenbeschichtungen aus (Ti,Nb)ON und (Ti,Zr)O. Biomed Tech 40:289–295
32. White SE, Whiteside LA, McCarthy DS et al (1994) Simulated knee wear with cobalt chromium and oxidized zirconium knee femoral components. Clin Orthop Relat Res 309:176–184
33. Willert HG, Buchhorn GH, Fayyazi A et al (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. J Bone Joint Surg Am 87:28–36