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Cobalt deposition in mineralized bone tissue after metal-on-metal hip resurfacing: Quantitative μ-X-ray-fluorescence analysis of implant material incorporation in periprosthetic tissue

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Abstract: Most resurfacing systems are manufactured from cobalt-chromium alloys with metal-on-metal (MoM) bearing couples. Because the quantity of particulate metal and corrosion products which can be released into the periprosthetic milieu is greater in MoM bearings than in metal-on-polyethylene (MoP) bearings, it is hypothesized that the quantity and distribution of debris released by the MoM components induce a compositional change in the periprosthetic bone. To determine the validity of this claim, nondestructive μ-X-ray fluorescence analysis was carried out on undecalcified histological samples from 13 femoral heads which had undergone surface replacement. These samples were extracted from the patients after gradient time points due to required revision surgery. Samples from nonintervened femoral heads as well as from a MoP resurfaced implant served as controls. Light microscopy and μ-X-ray fluorescence analyses revealed that cobalt debris was found not only in the soft tissue around the prosthesis and the bone marrow, but also in the mineralized bone tissue. Mineralized bone exposed to surface replacements showed significant increases in cobalt concentrations in comparison with control specimens without an implant. A maximum cobalt concentration in mineralized hard tissue of up to 380 ppm was detected as early as 2 years after implantation. Values of this magnitude are not found in implants with a MoP surface bearing until a lifetime of more than 20 years. This study demonstrates that hip resurfacing implants with MoM bearings present a potential long-term health risk due to rapid cobalt ion accumulation in periprosthetic hard tissue. © 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 00B: 000–000, 2016.

Key Words: microanalysis, micro-X-ray fluorescence, metal alloys, orthopedic pathology, hip implants

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INTRODUCTION

Formation, transport, and accumulation of metallic wear particles are associated with hip joint arthroplasty.[1,2] Increased concentrations of circulating metal degradation products derived from orthopedic implants may have deleterious biological effects over the long term that warrant investigation.[1–3] This is of particular concern due to current clinical trends, including the reintroduction of metal-on-metal bearing surfaces and the increasing popularity of extensively porous-coated devices with a large surface area of exposed metal. An increasing number of investigations reveal that the implantation of hip resurfacing systems with a metal-on-metal (MoM) bearing may enhance formation of heavy metal cobalt (Co) and chromium (Cr) particles, resulting in higher Co and Cr metal ion concentration in the periprosthetic tissue and blood compared with standard hip arthroplasty.[4,5]

Since the decline in their popularity in the 1990s, hip resurfacing implants are again being increasingly used in hip replacement surgery. In 2005 in Australia, for instance, this implant type accounted for almost 14% of primary joint replacement operations in male patients.[6] Revision rates higher than 8.5% are reported for the first 3 years after implantation in the group older than 75 years.[6] The reason for this is seen in the complicated surgical technique (choice of size, reaming of the femoral head, positioning, and cementing technique), but there is also some discussion about the selection of patients and the high implantation forces involved.[7–9]

In contrast to previous models, modern resurfacing implant systems all have a metal-on-metal surface bearing

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and a central pilot pin. According to the manufacturers, the quality of the surface and the congruency between the femoral and acetabular components has been enhanced due to improvements in production technology. Cobalt-chromium-alloy components (ASTM F 75 CoCr Alloy: ~63% Co, 27–30% Cr, 5–7% Mo, <0.5% Ni, <1% Mn, <0.75% Fe, <0.35 C) are used for the acetabular cups and femoral head caps. With resurfacing implant diameters of >50 mm, the bearing surfaces of implants have a large area. Besides the large diameters of the femoral caps,[4,5] positioning errors during implantation may lead to eccentric load-bearing, which has a negative effect on tribological behavior.[10,11] As a result, increased amounts of particles are released into the surrounding tissue and this elevated level of cobalt and chromium can be detected in serum.

Although there is less bone resection with a changed biomechanical loading at the femoral site compared with a standard hip replacement and the majority of patients that have received metal-on-metal based hip resurfacing appear to be in good health, a number of questions remain regarding the long-term effects of exposure to the articulation material. Dark field microscopy and particle-induced X-ray emission (PIXE) have revealed metal particles over large areas in the soft tissue and cobalt deposits locally in the mineralized bone tissue surrounding total joint implants.[1] A correlation between cobalt concentration, time since implantation, and distance from the implant has been observed in cases with metal-on-polyethylene (MoP) bearings.[1]

The potential risks of ion production (cobalt and chromium) therefore need to be clearly documented in clinical literature. There is a theoretical concern that metal ions may also pose a cancer risk.[12–16] A patient who has kidney disease may have difficulty filtering these ions from the blood.[17,18] Hip resurfacing is not recommended for women planning a pregnancy. Therefore women are advised to bear children before surgery because metal ions cross the placenta, which also shows a modulatory effect on the rate of metal ion transfer.[19] Hypersensitivity to metal ions is a risk that is being increasingly recognized, and therefore patients with a history of metal allergies should not undergo this procedure.[20–24] In view of these findings, patients undergoing bilateral hip resurfacing arthroplasty may need to be monitored more closely than patients receiving unilateral devices, since there is a greater risk of ion level toxicity.

It is frequently observed during explantation of resurfacing implants that the surrounding tissue takes on a grayish-black color due to the metal debris, but little is known about the quantity and distribution of the metallic particles in the tissue. It is also unclear if this deposition of hip resurfacing MoM alloy elements in the periprosthetic bone is related to the time since implantation and if the components of the implant material are primarily accumulated in the soft tissue or also in the mineralized hard tissue. To investigate this issue, quantitative elemental analysis was performed on samples of periprosthetic bone tissue taken from resurfacing prostheses, which had been explanted after different times since implantation. The investigations were carried out nondestructively by means of micro-X-ray fluorescence with high spatial resolution and high sensitivity for trace elements. This method enabled a selective measurement in both the mineralized bone tissue and the soft bone marrow tissue.

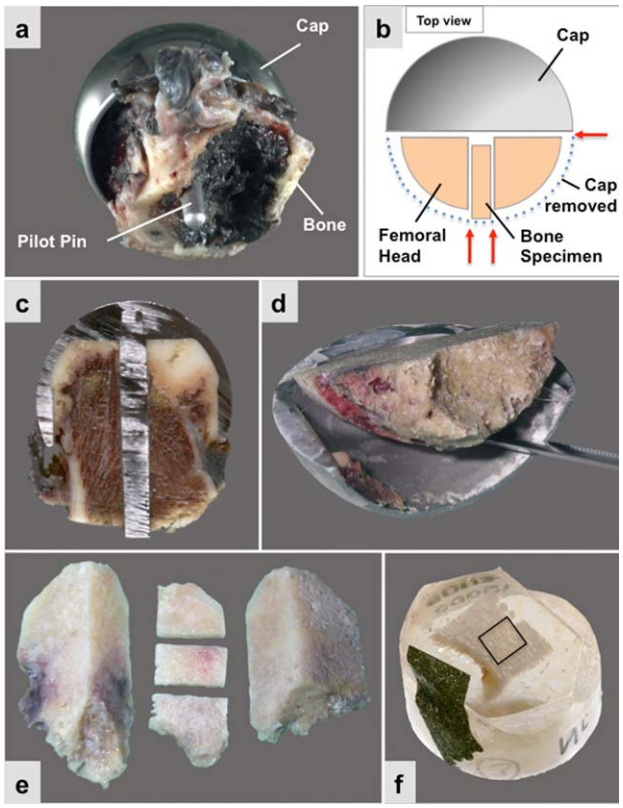

FIGURE 1. a) An explanted resurfacing prosthesis with gray-colored periprosthetic tissue due to an accumulation of wear particles and metallosis. b) The preparation of the implant is based on a defined scheme. The figure shows the schematic saw cut (red arrows) in the plan view. After separation of the hip resurfacing implant using a diamond band saw (c), the femoral head component is removed from one half of the implant (d) and then a 4 mm thick slice is resected from the femoral head half. This slice is then further split into two to three individual samples (e). The bone samples are embedded in plastic and prepared for histological sections. Afterwards, the sample block is ground to a co-planar geometry suitable for the μ-X-ray fluorescence elemental analysis in the scanning electron microscopy (SEM) (f). The microanalyses are performed in the defined regions of interest (box).

MATERIALS AND METHODS

Thirteen femoral heads with surface replacements that had been explanted during revision surgery were chosen for the investigation. In all cases, the revision was performed due to fracture of the femoral neck. The femoral implants were retrieved together with the remains of the femoral heads [Figure 1(a)] and fixed in formalin (3.5%, buffered).

The resurfacing prostheses consisted of four different models made of cobalt-chromium alloy (ASR, DePuy Orthopedics, Warsaw, Ind, USA; Cormet, Corin Group, Cirencester, UK; Durom, Zimmer, Winterthur, Switzerland; BHR, Smith & Nephew-MMT, Birmingham, UK). The femoral components of all the systems had been implanted with bone cement. No differentiation was made between the four models, as

TABLE I. Characteristics of Cases

	Group 1 ($n = 4$)	Group 2 ($n = 6$)	Group 3 ($n = 3$)	Controls ($n = 3$)	Implant ($n = 1$)
Implantation period	1356 d (±363)	452 d (±98)	21 d (±12)	–	23 d
Age	56.2 yr	54.8 yr	56.0 yr	52 yr	62 yr
Cap size	48 mm (±2.8)	50 mm (±4.1)	52 mm (±4.1)	–	42 mm
Tribological pairing	MoM[a]	MoM[a]	MoM[a]	–	MoP[b]

[a] Metal on metal.
[b] Metal on polyethylene.

the differences in design were not considered relevant for the study. Furthermore, as Davda et al. (2011) found, there are no differences in the concentration of metal ions in joint fluid obtained after implantation of different hip resurfacing implants.[25]

The resurfacing implants were retrieved from four women and nine men. The cohort was divided into three groups: group 1 ($n = 4$) had a mean time since implantation of 1356 (±363) days, group 2 ($n = 6$) of 452 (±98) days, and group 3 ($n = 3$) of 21 (±12) days (Table I). The mean age of the patients in each group was almost identical with 56.2 years in group 1, 54.8 years in group 2, and 56 years in group 3. The mean size of the resurfacing implant was 48 (±3) mm in group 1, 50 (±4) mm in group 2, and 52 (±4) mm in group 3 (Table I). Three femoral heads, which had been resected due to total hip arthroplasty (THA) served as controls. None of these prepared control heads had been in contact with an implant, therefore contamination of the tissue by preparation was excluded and verified by microanalysis. Additionally, a further resurfacing implant of the former generation (Interplanta/Link, Hamburg, Germany) with a time to failure of 23 years was also included in the study. This hip resurfacing model, which was used in the 1970s and 1980s, was also fixed with bone cement, but had a metal-on-polyethylene (MoP) surface bearing instead of metal-on-metal (MoM). The diameter of femoral implant was 42 mm. It was explanted because of pain symptoms of unknown origin.

All samples were prepared according to the method described in previous studies.[10,26,27] In the first step, all the hip resurfacing implants, together with the remains of the femoral heads inside, were cut in the anterior–posterior direction with a diamond band saw and the metal components removed for further preparation. The femoral head halves with the resurfacing implants were placed in acetone for 24 h to dissolve the bone cement slightly, as this has been found to facilitate removal of the metallic parts [Figure 1(b–d)]. The bone cement, however, remained on the femoral head. Then from one of the two halves, a slice of bone, 4 mm thick, was resected at an angle of 90° to the plane of the first cut and, depending on the size of the femoral head, divided into two to three sections [Figure 1(e)]. After degreasing and dehydration by means of a series of ascending ethanol concentrations, the undecalcified bone samples were embedded in polymethyl-methacrylate (PMMA) [Figure 1(f)].[28] Prior to the preparation of histological sections, a layer of about 0.5 mm thickness was taken off the sample with a rotation microtome equipped with a wolfram blade (microTec, Techno-Med GmbH, Munich, Germany) in order to remove any possible contamination of the sample surface from cutting implant material with the diamond-coated band saw (EXAKT, Norderstedt, Germany). For histological assessment, sections of 4 μm thickness were cut using the microtome and stained using standard staining techniques (von Kossa, Goldner trichrome, Toluidine blue). The stained sections were analyzed by bright and dark field microscopy[1] (Axioplan II, Zeiss, Germany).

After preparation of the sections, the residual PMMA blocks with the embedded bone specimen were further processed for examination in the scanning electron microscope (LEO VP 435, Leica Instruments Ltd, Cambridge, England) [Figure 1(f)]. The surfaces were ground co-planar and then sputtered with carbon (Bal-TEC/Leica, Balzers, Liechtenstein). Deposition of abrasive wear from the tribological pairing in the bone tissue was determined by micro-X-ray fluorescence elemental analysis. The fluorescence spectra were excited using a rhodium tube micro-spot X-ray source (iMOX, IFG, Berlin, Germany)[29,30] mounted to the scanning electron microscope. The focal diameter (FWHM) of the X-ray source was approximately 80 μm. The spectra were measured with an energy dispersive X-ray spectrometer (EDAX, Ametek, Germany) equipped with a Si(Li) detector. Within a defined region of interest 3 mm away from the resurfacing implant interface at least three measurements were carried out in the mineralized bone tissue and three in the soft tissue of each sample. These values were then averaged [Figure 1(f)]. Each sample's elemental distribution spectrum was taken at a tube voltage of 35 kV, 500 μA, and an acquisition time (live time) of 1000 s.

Quantification in X-ray fluorescence analysis is usually performed by measuring spectra of reference materials under identical conditions to get calibration curves (intensity versus concentration) for the elements of interest. No reference materials were available for the embedded specimens in this investigation, therefore spectra of bone tissue embedded in carbon (simulating PMMA) with increasing metal content were calculated to achieve calibration curves [Figure 2(a,b)]. The theoretical model takes into account both the characteristic and the scattered X-radiation. In order to check the assumed bone tissue to PMMA ratio, both intensity and shape of the spectral background were compared for calculated and measured spectra because the background is mainly determined by X-ray scattering at elements with low atomic number.[31] Cobalt and chromium concentrations in the mineralized bone tissue were determined on the basis of these calibration curves [Figure

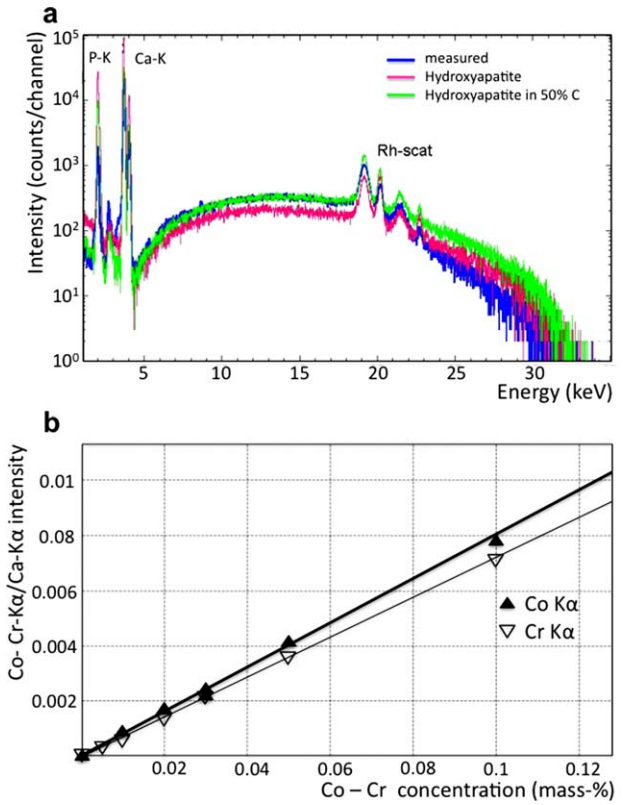

FIGURE 2. a) Calculated bone spectra for hydroxyapatite pure (pink) and embedded (green) in comparison with a measured spectrum of a specimen 553 days after implantation (blue). b) Calculated Co-K/Ca-K and Cr-K/Ca-K intensity ratios *versus* Co and Cr content in bone tissue. These calibration curves were used for quantitative X-ray fluorescence analysis.

2(a,b)]. The calculations also considered the spectrometer noise and showed that for 1000 s live time the detection limit of this approach is in the range of 100 ppm. Due to the inhomogeneous consistency of the bone marrow tissue, it was not possible to obtain a reproducible quantitative evaluation of the concentration of implant material in the soft tissue using this method.

Statistical Analysis

The type-I error probability was set at 5% ($\alpha = 0.05$). The standard deviation ($\pm$) was used throughout to describe the spread around mean values. A *t*-test was applied to describe differences of data for each group.

RESULTS

In the soft tissue, compact cement masses could be seen in the mantle and in the interdigitating extensions between the trabeculae of the remains of the femoral heads of all groups [Figure 3(a)]. Different degrees of infiltration by macrophages with ingested cement particles were also observed in Groups 1 and 2 [Figure 3(b)]. The accumulated wear particles in the soft tissue, which can be easily identified when switching from bright field to dark field illumination [Figure 3(c)], were not evenly distributed in the tissue. There were tissue areas with abundant quantities of particles immediately next to areas with very few particles. With elemental microanalysis, it was possible to show zirconium as a component of bone cement (zirconium dioxide, X-ray contrast medium) and the alloy component elements of the metal implant, cobalt and chromium, in the soft tissue areas [Figure 3(d)]. Both heavy metals—primarily Co—were also detected in the mineralized bone tissue and quantified as described in the previous section (Figure 4). The highest cobalt values in mineralized bone were found in group 2 with an average of approximately 300 ppm ($\pm$68.7 ppm). Group 1 had an average of 250 ppm ($\pm$30.97 ppm), group 3 had 230 ppm ($\pm$11.78 ppm), and the control samples with no implant were found to have a mean cobalt value of 136 ppm ($\pm$37.78 ppm) inside the trabeculae. The slight differences between the three implant groups were not significant. However, all three implant groups differed significantly ($p < 0.05$) from the control group. The mean cobalt concentration in the mineralized bone tissue of the resurfacing implant with a metal-on-polyethylene surface bearing, removed after 23 years, was 260 ppm ($\pm$181 ppm).

In contrast to the cobalt levels, the chromium concentration in the mineralized bone tissue of all analyzed groups with implants showed no significant differences to the control group. The chromium level ranged between 139 and 148 ppm (Figure 4).

DISCUSSION

Release of metal debris/ions into surrounding tissue remains a problem in orthopaedics. Generally, nondestructive quantitative detection of particulate metal products in tissue can only be performed using complex technology. The particles are very small and unevenly distributed in the tissue. In some individual cases, however, metal debris is already macroscopically visible only a short time after implantation in the form of dark coloring of the tissue surrounding the implant; under the microscope, accumulations of macrophages with incorporated metallic particles can be seen in this tissue (Figure 3).

In a retrospective evaluation in Sweden of >100,000 patients who had received a joint implant, there were no signs that the tumor rate had risen in comparison with the entire population over an observation period of 30 years.[32] It remains to be seen if the recent increased use of resurfacing implants with metal-on-metal surface bearings will affect the evaluation results published in 2001 by Signorello et al.[32] Smith et al. (2012) carried out a 7-year follow-up analysis of >40,000 patients with MoM hip replacement in comparison with nearly 250,000 with alternative bearings and found no increased risk of cancer.[33] In contrast, Visuri et al. (2010) showed that patients with MoM THA had higher cancer mortality than those with MoP THA during the first 20 years postoperatively, but not thereafter. Because some cancers have a long latency period, the examination of the influence of implant bearings on cancer risk is difficult.[34]

In vitro studies show that in patients who have received joint implants with metal-on-metal surface bearings there is

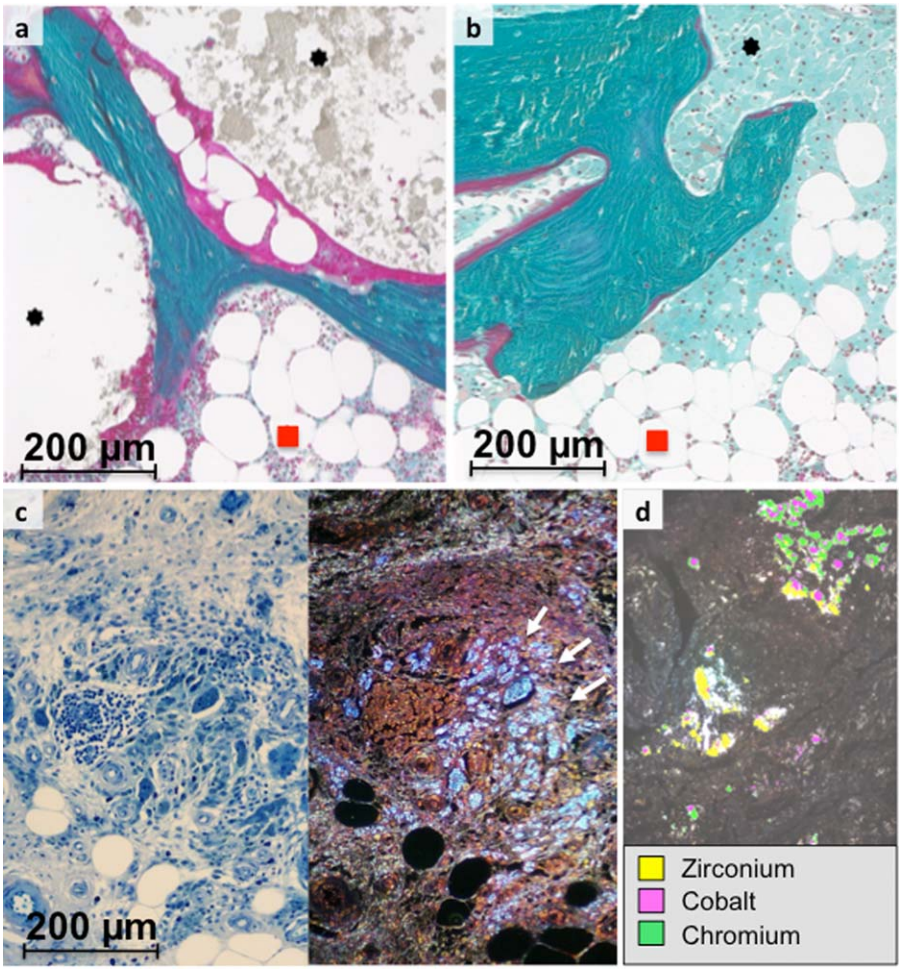

FIGURE 3. a) In the femoral head region of all groups, cement interdigitation (black asterisk) can be seen in the direct vicinity of trabeculae (green-blue) and hematopoietic bone marrow (red square). There are no signs of macrophage infiltration or a fibrous interface membrane. The viable bone trabecula does not show any remodeling activity (embedding in methyl-methacrylate, Goldner trichrome staining, magnification: 100×). b) Towards the deeper femoral remnant tissue of Groups 1 and 2, dense macrophage infiltration with phagocytized foreign material (black asterisk) can be seen in the hematopoietic bone marrow (red square), focal reaching the trabecular surface. The fibrous interface membrane is absent. Interestingly, a focal osteoid (nonmineralized newly formed bone) seam with active osteoblasts is seen on the trabecular surface (embedding in methyl-methacrylate, Goldner trichrome staining, magnification: 100×). c) In contrast to bright field illumination (left) to dark field illumination (right), even small non-birefringent wear particles in the soft tissue are visible as bright points (arrows). The large majority of the visible particles are of bone cement components, but metallic particles are also present (Toluidine blue staining, magnification: 100×). d) Periprosthetic soft tissues in dark-field illumination and superimposed elemental mapping revealing foreign material contamination of the tissue.

a marked initial phase during which particle release is elevated.[35,36] Although alloy elements can generally be detected in the serum and urine of patients, this initial phase observed *in vitro* is not detectable in serum during the first weeks after implantation.[5,35] The cobalt and chromium concentrations in serum increase slowly after implantation and then reach a relatively constant level. However, in their investigation of explanted surface replacement implants, Sieber et al. detected an increase in wear debris in the first year after implantation.[37]

The deposition of cobalt in mineralized bone tissue observed in previous studies on THA without MoM bearings[1] was confirmed in this study of resurfacing prostheses with MoM bearings by using a micro-X-ray fluorescence (µXRF) source. In comparison with electron excitation that offers a high spatial resolution, micro-XRF offers a higher sensitivity to trace elements due to improved peak-to-background ratio and higher excitation efficiency for heavy elements (higher Z number). Although the rhodium tube used for the measurements is suitable for a wider range of samples, the excitation of Co is less effective in comparison with a copper tube. However, the method of creating a calibration curve for the µXRF measurements is an exceptional feature of the current investigation. For the energy range of 2 keV to 20 keV, there is very good conformity both in the characteristic lines and the background between the calculated and the measured spectra [Figure 2(a,b)]. The detection limit achieved in this X-ray fluorescence analysis lies at about 100 ppm and is thus lower than a proton induced X-ray emission (PIXE) analysis (about 20 ppm) which was

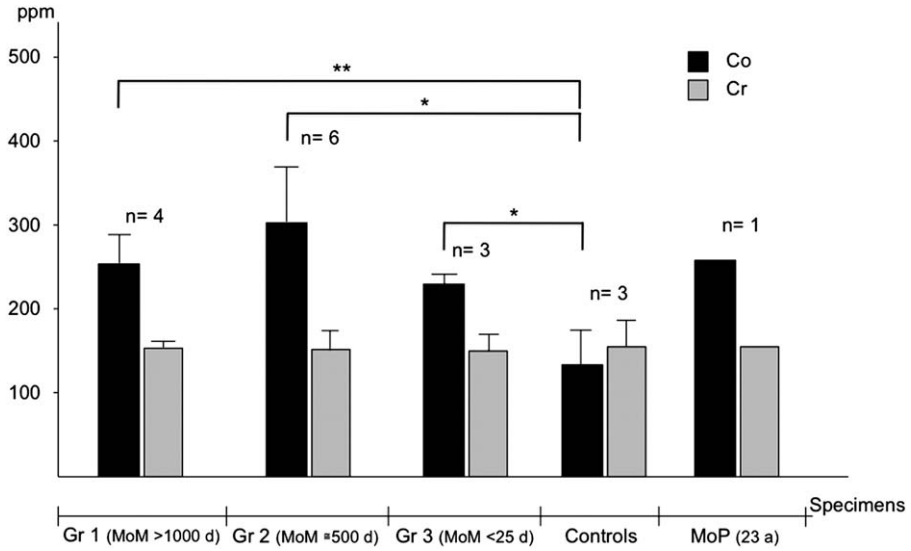

FIGURE 4. Co and Cr concentrations in mineralized bone. The cobalt values in the three implant groups differ significantly from those of the control group. In contrast, the chromium values are similar in all groups. The Co and Cr concentrations at the surface replacement of the former generation (Implanta) with a metal-on-polyethylene tribological pairing are, after an implantation period of 23 years, of the same magnitude as the implants with current metal-on-metal surface bearings.

used in our previous investigations of MoP total hip replacement.[1] Nevertheless, one considerable advantage of the μXRF is that it requires less preparation in contrast to the complex nonroutine preparation techniques, which are necessary for the PIXE analysis. However, this study has limitations: (a) even if the use of the μXRF reduced the amount of preparation in comparison to earlier measurements, nondestructive element analysis remains a time-intensive procedure due to the necessity to scan large regions of interest limiting the sample size for this type of method. Despite this, the chosen method of test execution and use of the calculated calibration curves revealed significant differences between the mineralized bone tissue in the implant groups and that in the control group. (b) Although the contamination in the soft tissue is significantly higher than in the mineralized bone tissue, it was not possible to calculate a definite calibration curve for this region of interest. Reference elements such as calcium and phosphorus, which are associated with mineralized bone tissue, are absent in soft tissue. Thus, the alloy elements could be only qualitatively detected in the soft tissue with the chosen method. (c) Further limitations of our study lie in the detection limit and the X-ray diameter. Although the spatial resolution of the technique chosen for this study was adequate for selective analysis of mineralized bone tissue, it was unfortunately not sufficient to determine the extent of cobalt deposition, specifically in mineralization fronts or individual osteocytes.[38] A sensitive elemental analysis with high spatial resolution (<5 μm) would be a suitable basis in order to find out more about the mechanism of cobalt deposition in mineralized bone tissue.

Cobalt is an essential trace element and a component of vitamin B12. The required dosage is given as 0.1 to 0.2 μg per day, whereas Biego et al. reported a daily intake of approximately 29 μg in France.[39] If larger doses, e.g. in the milligram range, are taken with nutrition, this may lead to organ damage and cancer as shown in animal experiments.[40] High values of up to 380 ppm were already detected in the mineralized bone tissue of the surface replacements in this study after only a few years of implantation. Comparably high values were found in THRs with metal-on-polyethylene bearing surfaces after 21 years since implantation.[1] Even the cobalt values in the mineralized bone tissue of the metal-on-polyethylene resurfacing implants did not reach this level until after 23 years post implantation, within our defined measurement area.

The broader spread of cobalt values in group 2 is due to two individual cases with remarkably high values. The high cobalt values of these two cases are possibly the consequence of malpositioning of the implant components, increasing the load on the rim, as described by Morlock et al.[10] In contrast to the cobalt values, the measurements obtained from the chromium analysis showed no difference between the three implant groups and the control specimens. The measured values are only slightly above the limit of detection of the technique used. Therefore, it is not clear if this method is sensitive enough for chromium detection above the background or if chromium is deposited in the bone matrix at all. However, the absence of significant chromium concentrations indicates that chromium is not deposited in the mineralized bone matrix like cobalt. Newton et al. found that Co is distributed equally between blood cells and plasma, whereas Cr is predominantly present in the plasma.[41] The different distribution of Co and Cr in blood also contributes to the half-life of the elements in the body. In the case Co and Cr ions are bound to proteins such as albumin or transferrin they may not be filtered by the kidney.[41] The differences in physiological handling of Co and Cr may affect the distribution in soft and hard tissue as well as the rate of renal excretion. However, Willert et al.

and Haynes et al.[42,43] have shown in their study that during corrosion of cobalt-based implants predominantly the alloy component Co is released which is also reflected by elevated concentration of Co in joint fluids.[44] But a literature review by Jantzen et al. has shown that there is no evidence for higher Co levels in blood and serum in comparison to the evaluated Cr concentrations.[45] It is therefore possible that the nonlinear discrepancy between metal ion concentrations in serum/blood and joint fluids plays a role in the accumulation of cobalt in soft and mineralized hard tissue.

The alloy element cobalt is incorporated into the bone matrix within a surprisingly short time. Cobalt values which were elevated in comparison with the control samples were measured in mineralized bone a short period after implantation of the prosthesis. Studies by other working groups have also revealed that a rise in the cobalt and chromium values in the serum of patients with surface replacements can be detected a few weeks after implantation.[5,35]

Although there has been much discussion about the possible biological effects of tissue contamination by the alloy elements in joint prostheses such as immune modulation, hypersensitivity, infection, chromosomal damage, and carcinogenesis,[34,46–48] the actual long-term consequences of the deposition of heavy metals are still difficult to assess. In view of these findings, further analyses should be carried out on surface replacement implants with periods since implantation of 5, 10, and more years. Such analyses would show if the rate of cobalt deposition in mineralized bone tissue rises only during the first years after implantation—as shown in this study—and then, as in urine or serum values, reaches a level which remains relatively constant as described by Daniel et al.[49]

CONCLUSIONS

Our investigations confirm that there is a tendency for cobalt deposition in mineralized bone tissue after arthroplasty with cobalt-alloy implants. Only a few weeks after surgery, surface replacement with metal-on-metal bearing leads to measurable quantities of metal alloy elements in periprosthetic tissue. Furthermore, after a 2-year implantation period, the cobalt concentration in mineralized bone tissue already reaches a level similar to that found in the tissue of patients who have had a metal-on-polyethylene implant for >20 years. The accumulation of heavy metal and potential hypersensitivity should be taken into account when the implantation of metal-on-metal hip replacements is planned.

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