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ORIGINAL STUDY

Differences in metal ion release following cobalt-chromium and oxidized zirconium total knee arthroplasty.

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Ions are released from all metals after implantation in the body through processes of corrosive and mechanical wear. The aim of this study was to investigate whether serum metal ion levels are raised in patients following total knee arthroplasty. Serum levels of chromium, cobalt, aluminium, molybdenum and zirconium were measured in two groups of patients at a minimum of 3 years after knee arthroplasty. Twenty three patients had a cobalt-chromium femoral component and 14 patients had an oxidized zirconium femoral component, acting as a control group as this femoral component is free from cobalt and chromium. All patients had the same titanium tibial base plates, and no patellae were resurfaced. Despite the lack of cobalt and chromium in the prostheses used in the control group, no statistically significant differences in serum cobalt and chromium ion levels were found between the groups. On the basis of these results there does not appear to be any significant rise in serum metal ion levels following total knee arthroplasty several years after implantation.

Keywords : knee arthroplasty ; oxidized zirconium ; cobalt-chromium ; metal ions.

INTRODUCTION

All metal implanted into the body will corrode to some extent over time (*11*). Tribocorrosion is a material degradation process resulting from simultaneous mechanical (wear) and chemical or electrochemical (corrosion) material removal mechanisms, and for metal implants it results in the release of metal ions. Arthroplasty components normally rely on a stable passive film, formed spontaneously in air, for their biocompatibility. This film protects the metal from corrosion but repetitive motion of the joint could lead to damage or removal of this protective layer, causing increased corrosion rates (*38*). Over recent years, the increasing use of metal-on-metal (MOM) bearing surfaces in hip arthroplasty has led to further research into the potential adverse effects of the metal ions produced, especially cobalt (Co) and chromium (Cr) ions. The recognised biological responses can either be local – for example, aseptic

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lymphocytic vasculitis associated lesions (ALVAL), osteolysis – or systemic, such as carcinogenesis and chromosomal aberrations (*4,10,17,23,26,36*).

Total knee arthroplasty (TKA) has been successfully carried out for many years and since 1999 over 164,000 TKAs have been performed in Australia alone (*2*) with about 30,000 having been performed in 2007. Despite the large numbers of TKAs that have been performed worldwide, little has been published in the literature on metal ion exposure resulting from TKA. Nevertheless the few studies undertaken thus far have demonstrated evidence of elevated levels of metal ions following TKA (*13,15, 16,21,29*). It has even been suggested that Co and Cr ion levels following TKA may be as high as those following the use of MOM bearings in total hip arthroplasty (THA) (*16*), despite the lack of direct mechanical metal on metal wear in TKA.

The present study utilises a control group of patients undergoing TKA with an oxidized zirconium (OxZr) femoral component containing zirconium and niobium with no cobalt or chromium, to investigate the relationship of metal ion levels in patients following TKA due to tribocorrosion.

PATIENTS AND METHODS

The present study was performed as a retrospective sub-study within a larger randomized clinical trial, and successfully underwent the local ethical review process. Between March 2003 and May 2006 all patients with osteoarthritis (OA) undergoing primary TKA in our institution were enrolled in a randomized, prospective trial (RCT) comparing the clinical outcomes of the cobalt-chromium (CoCr) and the oxidized zirconium (Oxinium™, OxZr) Profix cruciate substituting femoral components (Smith&Nephew Richards Inc., Memphis, Tennessee, USA). A total of 88 subjects were recruited, 46 patients were implanted with a CoCr femoral component and 42 patients were implanted with an OxZr femoral component. All of the components were cemented, and no patellae were resurfaced. The same Profix fixed bearing titanium tibial base plate was used in both groups. Composition of this tibial base plate is aluminum 5.5% to 6.75%, vanadium 3.5 % to 4.5%, iron 0.3%, oxygen 0.2%, nitrogen 0.05%, carbon 0.08%, hydrogen 0.015%, the balance being titanium (ASTM F-1472). The CoCr Profix femoral component is manufactured of chromium 27.0% to 30.0%, molybdenum 5.0% to 7.0%, nickel 0.5%, iron 0.75%, carbon 0.35%, silicon 1%, manganese 1%, with the balance being cobalt (ASTM F-75). The OxZr component composition is 2.5% niobium and 97.5% zirconium.

All patients entered into the RCT described above were retrospectively assessed for their suitability for inclusion in this metal ion testing substudy. Exclusion criteria consisted of any other metallic implants (except contralateral TKA if the same femoral component was used), health supplements containing Cr or Co, and renal impairment. This resulted in the exclusion of 51 patients in total (58%) leaving 23 patients in the CoCr group and 14 in OxZr group. Demographics for the included patients are shown in table I. At the time of undertaking this study all of the TKAs performed were functioning well, and there was no clinical or radiological suspicion of any component loosening among included patients.

Table I. — Patient Demographics

	CoCr (n=23)	**OxZr (n=14)**	**p-value**
Number of Males (%)	12 (63%)	11 (61%)	0.898
Number Bilateral (%)	2 (9%)	5 (36%)	0.080
Height (cm) *	168.9 (157.0-182.0)	170.6 (149.0-189.0	0.571
Weight (kg) *	83.2 (58.0-114.0)	87.1 (52.0-110.0)	0.417
BMI (kg/m^2) *	29.2 (20.1-46.2)	29.8 (21.6-41.4)	0.694
Age (yrs) *	65.0 (54.1-75.6)	63.6 (52.9-76.2)	0.539
Age of Implant (yrs) *	5.5 (3.2-0.1)	4.5 (3.0 -6.0)	0.029

** Result expressed as mean (range)*

All blood samples were collected by the primary author (SG) using a standardized technique. Venepuncture was performed using a butterfly needle (Terumo, Tokyo, Japan, 21G × 9-cm tube, 0.2-mL tube volume) in the antecubital fossa. Ten milliliters (ml) of blood was extracted into a standard syringe (10 ml latex-free syringe ; BD, Franklin Lakes, NJ) to flush out the butterfly. Then 4.5 ml of blood was dripped into a trace element-certified natural polypropylene aliquot tube (Interpath, Sydney, Australia) without additives for serum measurement. Samples were kept cool for transport to the PaLMS laboratory, North Sydney, Australia, where the heparinized sample was analyzed within 48 hours. All ion levels were measured by the use of a quadrupole inductively coupled plasma mass spectrometer, Varian 820MS (Varian Inc, Mulgrave, Victoria, Australia). Helium and hydrogen are used as collision / reaction gases to minimise the formation of spectroscopic interferences.

Statistical analysis was performed using Intercooled Stata 9.2 for Windows (Statacorp, College Station, Texas, USA). Categorical data were analysed using the chi-squared test. Continuous data were analysed using repeated measures t-tests, with unequal variances where Levene's test for equality of variance was significant. Mann-Whitney U tests were performed to confirm inferences in the case of severely skewed dependent variables. Statistical significance was set at $p \leq 0.05$. Pre-hoc power analysis was performed and determined that a sample size of 15 subjects in each group would give power of 78% to detect a difference of one standard deviation in the mean ion levels between groups.

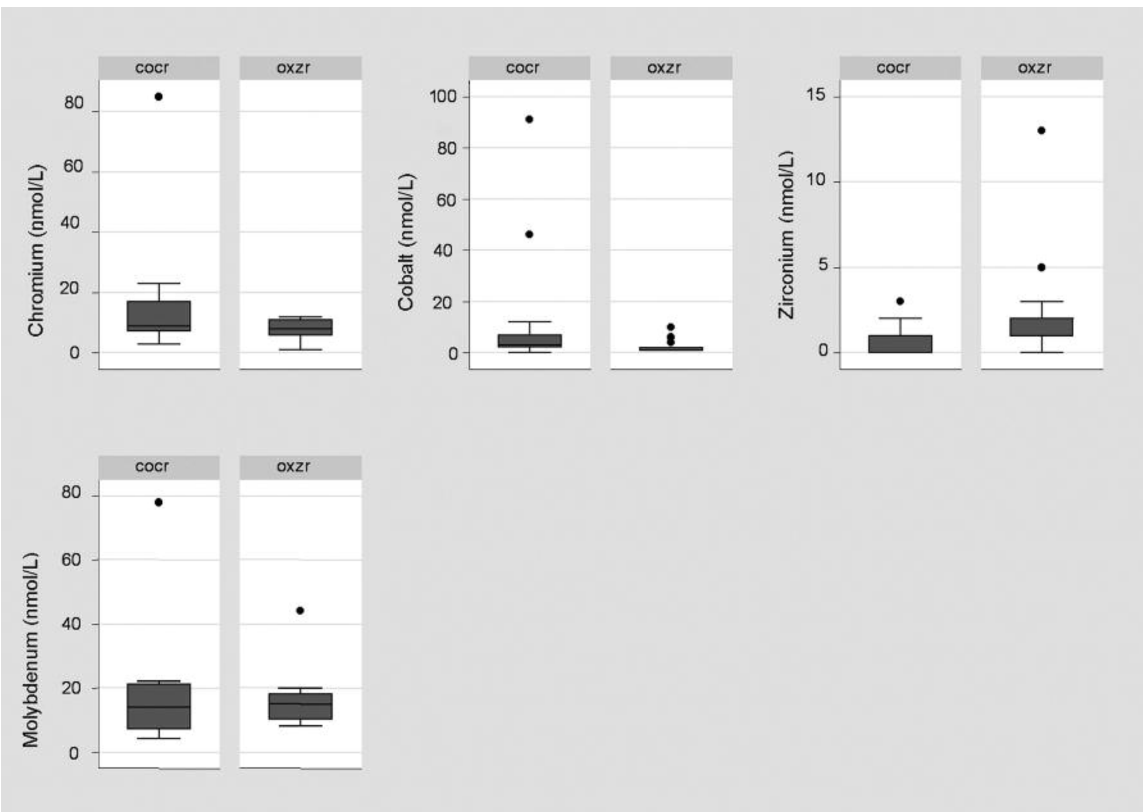

Fig. I. — Box plots of serum metal ion concentrations following TKA with either CoCr or OxZr femoral components. Plots show median, interquartile range and outliers.

RESULTS

As shown in table I, the CoCr and OxZr study groups were well matched with respect to age, gender mix and body size, although the mean implant age at time of metal ion analysis in the CoCr group was significantly higher than in the OxZr group (5.5 versus 4.5 years). Serum ion levels for both groups are provided in table II and represented graphically in figure I. There was a trend toward higher serum chromium and cobalt in the CoCr group, but this was not statistically significant (mean difference and 95% CI ; 6.07 (-3.03 to 15.17) nmol/L and 6.66 (-2.14 to 15.47) nmol/L respectively).

There was a higher proportion of subjects with bilateral knee arthroplasty in the OxZr group (not statistically significant), however subgroup analysis revealed no evidence of significantly higher ion levels among subjects with bilateral TKA in either group. Similarly, although the implants had been *in situ* for a longer period of time in the CoCr group, subgroup analysis demonstrated no significant correlation between implant age and ion levels in either group. Interestingly, serum aluminium levels were found to be significantly higher in the OxZr group (mean difference 0.03 μmol/L, 95% CI 0.00 to 0.06 μmol/L, p = 0.038, see table II).

DISCUSSION

All metal implants in the body will corrode over time, producing metal ions which can enter into the circulation (*11*). The metal ions are in the nanometer size range (*8*) which may explain their wide distri-

Table II. — Serum metal ion results following TKA with either CoCr or OxZr femoral component

Metal ion	CoCr (n=23)	OxZr (n=14)	Difference in mean (95% CI)	p-value
Chromium (nmol/L)				
mean (SD)	13.78 (16.40)	7.71 (3.95)	6.07 (-3.03 to 15.17)	0.184
median	9.00	8.0		
range	3.00 to 85.00	1.00 to 12.00		
Cobalt (nmol/L)			6.66 (-2.14 to 15.47)	
mean (SD)	9.30 (20.16)	2.64 (2.53)		
median	3.00	2.50		0.131
range	0.00 to 91.00	1.00 to 10.00		
Zirconium (nmol/L)				
mean (SD)	0.91 (0.95)	2.50 (3.27)	-1.59 (-3.51 to 0.33)	0.098
median	1.00	2.00		
range	0.00 to 3.00	0.00 to 13.00		
Molybdenum (nmol/L)				
mean (SD)	16.17 (14.62)	16.16 (8.92)	0.03 (-7.83 to 7.89)	0.994
median	14.00	8.90		
range	4.00 to 78.00	8.00 to 44.00		
Aluminium (umol/L)				
mean (SD)	0.08 (0.05)	0.11 (0.04)	-0.03 (-0.06 to -0.00)	0.038
median	0.07	0.12		
range	0.00 to 0.19	0.05 to 0.17		
Niobium (nmol/L)				
number +ve (%)	3 (13.0)	3 (21.4)		0.502

bution throughout the body (*32*). Unlike most organic chemicals, metals cannot be eliminated from tissues by metabolic degradation and must therefore be excreted through the kidney (*12*). Concern remains that in the long term these metal ions could cause damage to DNA and chromosomes and also induce genomic instability. Epidemiologic studies thus far, however, suggest there is little risk of a malignancy developing after implantation of metal prostheses. Tharani *et al* (*31*) in their 2001 meta-analysis found no causal link between TKA and cancer, but noted the available data were limited and further long-term studies are required. The 2003 meta-analysis by Visuri *et al* (*33*) showed cancer rates in patients with TKAs were in line with that of the general population. In another study, data from the Swedish Cancer Registry showed that patients who had a THR had rates of most types of cancer similar to those of the general population (*28*).

Published studies on the modern MOM hip bearings have regularly demonstrated higher serum Co and Cr levels when compared to preoperative values, control groups and patients with conventional metal on polyethylene (MOP) bearings (*3,5,6,18,27*). Serum Co and Cr levels have also been monitored prospectively following implantation of hip resurfacing prostheses (*3,7*), with peak levels seen at 6 and 9 months respectively, compared to the preoperative levels. These levels subsequently fall slightly but never return to pre-operative levels. Raised serum metal ion levels have also been demonstrated following the implantation of other orthopaedic devices such as spinal instrumentation, disc replacement and intramedullary nails (*14,24,39*).

Very little investigation has been carried out into metal ion exposure in well functioning TKA. Luetzner *et al* (*16*) studied metal ion levels in 41 patients with a cemented unconstrained TKA (18 unilateral and 23 bilateral), and compared these with those of a historic control group of 130 patients awaiting hip or knee arthroplasty reported in a previous study (*37*). A significant elevation in serum Co and Cr was demonstrated following the TKA and it was comparable to levels observed after MOM THA (*5,6,12,37*). They found no difference however, between unilateral and bilateral TKA. Other studies have reported the increase of serum metal ions in loose TKA or in knees with a failed patellar component (*15,30,34*).

Zirconium is a transitional metal element, which as a result of the oxidization process used to create Oxinium™ is transformed from a metallic to a ceramic material. Piconi and Maccauro (*25*) have carried out a thorough review of both *in vitro* and *in vivo* tests of the biocompatibility of zirconia ceramics, concluding that zirconia ceramics have no cytotoxic effect on fibroblasts and cause no genotoxicity, carcinogenicity or chromosomic aberration. The composition of Oxinium™ is 97.5% zirconium and 2.5% niobium, with absolutely no cobalt or chromium. Similarly the tibial base plates utilised in this study did not contain cobalt or chromium, and therefore the OxZr group forms an ideal control group of patients who have undergone arthroplasty surgery but without cobalt and chromium containing prostheses. The cobalt and chromium ion levels observed among the OxZr group are comparable with control values reported in other studies. We have summarized previously published control metal ion levels in Table III, and in order to make comparison between different published ion levels easier, we have converted results where necessary to express them in both µg/L and nmol/L.

We have demonstrated a trend for higher mean levels of serum Cr ions in the CoCr group compared to the OxZr group. However, these differences were not statistically significant and therefore in contrast to the results published by Luetzner *et al* (*16*). Among our results there was one outlier in the Cocr group, who had a serum Co of 5.36µg/L (91nmol/L) and a Cr of 4.42µg/L (85nmol/L), his knee was functioning well and renal function was normal.

As would be expected, there was a trend for higher serum levels of Zr among the OxZr group, but again this did not reach statistical significance compared with the CoCr group. We have however demonstrated significantly higher aluminium levels in the OxZr group compared with the CoCr and this remains difficult to explain given the use of the same tibial tray (5% aluminium) in both groups and no aluminium containing femoral prostheses.

Despite the extensive research that has been carried out on this subject, joint replacements contain-

Table III. — Published control group/pre-operative metal ion levels, µg/L (nmol/L)

Study	No. of patients	Serum Co µg/L (nmol/L)	Serum Cr µg/L (nmol/L)
Published Reference Values [22]	59	Mean 0.15 (2.55)	Mean 0.26 (5)
Witzleb [37]	130	Median 0.25 (4.24)	Median 0.25 (4.8)
Back [3]	16	Mean 0.33 (5.69) Range 0.12-0.53 (2-9)	Mean 0.32 (6) Range 0.16-0.68 (3-13)
Savarino [27]	47	Mean 0.24+/-0.02 (4.07+/-0.34) Range 0.08-0.50 (1.358-8.48) Median 0.23 (3.9)	Mean 0.28 +/-0.04(5.38+/-0.78) Range 0.06-0.93 (0.12-17.88) Median 0.29 (5.58)
Sauve [26]	8	Mean 0.46 (7.82) Range 0.29-0.654 (5 to 11)	Mean 1.02 (19.7) Range 0.57-1.3 (11 to 25)
Our Results (OxZr group)	**14**	**Mean 0.156 (2.64)** **Median 0.12 (2)**	**Mean 0.4 (7.71)** **Median 0.42 (8)**

ing CoCr are not subject to standard biological monitoring and 'safe' metal-ion levels have not been defined. Reference values have been established using inductively coupled plasma mass spectrometry in 59 healthy controls. Serum cobalt levels 0.15 µg/L (2.55 nmol/L) with a limit of detection of 0.02 µg/L and serum chromium levels 0.26 µg/L (5 nmol/L) with the detection limit of 0.01 µg/L were cited as reference values for normal control subjects (*22*).

Our study, along with the majority of others reported elsewhere, measured serum rather than whole blood levels. However, Cr may also accumulate in red blood cells (RBCs). The form in which Cr ions are released is thought to vary depending on the mechanism of release. Mechanical wear appears to cause Cr ion release predominantly in its trivalent form (*35*). Hexavalent Cr ions arising as a result of corrosion on the other hand, are considered to be a more biologically active form and are readily transported into RBCs (*1,9,19,20*). As a result, standard serum measurements may underestimate true blood Cr levels. Walter *et al* (*35*) have looked at the distribution of chromium and cobalt ions in all blood fractions (serum, plasma, whole blood and red blood cells) following MOM hip resurfacing. They found most of the Cr and Co to be in the plasma and serum fractions with minimal levels in the RBCs. Compared with hip arthroplasty however, tribocorrosion may play a proportionally greater role and mechanical wear a proportionally smaller role in metal ion release. The RBC metal ion levels may therefore be of more significance for studies investigating TKA.

Other limitations of this study include its retrospective nature and absence of pre-operative measurements. A control group has been utilised however in the form of subjects with an OxZr femoral component, and the Co and Cr levels in these patients are comparable with pre-operative control measurements from other studies. Had they been done, the use of pre-operative measurements in this study may have been able to confirm the validity of OxZr subjects as a useful control group. The withdrawal of blood samples through a metal butterfly needle could be criticized as a source of metal ion contamination, however the method used in this study was standardized in keeping with previous studies so that our results could be comparable. This study also suffers from an unfortunately high exclusion rate in selecting appropriate patients for inclusion. This has resulted in a small final study population, although the study was sufficiently powered to have a 78% probability of detecting a difference of 1SD in mean ion levels. The mean age of implants in this study was 5.5 years and 4.5 years for the CoCr and OxZr groups respectively. This is clearly beyond the time of the 6 and 9 months peaks in serum metal ions observed after hip resurfacing, but may not be great enough to detect patterns of metal ion release from tribocorrosion as opposed to mechanical wear.

We have analysed serum metal ion levels following Profix cruciate substituting fixed bearing TKA.

Our control group comprised patients with OxZr ceramic femoral components. Despite the lack of any Co or Cr containing implant among the control patients, there were no significant differences in Co or Cr levels between the control patients and those with a standard cobalt-chromium femoral component. We therefore conclude that, on the basis of our results, there does not appear to be any significant rise in serum metal ion levels following TKA with the Profix knee system.

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