**Metal ion levels post primary unilateral total knee arthroplasty**

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**ABSTRACT**

**Background**
Metal ion release from metal implants through the processes of mechanical wear and corrosion has been one of the main concerns post total joint arthroplasty. However, there have been very few studies to show metal ion exposure post total knee implants.

**Aims**
The aim of this study was to investigate whether blood metal ion levels are raised in patients with well-functioning unilateral primary total knee arthroplasty in the short and the long term after surgery.

**Methods**
Whole blood Chromium and serum Cobalt levels were measured in 22 patients following primary total knee arthroplasty at a minimum of 12 months after surgery and then repeated at a mean of four years. Eleven patients had the cemented triathlon knee system and 11 patients had an uncemented ACS knee system with multilayer coatings.

**Results**
Cobalt levels in our study are low one year after TKR and stayed within normal limits with no significant rise at four years (\(p=0.300\)). Chromium levels raised significantly by four years (\(p=0.007\)), but remained within normal range with no evidence of toxic systemic effects. Our data showed no statistically significant difference for cobalt and chromium levels between ACS and Triathlon groups (\(p=0.62\); \(p=0.54\) respectively).

**Conclusion**
At an average of 50-months post well-functioning total knee arthroplasty, whole blood Chromium levels and serum Cobalt levels are within the normal range. The use of cement is unlikely to influence metal ion release and titanium nitride coating did not influence metal ion release from TKR implants.

**Key Words**
Knee arthroplasty, Cobalt-Chromium, metal ions

**What this study adds:**

1. **What is known about this subject?**
   Blood metal ion level post joint replacement has been a raising concern in last few years.

2. **What new information is offered in this study?**
   Metal ion levels after well-functioning total knee replacement and the differences between two different types of prosthesis.
3. What are the implications for research, policy, or practice?
Common questions from our patients and also ongoing concern about this matter.

Background
Although total knee arthroplasty (TKA) has been a successful treatment for degenerative joint disease by achieving good long-term results, there has been various concerns regarding exposure to the metal ion elements which could potentially release form these implants through various mechanisms. However, the systematic and long-term effects of metal ions and particles on the human organism and their effect on the clinical outcome of TKA are still unknown. In recent years, the release of metal ions such as cobalt and chromium from artificial joints has gained increasing interest. The wear and failure rate of such implants as well as the biological reactivity caused by released trace metals are under debate. Kretzer et al. reported continuous release of the relevant levels of cobalt, chromium, molybdenum and titanium from the total knee replacement implants to the local environment; raising a concern about their interaction with immune system and potentially causing immunotoxic effects.

Cobalt and Chromium are the main metal alloys in conventional total knee arthroplasty, however different surface engineering methods have been used for coating metal components to reduce wear rate and metal ion exposure to the body. In this study, one of the prostheses (ACS knee system) is manufactured with multilayer Titanium Nitride coating.

This study aimed to assess metal ion release in the serum of patients with well-functioning unilateral total knee arthroplasty at one and four years after surgery to determine if metal ions are elevated.

Method
The institutional ethics committee on human research approved the design of the study.

Patients for this study were recruited from two senior surgeons’ outpatient clinics at routine one year postoperative reviews. Patients were selected to this study if they met the inclusion criteria and had their operation over a two-year period from April 2011 until June 2012. The first 11 patients from each group for the study period that met the inclusion criteria and who were happy to participate were included in this study. Informed consent was obtained from all of the patients.

The inclusion criteria for this study were
1. Minimum one year post primary unilateral total knee arthroplasty with no other metal implants
2. Well-functioning knee based on clinical findings; including pain, range of movement and stability of the knee. Active patients with no pain, no limited range of movement, mobility without any walking aids and stable knee in clinical assessment were included in this study.
3. No clinical signs or symptoms of infection
4. No radiographic signs of loosening.

Patients with prosthesis or metalwork elsewhere in the body, systemic disease affecting metal metabolism, renal impairment (including chronic renal failure with eGFR <30) or chronic/occupational exposure to metal ions were excluded from this study.

All operations were performed by one of the two senior authors (RC, HE) at two separate institutions. Femoral and tibial components inserted in all of these patients divided in two groups based on the surgeon preference; cemented unconstrained Triathlon knee system (Stryker Orthopedics, Mahwah, NJ), consisting of Chromium (Cr) 27-30 per cent, Molybdenum (Mo) 5-7 per cent, Nickel (Ni) 1 per cent, Iron (Fe) 0.75 per cent, Manganese (Mn) 1 per cent, Tungsten (W) 0.2 per cent, Aluminium (Al) 0.3 per cent, Cobalt (Co) balance, or uncemented ACS knee system (Implantcast, Buxtehude, Germany) consisting of Iron (Fe) 0.2 per cent, Chromium (Cr) 26.5 per cent, Carbon (C) 0.1 per cent, Nickel (N) 0.03 per cent, Cobalt (Co) balance, with coating of Titanium Nitride. X3 highly cross-linked polyethylene and ultra-high molecular weight polyethylene were used as the bearing surface in Triathlon and ACS knees, respectively.

Currently no whole blood, serum or urine reference materials with certified concentrations of Cobalt, Chromium, Molybdenum, and Nickel of unexposed individuals are commercially available. While the United Kingdom’s Medicine Healthcare and Regulatory Agency (MHRA) recommends cobalt or chromium levels more than 7 ppb as a cutoff for further investigations post metal on metal total hip arthroplasty. Consideration for different laboratory tolerances and testing protocols should also be made when reporting metal ion levels. 1

1 One part per billion is one part of solute per one billion parts solvent.
Whole blood levels of Chromium and plasma levels of Cobalt were measured. The primary endpoint was metal ion concentration at one year after surgery. The blood test was repeated three years later with same standards.

Blood samples were analysed for Cobalt and Chromium levels by Sullivan Nicolaides Pathology, Queensland. Samples were collected from patients into EDTA trace element vacutainers (Becton Dickinson, Franklin Lakes, NJ) using a stainless steel needle at a collection centre and transported to the laboratory at ambient temperature for analysis.

Whole blood Chromium was analysed initially followed by plasma Cobalt levels. Samples were diluted 1 in 20 with diluent and distilled water using a Starlet Robot (Hamilton Robotics, Reno, NV) by directly sampling from the barcoded EDTA trace element tube after thorough mixing. The diluted samples were vortexed and transferred to an Agilent 7500CE inductively coupled plasma mass spectrometer (ICPMS) equipped with Octopole reaction cells (Agilent Technologies, Santa Clara, CA) for analysis. Helium gas was used in the reaction cell for both Chromium and Cobalt analysis to reduce interference from polyatomic species formed in the plasma. The ICP-MS counts for each analyte were processed using the Agilent 7500CE software. A calibration graph was constructed using the counts obtained from the ICPMS expressed as a ratio to the internal standard counts for each analytical run and specimen type. Quality control samples were run every 20 samples and their acceptability was checked.

The results were calculated from the calibration graphs, and downloaded to the laboratory computer for authorization. Sullivan Nicolaides Pathology defined levels of 2-20nmol/L (0.002-0.02 ppb) for Cobalt and 10-100nmol/L (0.01-0.1 ppb) for Chromium as normal for an Australian population using the method of testing mentioned above. These “normal” levels are similar to the levels detected in the control and preoperative groups of other studies.\(^2,9,10,19,20\) Levels below the detectable ranges (<2 for Cobalt and <10 for Chromium) were assigned values of 1 and 5 (respectively) for analysis purposes, and the number of undetectable readings compared.

Data for age at surgery was normally distributed and is presented as mean (range). As the data for Cobalt and Chromium measurements was not normally distributed, non-parametric methods were used for analysis. Frequencies were compared between groups with the chi-squared test or Fishers Exact test where appropriate.

**Results**

Twenty-two patients with unilateral total knee arthroplasty, with well-functioning knees based on clinical findings and well-seated prosthesis on x-ray without any sign of infection or loosening, were included.

There were 11 uncemented ACS knee systems and 11 cemented Triathlon knee system. The mean age of patients at surgery was 69.0 years (range: 58–84 years, SD 7.0), with eight male and 14 female patients. The minimum time between surgery and first evaluation was 12 months with a mean of 13.0 months (range 12–20 months, SD 1.8), and a mean of 49.9 months (range 46–59 months, SD. 3.8) at the second test.

All patients participated in regular follow-up, with 100 per cent participation for surviving patients in the second test. One patient died between the two testing periods (Table 1).

At the initial review, there were four readings that were below detectable range for Cobalt of less than two (3 ACS and one Triathlon, no significant difference with Fishers exact test, \(p=0.59\)), and 12 for Chromium of below 10 (6 ACS and 6 Triathlon, no significant difference, Fishers exact test, \(p=1.0\)). Detectable readings were generally low and similar between groups (\(p=0.90\) Cobalt and \(p=0.55\) Chromium, Mann-Whitney U-test) (Table 1, Figures 1 and 2).

The cobalt levels stayed low after 4 years with no significant rise (\(p=0.30\), Wilcoxon signed rank test). One of the patients had slightly raised cobalt level of 15nmol/L in the first test, her cobalt level dropped to 9nmol/L in the second test, this fall could possibly be related to the peak level of metal ions mentioned in the literature during the first 0.5–1.0 \(10^6\) cycles indicating the running-in period followed by lower steady-state levels.\(^15\)

Chromium levels showed a significant increase in the second test (\(p=0.007\), Wilcoxon signed rank test), however these levels stayed below normal limits and there was no report of related toxic effects. One of the patients had slightly raised chromium level of 24nmol/L at 13 months after operation, which reduced to 16nmol/L at 46 months after operation with no other symptoms. Scatterplots of the Cobalt and Chromium levels at both reviews are shown in Figures 1 and 2.

There was no significant difference in either Cobalt or Chromium levels between ACS and Triathlon groups (\(p\)-values 0.62 and 0.54 respectively, Mann-Whitney U test).
Discussion

This study shows that the metal ion levels (Cobalt and Chromium) at one year and four years post well-functioning total knee replacement are within the normal range with no significant difference between the two types of prosthesis. We intended to show metal ion trend in the long term and we repeated the tests at around four years after operation. Our second set of data showed maintained low level for cobalt but raised levels of chromium which remained within normal limits.

Despite the obvious advantages of total joint arthroplasty (i.e., pain relief and functional improvement), there are ongoing concerns regarding potential disadvantages including implant related complications. All metallic implants corrode in a biologic environment over time; therefore exposure to the metal ions is expected after TKR. However, there are very few published data to report these metal ion levels post TKR. Furthermore, it has been suggested that ion levels post TKA may be as high as total hip arthroplasty,\(^{21}\) while there is no mechanical metal-on-metal wear in total knee arthroplasty. Our aim was to investigate whether metal ion levels are elevated following commonly used TKR implants.

Previous studies show significant release of the metal ions following failed total knee arthroplasty and raised concerns regarding the local and systemic effect of these chemicals in the body including their dissemination to synovial tissue, lymph nodes, liver, spleen and body fluids.\(^9\) However, there is no reference level regarding the normal ion levels post well-functioning TKA (Table 2). Mechanical (wear) and chemical or electrochemical (corrosion) material degradation processes are two mechanisms that result in the release of metal ions from metal implants.\(^{22}\)

Chromium ion could be released in two forms from metal implants based on the mechanism of the wear; mechanical wear produces the trivalent form, while hexavalent Chromium is mostly the result of corrosion. Chromium is not rapidly eliminated in the urine, it can accumulate in the tissues and red blood cells.\(^{23}\) The hexavalent form is the more biologically active form which can be readily transported in to the red blood cells. Consequently, measuring only serum Chromium levels could underestimate true blood Chromium levels.\(^{23,24}\) Compared with hip arthroplasty, corrosion may play a proportionally greater role and mechanical wear a proportionally smaller role in metal ion release post total knee arthroplasty.\(^{25}\) Kretzer reported lower levels of metallic wear rate for TKR compared to MOM THR.\(^{26}\) In their in-vitro study, Kretzer related most of the wear to the abrasive processes and corrosion of the metallic wear particles rather than corrosion of the bulk material.

While most of the other studies measured serum Chromium levels, ours measured whole blood levels, which could provide more reliable results, as could reflect both Chromium levels in the plasma and red blood cells.

Very few studies have also looked at metal ions post TKR; studies by Liu et al. and Savarino et al. demonstrated raised level of ions post TKR as a marker of loose prosthesis.\(^{26,27}\)

Luetzner et al. demonstrated the possibility of the higher ion levels post unilateral and bilateral TKR compare to their control group in the mean period of 66 month. They used cemented unconstrained Foundation Knee System (Plus Orthopedics GmbH, Marl, Germany). Luetzner’s study compared 18 unilateral and 23 bilateral TKR patients with their control group and demonstrated significant raise of metal ion levels in TKR group. However their reported data is not highly elevated and they observed no evidence of toxic systemic effects or increased cancer risk from these elevations.\(^{21}\) Garrett et al. compared metal ion levels after two types of femoral component for TKR (Cobalt/Chromium and the oxidized zirconium) at a mean period of 60 months after operation which did not show high Cobalt and Chromium levels compared to their control (oxidized zirconium) group.\(^{27}\)

Our study shows slightly higher chromium levels compared to these two studies, which could be related to whole blood chromium measured in our study rather than serum chromium levels measured with their studies which could underestimate chromium levels.

The two types of prostheses in our study have been performed with both cemented and uncemented techniques. Cemented fixation uses a fast-curing bone cement (polymethylmethacrylate) to hold the prosthesis in place, while cementless fixation relies on bone growing into the surface of the implant for fixation. However, the use of cement is unlikely to influence metal ion release. However, larger studies might require confirming this finding.

The ACS knee system has titanium nitride coating over the implant to reduce the release of metal ions. Our data did not support this theory however, as there were similar findings with both implants. While our primary intention was not the comparison between these two techniques, our data provided the opportunity to assess whether the use of cement influenced metal ion levels. The results confirm
that, irrespective of the surgical technique, metal ion levels one year and four years post well-functioning TKR are within normal limits.

Our aim was to define a base level for metal ions in this specific population which has not been investigated in previous studies and to assess the potential risk for people with TKR. This study concentrated on two prostheses to minimize confounding factors at a minimum period of three years. This study has some limitations including small sample, retrospective selection of patients, possibility of change in lab equipment and its effect on the measurement between the first and the fourth year, on the other side, while standard serum measurements may underestimate true blood Chromium levels, measuring whole blood Chromium adds to the strength of our study compared to previous studies. Furthermore, we had two separate measurements of metal ion levels which have not been done by other publications prior to this study.

**Conclusion**

In conclusion, this study shows that at the mean period of 50-month post well-functioning total knee arthroplasty in our group of patients, whole blood Chromium levels and serum Cobalt levels are within the normal range.

**References**


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PEER REVIEW
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CONFLICTS OF INTEREST
The authors declare that they have no competing interests.

FUNDING
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Table 1: Cobalt and Chromium whole blood serum levels at 1 and four years. “Normal” ranges are 2-20nmol/L for Cobalt and 10-100nmol/L for Chromium

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Table 2: Previously published studies

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Figure 1: Cobalt readings (nmol/L) at one year and latest (50 months), by prosthesis with “normal” limits as shown by black lines, defined by Sullivan Nicolaides. Dashed lines indicate detectable limits.

Figure 2: Chromium readings (nmol/L) at one year and latest (50 months), by prosthesis with “normal” limits as shown by black lines, defined by Sullivan Nicolaides. Dashed lines indicate detectable limits.