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HIP

Is the synovial fluid cobalt-to-chromium ratio related to the serum partitioning of metal debris following metal-on-metal hip arthroplasty?

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Objectives

We investigated the reliability of the cobalt-chromium (CoCr) synovial joint fluid ratio (JFR) in identifying the presence of a severe aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) response and/or suboptimal taper performance (SOTP) following metal-on-metal (MoM) hip arthroplasty. We then examined the possibility that the CoCr JFR may influence the serum partitioning of Co and Cr.

Methods

For part A, we included all revision surgeries carried out at our unit with the relevant data, including volumetric wear analysis, joint fluid (JF) Co and Cr concentrations, and ALVAL grade (n = 315). Receiver operating characteristic curves were constructed to assess the reliability of the CoCr JFR in identifying severe ALVAL and/or SOTP. For part B, we included only patients with unilateral prostheses who had given matched serum and whole blood samples for Co and Cr analysis (n = 155). Multiple regression was used to examine the influence of JF concentrations on the serum partitioning of Co and Cr in the blood.

Results

A CoCr JFR > 1 showed a specificity of 83% (77% to 88%) and sensitivity of 63% (55% to 70%) for the detection of severe ALVAL and/or SOTP. In patients with CoCr JFRs > 1, the median blood Cr to serum Cr ratio was 0.99, compared with 0.71 in patients with CoCr JFRs < 1 ($p < 0.001$). Regression analysis demonstrated that the blood Cr to serum Cr value was positively associated with the JF Co concentration ($p = 0.011$) and inversely related to the JF Cr concentration ($p < 0.001$).

Conclusion

Elevations in CoCr JFRs are associated with adverse biological (severe ALVAL) or tribocorrosive processes (SOTP). Comparison of serum Cr with blood Cr concentrations may be a useful additional clinical tool to help to identify these conditions.

Cite this article: *Bone Joint Res* 2019;8:146–155.

Keywords: Hip, Arthroplasty, Metal-on-metal, Cobalt, Chromium

Article focus

- Can a synovial fluid cobalt-chromium (CoCr) ratio be used clinically to identify a failing taper or a severe aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) response?
- Are differences in synovial fluid biochemistry associated with changes in serum partitioning of Co and Cr?

Key messages

- A CoCr joint fluid ratio > 1 shows good specificity for the presence of severe ALVAL and/or suboptimal taper performance.
- The metal present in the greatest concentration in the synovial fluid tends to fill the serum compartment preferentially. By extension, ALVAL and taper failure are associated with an elevation in the blood Cr to serum Cr ratio.
- Chromium released from the taper junction is taken into blood cells to a greater extent than Cr released from bearing wear. This indicates hexavalent Cr release via corrosion.

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doi: 10.1302/2046-3758.83.BJR-2018-0049.R1

Bone Joint Res 2019;8:146–155.

Strengths and limitations

- No previous studies have examined the influence of the source, volume, and synovial fluid metal concentrations on the serum partitioning of Co and Cr.
- Currently, no national or international guidelines are in place to help clinicians interpret differences in serum and whole blood metal concentrations.
- The study is limited to one centre.

Introduction

It is known that chromium (Cr) and cobalt (Co) concentrations in blood, serum, and synovial fluid samples correlate closely with the rate of material loss from metal-on-metal (MoM) hip arthroplasties.[1] However, the relative concentrations in these compartments can vary widely. These variations are not fully understood. One observation, which has been reported by several authors,[2] is counterintuitive. In general, synovial fluid samples taken from hip prostheses experiencing high rates of bearing wear contain greater amounts of Cr than Co (a low CoCr joint fluid ratio (JFR)). Yet, by weight, the Cr content of standard CoCr molybdenum (CoCrMo) alloys used in orthopaedics is more than twice the Co content.

It is now recognized that the presence of a severe aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL)[3] may influence (or be influenced by) the CoCr JFR.[4] ALVAL is associated with impaired clearance of Co and Cr from synovial fluid surrounding failed MoM prostheses. This impairment is more pronounced with Co than with Cr, often resulting in a CoCr JFR $>$ 1.

The phenomenon of taper failure has complicated these issues further. The CoCr JFR can also become elevated when metal debris is generated primarily from the head/neck taper junction.[5] This is likely due to the tendency of taper debris to precipitate and adhere to the metal taper surface (Fig. 1), reducing the release of Cr ions into the surrounding fluid. The rate of Co release appears relatively unaffected during this process, largely, it is thought, due to its greater solubility. These combined effects result, as is the case with ALVAL, in an elevated CoCr JFR.[5]

For the first part of this study, we investigated the possibility that a raised CoCr JFR may be used in clinical practice as an indicator of an adverse biological response (severe ALVAL) or a failing taper junction.

The concentration of solutes in synovial fluid depends on the balance between the input and the output (clearance).[6] Synovial fluid solutes exhibiting either poor or moderate protein binding are essentially removed by clearance of unbound solute (in the case of MoM arthroplasty, metal ions) from the synovial space. Removal of bound solutes by protein flux will limit the efflux half-time for any solute from the joint to that of the protein to which it is bound.[7] In the absence of protein binding, the clearance of a solute is largely dependent on diffusion.[6]

We have previously used asymmetrical flow field-flow fractionation (AF4) coupled with inductively coupled plasma mass spectrometry (ICP-MS) to investigate metal protein binding in serum and hip aspirates from MoM hip arthroplasty patients.[8] Results indicated that not only are Co and Cr bound to the same protein carriers in synovial fluid and serum (transferrin and albumin), but that there is competition between these metals for the same binding sites.[8]

For the second part of this study, we therefore investigated the possibility that changes in joint fluid (JF) biochemistry could be identified by the serum partitioning of Co and Cr. We hypothesized that:

1) The dominant JF metal is an indicator of delayed clearance from the joint space due to a greater extent of protein binding. These proteins, by definition, are found only in the serum compartment of blood. The dominant JF metal would therefore preferentially fill the serum compartment.

2) With taper failure, Cr debris precipitates, loosely adhering to the metal surface, where it may be exposed to corrosive biological fluids. Merritt and Brown[9] showed that this type of material release would lead to hexavalent Cr species release, which would be taken primarily into the red blood cells (RBCs). Thus, we hypothesized that material release from the taper junction would be reflected in higher blood Cr to serum Cr ratios.

Materials and Methods

Terminology. Cobalt-chromium JFRs are expressed in the form of 'CoCr JFR' throughout. A CoCr JFR $>$ 1 indicates a synovial fluid Co concentration greater than that of the Cr concentration. The 'dominant' metal indicates the element (Co or Cr) that is present in the greatest amount in the undigested synovial fluid sample. Relationships between whole blood (WB) and serum concentrations are expressed in terms of serum Cr to blood Cr. For example, a serum Cr to blood Cr ratio of 2 would indicate a serum Cr concentration double that of the corresponding WB Cr concentration.

Whole blood consists of 55% plasma, 45% RBCs, and $<$ 1% platelets and white blood cells. Since RBCs and plasma are the main constituents of WB, we have used the term 'blood cells' throughout to refer to the blood compartments outside of the serum compartment.[10]

Explants designated 'low/no taper damage' indicate either a hip resurfacing device or a total hip arthroplasty (THA) in which less than 10% of the total volume of material had been lost from the female taper surface. Explants designated 'suboptimal taper performance (SOTP)' indicate THAs in which at least 10% of the total material loss occurred at the female taper surface (Supplementary Material).

Patients. From 2008 to present, all patients experiencing failure of MoM hip prostheses at our centre routinely

Fig. 1

Explanted Articular Surface Replacement (ASR) XL head (DePuy Synthes, Raynham, Massachusetts) exhibiting obvious taper damage. There is adherent debris most prominent above the transition between the worn and unworn surface.

undergo pre-revision blood and serum and hip joint synovial fluid Co and Cr ion measurements. Tissue samples excised at revision surgery from multiple sites surrounding the prosthesis are analyzed by a pathologist (SN) with extensive experience in MoM cellular responses using published methodology.[4] Explanted prostheses are analyzed to determine the volumetric loss of material from the bearing and female taper surfaces that had occurred *in vivo*.

From 2016, however, routine serum metal ion testing at our centre was terminated for rationalization of resources. The division of the overall patient cohort for the two parts of this study are simply a reflection of this change in clinical practice.

Explant analysis. Explanted prostheses were analyzed using a coordinate measuring machine (Legex 322; Mitutoyo Ltd, Halifax, United Kingdom) to calculate the total amount of material that had been removed from the components *in vivo*. Explant analysis was used initially to divide patients into two groups for the first part of this study, depending on the extent of taper involvement in metal debris generation. If the taper contributed less than 10% of the total CoCr volumetric loss, the implant was labelled as 'low/no taper damage'. If the taper contributed 10% or more of the volumetric loss, the implant was labelled, for the purposes of this study only, as 'SOTP' (Supplementary Material).

Blood and serum metal ion sampling and analysis. Samples were frozen and sent for blinded trace-element analysis at the Supra-Regional Assay Service (SAS), Trace Element Centre, Surrey Research Park, Guildford, United Kingdom. The laboratory participates in the Trace Element Quality Assurance Scheme (TEQAS) of the United Kingdom. The concentrations of Cr and Co in serum and WB were measured using ICP-MS as described previously (Supplementary Material).[11]

Joint fluid Co and Cr concentrations. Prior to revision surgery, joint fluid was extracted under local anaesthetic to rule out infection, and to analyze the Co and Cr concentrations using the same technique and equipment as previously described in the collection of blood specimens. Samples did not undergo acid digestion prior to analysis, as previously discussed in depth.[4]

Histopathological tissue assessment. Samples were processed as previously described. A single consultant histopathologist examined the slides independently of the clinical findings, blinded to the results of the wear or fluid metal ion analyses. The ALVAL response was graded from 0 (absent) to 3 (severe), according to the integrity of the synovial membrane and the stage of lymphocytic infiltration as previously described in detail.[4] For the purposes of the statistical analyses, patient samples were divided into two groups only: 'severe' ALVAL (grade III) and 'non severe' (grades 0 to II). This distinction was made due to the change in metal handling that occurs in association with severe ALVAL, as previously described.[4]

Part A: CoCr JFRs, ALVAL, and taper damage. Patients: The first part of this investigation focused solely on the capsular environment, specifically the relationship between ALVAL and the synovial fluid concentrations. We therefore included all surgeries in which retrieved explants were available, the fluid metal ion concentrations had been measured, and the ALVAL response graded, irrespective of the presence of bilateral arthroplasties or the absence of matched serum/blood metal ion concentrations. Data collection, as described above, was continuous, taking place from January 2008 up to January 2018. This group of patients was largely made up of a cohort for which we have previously published details.[5] However, the present cohort included additional patients, reflecting the longer duration of data collection, as well as the inclusion of patients without recorded serum metal ion concentrations.

Statistical analysis: 1) Can the CoCr JFR be used to identify the presence of a severe ALVAL-type reaction or SOTP? Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of the CoCr JFR to detect the presence of severe ALVAL and/or SOTP. All part A patients were included in this analysis (Table I). The resulting area under the curve (AUC) was compared with the AUCs generated from ROC analyses, using absolute values of JF Co and JF Cr, to determine wahether the ratio added greater diagnostic accuracy. Next, the ROC analysis of CoCr JFR was repeated, but this time with the patients divided into two groups that were determined by the volumetric wear measurements. If a patient's implant was found to have worn at a rate of < 3 mm^3 per year (this value refers to the combined CoCr wear from the bearing surface and

Table I. Patient and implant details

Part	Value
Part A	**All revisions with explant data, graded tissue samples and joint fluid metal ion analysis**
Joint fluid samples, n	315
Mean age, yrs (range)	59 (22 to 84)
Male:female, n	111:204
Mean time to revision, mths (range)	67 (8 to 121)
Unilateral *vs* bilateral, n	233:82
Device	
Articular Surface Replacement (ASR; DePuy Synthes, Raynham, Massachusetts)	137
Birmingham Hip Resurfacing (BHR; The McMinn Centre, Birmingham, United Kingdom)	32
PINNACLE (DePuy Synthes)	143
ADEPT (MatOrtho, Leatherhead, United Kingdom)	1
Durom (Zimmer Biomet, Warsaw, Indiana)	2
Median bearing surface volumetric wear rate for hip resurfacings, mm^3/yr (IQR)	6.70 (2.66 to 14.6)
Median combined volumetric wear rate for THAs, mm^3/yr (IQR)	2.11 (1.16 to 3.71)
THAs with suboptimal taper performance, n	104
THAs with low/no taper damage, n	99
Hip resurfacings, n	112
ALVAL grades, n	
None	48
Mild	103
Moderate	99
Severe	65
Median joint fluid Co to Cr ratio, μg/l (IQR)	0.76 (0.43 to 1.73)
Median joint fluid Co levels, μg/l (IQR)	664 (226.3 to 2183)
Median joint fluid Cr levels, μg/l (IQR)	626 (178.4 to 2682)
Part B (unilateral patients only)	**Patient cohort previously described in full[5]**
n	155
Median blood Co levels, μg/l (IQR)	9.60 (3.50 to 21.1)
Median blood Cr levels, μg/l (IQR)	9.90 (5.49 to 15.7)
Median joint fluid Co levels, μg/l (IQR)	926 (229 to 2230)
Median joint fluid Cr levels, μg/l (IQR)	894.4 (223.6 to 3062.8)

THA, total hip arthroplasty; ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesion; IQR, interquartile range

taper, if present), they were placed into Group 1. If the implant was found to have worn at a rate greater than or equal to this value, they were placed into Group 2. This wear threshold was chosen for two reasons, the first being that this value was approximately the median value of wear rates in the total cohort. The second reason was that this wear rate approximates to the blood Co concentration of 5 μg/l, which clinical and retrieval studies have shown to be a reliable threshold for the detection of clinically relevant levels of wear.[11,12]

2) Can the CoCr JFR be used to identify the presence of a severe ALVAL-type reaction in the absence of SOTP? To exclude the influence of taper debris in this analysis, only patients in whom explant analysis had ruled out significant taper damage were included. It was hypothesized that any change in CoCr JFRs in this group of patients would be brought about primarily by the biological response (severe ALVAL). Accordingly, ROC curves were constructed to assess the sensitivity and specificity of the CoCr JFR to detect the presence of severe ALVAL. The JF Co and Cr concentrations were then tested in isolation, and finally with the patient group divided into two, according to wear rates, as described above.

Part B: CoCr JFRs and serum partitioning of metal. For this part of the study, only patients with unilateral prostheses who had been monitored using serum and WB Co and Cr samples were included. This patient group has been described in detail in our previous work.[5]

1) Does the dominant JF metal preferentially fill the serum compartment? In the first instance, the relationships between CoCr JFRs and the blood Cr to serum Cr ratios were examined using Spearman's rank correlation. Next, the median blood Cr to serum Cr ratios for patients with CoCr JFRs > 1 were calculated and compared with the equivalent median value in patients with CoCr JFRs < 1. The difference in these median values was tested for significance using the Mann–Whitney U test for non-parametric data. Regression analysis was conducted using logged serum Cr as the response variable, and logged values of blood Cr, JF Cr, and JF Co concentrations as the predictor variables. Finally, to eliminate concerns of the source of debris release affecting the results, a regression model was constructed using only the patients with hip resurfacings. The blood Cr to serum Cr ratio acted as the dependent variable, with bearing wear rate and CoCr JFR acting as the predictor variables.

2) Can the blood Cr to serum Cr ratio be used to determine the dominant JF metal? ROC curves were used to assess the sensitivity and specificity of the blood Cr to serum Cr ratio to detect the presence of a CoCr JFR > 1, with the patients split according to the wear rate threshold ($\geqslant 3$ mm^3 per year).

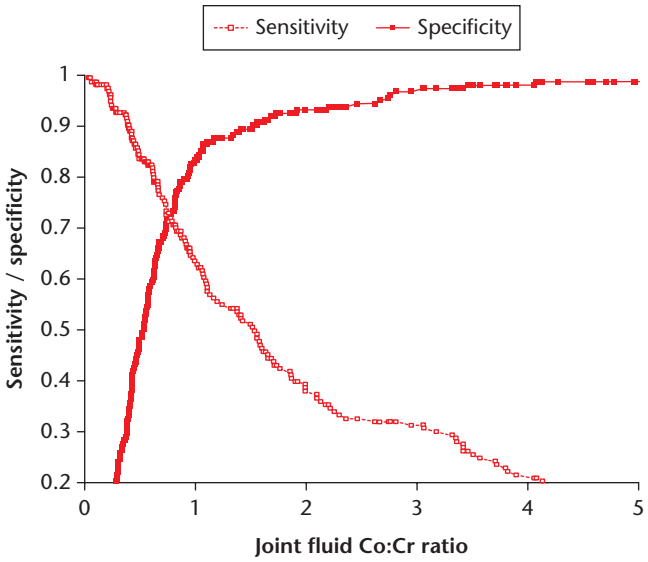

Fig. 2

Sensitivity and specificity of the cobalt-chromium (CoCr) synovial joint fluid ratio (JFR) to detect the presence of a severe aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) response and/or suboptimal taper performance (SOTP).

3) Can the blood Cr to serum Cr ratio be used to identify ALVAL/SOTP? Receiver operating characteristic curves were used to assess the sensitivity and specificity of the blood Cr to serum Cr ratio to detect the presence of a severe ALVAL reaction and/or SOTP. These tests were repeated as described in part A to examine the diagnostic use of absolute JF Co and Cr values and to investigate the effects of the magnitude of the wear volume.

4) Is Cr released from taper junctions distributed differently from Cr released from bearing surfaces? Receiver operating characteristic curves were constructed to assess the sensitivity and specificity of the blood Cr to serum Cr ratio to detect the presence of SOTP. Next, the median blood Cr to serum Cr ratios for patients with resurfacings and MoM SOTP were calculated and compared with the equivalent median value in patients with low/no taper damage.

Throughout, beta (β) standardized coefficients are reported as β with standard error (SE). Significance was set at $p < 0.05$.

Results

Part A: CoCr JFRs, ALVAL, and taper damage. A total of 315 patients were included in the analysis. The vast majority of revisions (95%) were performed for adverse reactions to metal debris (ARMD). The ARMD were diagnosed on the basis of the macroscopic operative findings, metal ion tests, and histology.

1) Can the CoCr JFR be used to identify the presence of a severe ALVAL reaction or SOTP? With all patients included, the AUC was 0.79 ($p < 0.001$) for the detection of severe ALVAL and/or SOTP. A CoCr JFR > 1 showed a diagnostic specificity of 83% (77% to 88%) and sensitivity of 63% (55% to 70%) (Fig. 2). For male patients, a CoCr JFR > 1 was 81% specific (70% to 89%) and 70% sensitive (55% to 81%) for the detection of severe ALVAL and/or SOTP. For female patients, the equivalent values were a specificity of 86% (78% to 92%) and a sensitivity of 60% (51% to 69%). There was no significant difference between the AUCs for the male and female patients ($p = 0.490$). The AUC for the absolute JF Co concentration was 0.517 ($p = 0.607$). For JF Cr, the AUC was 0.355 ($p < 0.001$), indicating that greater JF Cr concentrations were inversely related to SOTP/ALVAL.

Repeating the tests, however, this time sectioning the cohort according to the wear rate of 3 mm^3/per year, showed that the CoCr JFR had greater discriminatory ability in patients exposed to lower wear than in those exposed to greater wear (AUC = 0.784 *vs* 0.682; $p < 0.001$) (Fig. 3). With the patient group divided as such, individual values of JF Co and Cr produced AUCs that were non-significant.

2) Can the CoCr JFR be used to identify the presence of a severe ALVAL reaction in the absence of SOTP? There were 211 data sets included in this analysis, with the 104 THA SOTPs excluded. A CoCr JFR > 1 showed a specificity of 83% (77% to 88%) for the detection of severe ALVAL, with an AUC of 0.675 ($p < 0.001$). Sensitivity was poor, at 38% (51% to 64%). Using a CoCr JFR > 2 increased the specificity to 94% (88% to 98%) for the presence of severe ALVAL, with a corresponding reduction in sensitivity to 17% (16% to 40%). There were no significant differences in the ROC curves for male and female patients.

Using the absolute value of JF Co as the diagnostic test returned a similar AUC to CoCr JFR (0.661; $p = 0.002$). The JF Cr concentration showed no significant discriminatory ability to detect ALVAL (AUC = 0.560; $p = 0.266$).

Repeating the tests, however, this time sectioning the cohort using a cut-off wear rate of 3 mm^3 per year, showed that the CoCr JFR again had greater discriminatory ability in patients exposed to lower wear (AUC = 0.746 *vs* 0.671; $p < 0.013$). In the higher-wear group, there was no significant difference between the AUCs for CoCr JFR and JF Co ($p = 0.330$), but in the lower-wear group the AUC for CoCr JFR was significantly higher than for JF Co (0.75 *vs* 0.62; $p = 0.002$).

Part B: Synovial fluid metal ratios and serum partitioning of metal. The median CoCr JFR for the resurfacing group was 0.48 (IQR 0.32 to 0.82). The equivalent median value in the THA group was 0.94 (IQR 0.55 to 2.50). The difference in the distribution of CoCr JFRs between the two groups was significant ($p = 0.003$). The median blood Cr to serum Cr ratio was 0.70 (IQR 0.58 to 0.89) for the resurfacing group, 0.79 (IQR 0.54 to 1.00) for the THA group with low/no taper damage, and 0.98 (IQR 0.79 to 1.11) for the THA group with SOTP (Fig. 4). The median blood Co to serum Co ratio was 0.92 (IQR 0.74 to 0.90)

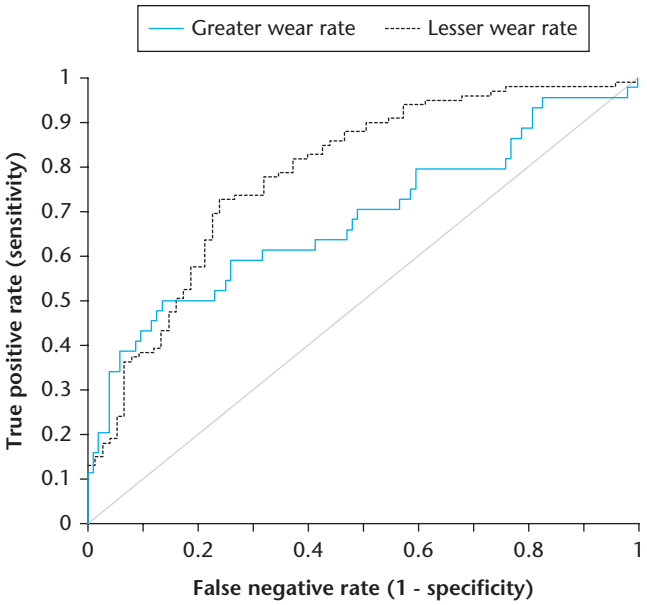

Fig. 3a

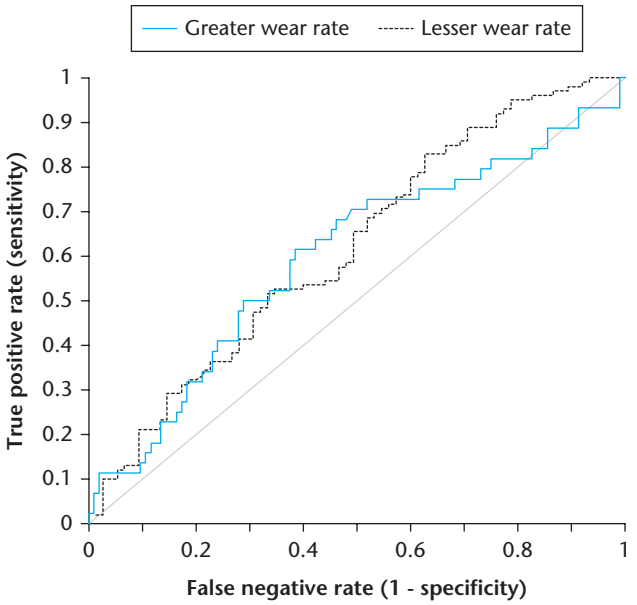

Fig. 3b

Area under the curve (AUC) charts for the detection of a severe aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) response and/or suboptimal taper performance (SOTP). a) Cobalt-chromium (CoCr) synovial joint fluid ratio (JFR), with patients split into greater or lesser wear rates. b) The corresponding AUCs using the absolute value of joint fluid cobalt.

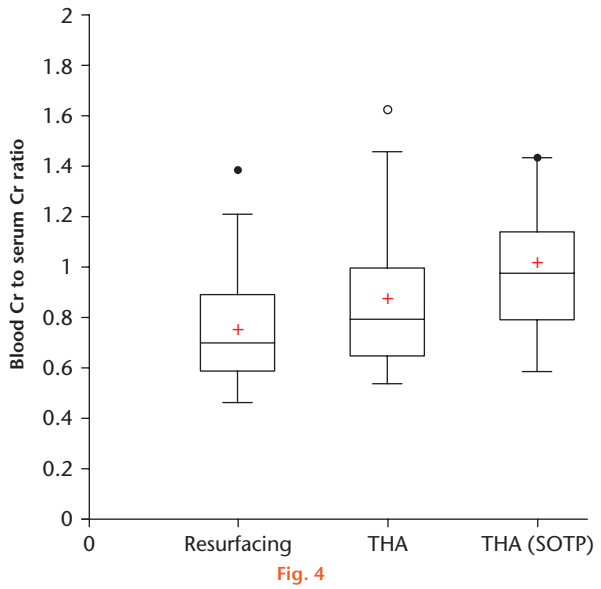

Fig. 4

The distribution of blood chromium (Cr) to serum Cr ratios in the resurfacing, total hip arthroplasty (THA; low/no taper damage), and THA suboptimal taper performance (SOTP) patient groups.

for the resurfacing group and 0.84 (IQR 0.77 to 0.96) in the THA group ($p = 0.020$).

1) Does the dominant JF metal preferentially fill the serum compartment? There was a significant correlation between a greater CoCr JFR and a greater blood Cr to serum Cr ratio (Spearman's coefficient 0.411; $p < 0.001$). This indicated that Co accumulation in the joint fluid was associated with a greater uptake of Cr ions into blood cells. In patients with CoCr JFRs > 1, the median blood Cr to serum Cr ratio was 0.99. With CoCr JFRs < 1, the median blood Cr to serum Cr ratio was significantly lower at 0.71 ($p < 0.001$) (Fig. 5). There was also a significant positive correlation between the blood Cr to serum Cr ratio and the serum Co to blood Co ratio (0.275; $p < 0.001$).

Regression analysis demonstrated that the blood Cr to serum Cr value was positively associated with the JF Co concentration (0.338, SE 0.132; $p = 0.011$) and inversely related to the JF Cr concentration (-0.591, SE 0.132; $p < 0.001$).

With analysis limited to the hip resurfacing patients, blood Cr to serum Cr ratio was positively correlated to a greater CoCr JFR ($p < 0.001$) and negatively correlated to the wear rate ($p < 0.001$). In resurfacing patients with a CoCr JF $\geqslant 1$, the median blood Cr to serum Cr ratio was 0.99 (IQR 0.64 to 1.14) compared with equivalent values of 0.66 (IQR 0.58 to 0.77) in patients with CoCr ratios < 1 (Fig. 6).

There was a significant correlation between an increasing CoCr JFR and a lower blood Co to serum Co ratio (Spearman's rank coefficient -0.358; $p < 0.001$). In other words, as Co accumulated in the JF, Co preferentially filled the serum compartment. In patients with CoCr JFRs > 1, the median blood Co to serum Co was 0.80 (IQR 0.74 to 0.86). In patients found to have CoCr JFRs < 1, the median blood Co to serum Co ratio was significantly higher at 0.92 (IQR 0.79 to 1.06; $p = 0.001$) (Fig. 5). Regression of blood Co *versus* serum Co, JF Co, and JF Cr showed that a higher JF Cr was significantly associated with greater blood Cr concentrations when the serum Cr concentration was adjusted for (0.149, SE 0.034; $p < 0.001$).

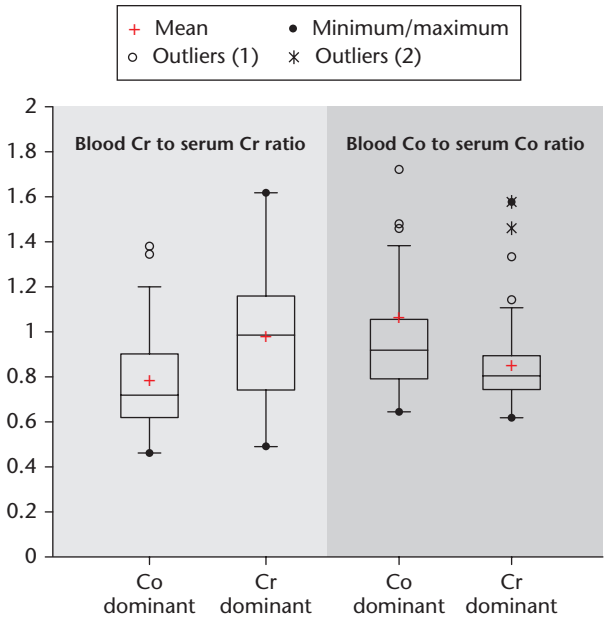

Fig. 5

All part B patients included. The dominant metal in the joint fluid concentrates more heavily in the serum compartment. For example, if the cobalt-chromium (CoCr) synovial joint fluid ratio is < 1, then there is a greater tendency for Cr to preferentially gill the serum compartment.

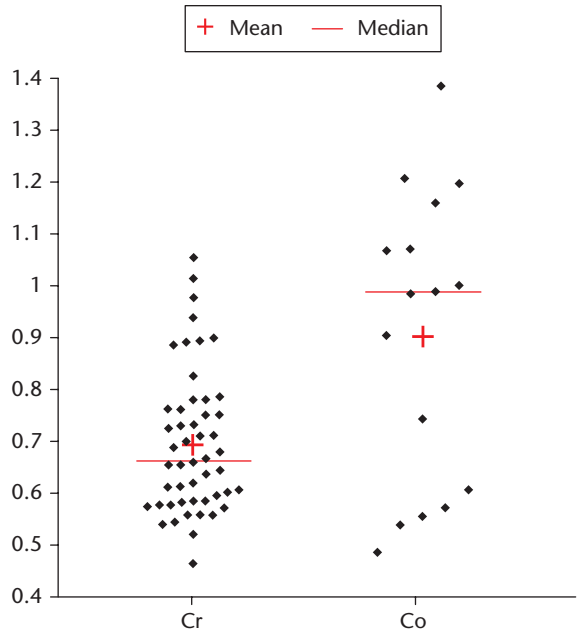

Fig. 6

Resurfacing patients only included to eliminate effects of taper debris contribution. Here, the patients have been divided into two groups: those with cobalt (Co)-dominant joint fluid (JF) *versus* those with chromium (Cr)-dominant JF. The blood Cr to serum Cr ratios were then plotted.

These findings together appeared to confirm our hypothesis that the dominant JF metal preferentially fills the serum compartment.

2) Can the blood Cr to serum Cr ratio be used to determine the dominant JF metal? In the patient group as a whole, the AUC was 0.740 ($p < 0.001$). A WB to serum Cr ratio > 1 was found to be 89% (82% to 94%) specific for a CoCr JFR of > 1. However, it showed poor sensitivity, at 43% (31% to 56%). There was no significant difference in the AUCs between the two wear groups ($p = 0.423$).

3) Can the blood Cr to serum Cr ratio be used to identify ALVAL/SOTP? Receiver operating characteristic analysis returned an AUC value of 0.70 ($p < 0.001$) for the blood Cr to serum Cr value. This was significantly better than for blood Co alone (Fig. 7).

4) Is Cr released from taper junctions distributed differently from Cr released from bearing surfaces? The median blood Cr to serum Cr value was 0.98 (IQR 0.79 to 1.11) in samples taken from hips with taper wear, which was significantly higher than the equivalent value in the patients with low/no taper involvement (0.73, IQR 0.62 to 0.94; $p < 0.001$) (Fig. 4). A blood Cr to serum Cr ratio > 1 was found to be 84% specific (76% to 89%) and 39% sensitive (26% to 54%) for the identification of SOTP.

Discussion

It has been shown in previously published work that the 'expected' biochemical changes encountered with MoM hips are as follows: 1) a synovial fluid dominated by Cr ions (i.e. a CoCr JFR < 1); and 2) chromium concentrations in the serum compartment that tend to exceed those of the corresponding WB sample.

We conducted this study to investigate whether results deviating from the typical biochemical picture may aid clinicians in identifying developing problems with either the implant or the host response to the implant.

Part A: CoCr JFRs, ALVAL and taper damage. The main finding of this investigation, we believe, is that a synovial CoCr JFR > 1 (i.e. Co dominant) can be regarded as a clinical concern. It may be associated with either an adverse biological response (the development of severe ALVAL) and/or tribological dysfunction (SOTP).

Regarding biological changes, it has been shown that the development of high-grade ALVAL is associated with a reduced clearance of Co from the joint space. In tribological terms, an increased JFR is highly suggestive of a malfunctioning taper, in which Cr precipitates and adheres to the metal surface.

In the total patient cohort ($n = 315$), we found that a CoCr JFR > 1 showed a specificity of approximately 83% for detection of the presence of severe ALVAL and/or SOTP. However, the sensitivity was less reliable, at around 63%. It appears, therefore, that low CoCr JFRs are unable to exclude these conditions reliably.

In the absence of SOTP (a hip resurfacing or a THA where > 90% of the metal debris volume was generated from the bearing surfaces), we found that a CoCr JFR > 1 was 83% specific for the identification of a severe ALVAL response. The sensitivity, however, was again less satisfactory, at 38%. Therefore, consistent across the patient

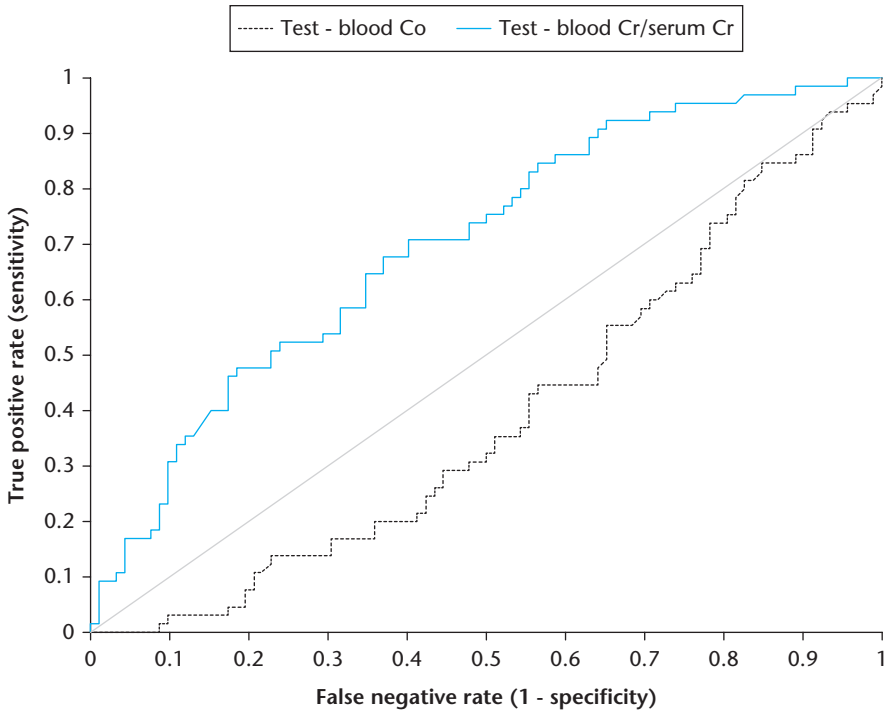

Fig. 7

Comparison of the receiver operating characteristic (ROC) curves for the detection of a severe aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) response and/or suboptimal taper performance (SOTP) for whole blood cobalt (Co) concentration *versus* whole blood chromium (Cr) to serum Cr ratio. The area under the curve (AUC) for Co (0.39) was significantly different to that for the blood Cr to serum Cr ratio (0.70; $p < 0.001$).

groups and implant type, an elevated CoCr JFR should be viewed as potentially troubling; however, a low JFR cannot be relied upon to exclude ALVAL or SOTP.

Part B: Synovial fluid metal ratios and serum partitioning of metal. Several *in vivo* and *in vitro* studies have previously investigated the relationship between the concentrations of Cr and Co in serum, WB, and erythrocytes. In general, the results have been consistent: 1) serum and WB samples, while closely correlated, cannot be used interchangeably due to unexplained variation;[13,14] 2) serum concentrations of Cr tend to be higher than WB samples, indicating Cr is released from MoM hips mostly in the trivalent (Cr^{3+}) form;[11,15-17] and 3) serum partitioning of Co is less well understood, with conflicting evidence.[10,15] However, variations in serum and WB concentrations of Co are, in general, smaller than those observed with Cr samples. It has therefore been argued that when Co enters the bloodstream, equilibrium is reached between blood cells and plasma.[10]

In a previous study, we conducted AF4-ICP-MS analysis of hip and serum fluids extracted from patients with MoM hips.[8] This methodology provides extremely useful data in terms of the size and characteristics of particulate debris. It is, however, prohibitively expensive and labour-intensive, and thus impractical to perform routinely. The results from processing a limited number of samples using this technology have so far been consistent: Co is largely bound to albumin; Cr is predominantly bound to transferrin. When higher concentrations of Cr are present, however, AF4-ICP-MS indicates binding of Cr to both transferrin and albumin. The results demonstrate that not only are Co and Cr bound to the same protein carriers in synovial fluid and serum, but that there is competition for the same binding sites.

It reflects the lack of understanding in this area that healthcare regulatory guidance fails to distinguish between serum and WB metal ion interpretation. We conducted the second part of this study to address this issue. We hypothesized that the explanation for variations in the partitioning of metal may lie in the binding of metals to serum proteins occurring in the synovial fluid. Given our concern that an elevated CoCr JFR indicated a biological or tribological issue, we also aimed to determine whether the relationship between matched serum and WB metal ion tests might prove to be a clinically useful, less invasive means of identifying abnormal synovial fluid biochemistry.

A raised CoCr JFR is associated with an increased Cr uptake in blood cells and increased serum compartmentalization of Co. These findings support the idea of competition between Co and Cr for binding sites on synovial proteins. If the rate of clearance of metal ions from the synovial fluid is determined by protein binding, one would expect that the element that 'loses the competition' will have a greater tendency to diffuse more rapidly from the joint space into the bloodstream in ionic form. A low CoCr JFR

indicates greater Cr binding, with greater diffusion of free Co ions. Cobalt uptake in red cells reflects uptake only of free ionized Co (Co^{2+}/Co^{3+}), and binding is practically irreversible.[18]

Patients implanted with devices with malfunctioning tapers have greater concentrations of Cr in their blood cells than patients exposed to predominantly bearing wear. It is well recognized that material debris produced from the taper surface tends to adhere to the metal surface in the form of flake-like deposits that are primarily composed of Cr phosphate compounds (Fig. 1). These large flakes of metal debris are rarely seen in cases of excessive bearing wear, even in cases with rates of bearing wear reaching over 100 times the rate of a taper junction. It is a fair assumption that debris produced by the bearing and taper surfaces is acted upon differently by the body.

In 1995, Merritt and Brown[9] undertook experiments that determined that hexavalent Cr (Cr^{6+}) was released during corrosion of orthopaedic implants. The hexavalent Cr became mostly associated with RBCs, as opposed to proteins. We replicated these findings in an *in vitro* study by spiking human blood samples with trivalent and hexavalent samples[11] (Supplementary Material). We found that while trivalent Cr was preferentially taken into the serum compartment, hexavalent Cr was indeed taken up primarily by erythrocytes.

It is therefore worrying that some of our patients were found to have greater Cr concentrations in their WB than in their serum samples. Chromium partitioning into blood cells was associated with a greater proportion of metal release from the taper, a situation in that one would expect a greater amount of debris to be produced by chemical corrosion. This observation would therefore be consistent with Merritt and Brown's[9] conclusion that corrosion produces hexavalent Cr species. Hexavalent Cr is classified by the World Health Organization as a class 1 human carcinogen,[19] and is considered to be up to 1000 times more toxic than trivalent Cr, likely due to its propensity to enter blood cells.[20]

What might this mean in the orthopaedic outpatient review clinic? A blood Cr concentration that exceeds the corresponding serum Cr concentration should be viewed as troubling. However, the clinician should not interpret the results in isolation, rather in the context of the other metal ion parameters. Most importantly, and fundamental to patient surveillance, Co (blood or serum) has been shown to be a reliable indicator of the volumetric material released from an implant. Our results suggest that following analysis of Co levels, a comparison of blood and serum Cr concentrations may provide more information about the capsular environment and the metal species released.

In conclusion, the ratio of serum to WB metal ion concentrations appears to be influenced by the relative concentrations of Co and Cr in the fluid surrounding MoM hip arthroplasties. A blood Cr concentration exceeding the corresponding serum Cr value in samples taken from a patient with a MoM hip arthroplasty has a high specificity for an adverse cellular response or a failing taper junction. We recommend investigation of the clinical utility of blood Cr to serum Cr ratios in metal-on-polyethylene hips, in which the relative absence of metal debris may prove to be a more reliable diagnostic test.

Supplementary Material

Additional information with regard to the aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) grading system, the definition of 'suboptimal taper performance' and the *in vitro* studies of metal ion distributions in spiked blood samples.

References

1. **De Smet K, De Haan R, Calistri A, et al.** Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. *J Bone Joint Surg [Am]* 2008;90-A(Suppl 4):202-208.
2. **Davda K, Lali FV, Sampson B, Skinner JA, Hart AJ.** An analysis of metal ion levels in the joint fluid of symptomatic patients with metal-on-metal hip replacements. *J Bone Joint Surg [Br]* 2011;93-B:738-745.
3. **Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP.** An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg [Am]* 2005;87-A:18-27.
4. **Langton DJ, Sidaginamale RP, Joyce TJ, et al.** Aseptic lymphocyte-dominated vasculitis-associated lesions are related to changes in metal ion handling in the joint capsules of metal-on-metal hip arthroplasties. *Bone Joint Res* 2018;7:388-396.
5. **Sidaginamale RP, Joyce TJ, Bowsher JG, et al.** The clinical implications of metal debris release from the taper junctions and bearing surfaces of metal-on-metal hip arthroplasty: joint fluid and blood metal ion concentrations. *Bone Joint J* 2016;98-B:925-933.
6. **Simkin PA.** Assessing biomarkers in synovial fluid: consider the kinetics of clearance. *Osteoarthritis Cartilage* 2013;21:7-9.
7. **Owen SG, Francis HW, Roberts MS.** Disappearance kinetics of solutes from synovial fluid after intra-articular injection. *Br J Clin Pharmacol* 1994;38:349-355.
8. **Loeschner K, Harrington CF, Kearney JL, Langton DJ, Larsen EH.** Feasibility of asymmetric flow field-flow fractionation coupled to ICP-MS for the characterization of wear metal particles and metalloproteins in biofluids from hip replacement patients. *Anal Bioanal Chem* 2015;407:4541-4554.
9. **Merritt K, Brown SA.** Release of hexavalent chromium from corrosion of stainless steel and cobalt-chromium alloys. *J Biomed Mater Res* 1995;29:627-633.
10. **Newton AW, Ranganath L, Armstrong C, Peter V, Roberts NB.** Differential distribution of cobalt, chromium, and nickel between whole blood, plasma and urine in patients after metal-on-metal (MoM) hip arthroplasty. *J Orthop Res* 2012;30:1640-1646.
11. **Sidaginamale RP, Joyce TJ, Lord JK, et al.** Blood metal ion testing is an effective screening tool to identify poorly performing metal-on-metal bearing surfaces. *Bone Joint Res* 2013;2:84-95.
12. **Hart AJ, Sabah SA, Bandi AS, et al.** Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. *J Bone Joint Surg [Br]* 2011;93-B:1308-1313.
13. **Daniel J, Ziaee H, Pynsent PB, McMinn DJ.** The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. *J Bone Joint Surg [Br]* 2007;89-B:736-741.
14. **Malek IA, Rogers J, King AC, et al.** The interchangeability of plasma and whole blood metal ion measurement in the monitoring of metal on metal hips. *Arthritis (Egypt)* 2015;2015:216785.
15. **Walter LR, Marel E, Harbury R, Wearne J.** Distribution of chromium and cobalt ions in various blood fractions after resurfacing hip arthroplasty. *J Arthroplasty* 2008;23:814-821.
16. **Mazoochian F, Schmidutz F, Kiefl J, et al.** Levels of Cr, Co, Ni and Mo in erythrocytes, serum and urine after hip resurfacing arthroplasty. *Acta Chir Belg* 2013;113:123-128.
17. **Smolders JM, Bisseling P, Hol A, et al.** Metal ion interpretation in resurfacing versus conventional hip arthroplasty and in whole blood versus serum. How should we interpret metal ion data. *Hip Int* 2011;21:587-595.
18. **Simonsen LO, Harbak H, Bennekou P.** Cobalt metabolism and toxicology—a brief update. *Sci Total Environ* 2012;432:210-215.

19. No authors listed. Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum* 1990;49:1-648.

20. Bhamra MS, Case CP. Biological effects of metal-on-metal hip replacements. *Proc Inst Mech Eng H* 2006;220:379-384.

Author contributions

- D. J. Langton: Designed the study, Wrote and edited the manuscript.
- S. Natu: Designed the study, Wrote and edited the manuscript.
- C. F. Harrington: Designed the study, Wrote and edited the manuscript.
- J. G. Bowsher: Designed the study, Wrote and edited the manuscript.
- A. V. F. Nargol: Designed the study, Wrote and edited the manuscript.

Funding statement

- This study was partly funded by a grant from the United States Food and Drugs Administration (FDA). The mention of commercial products, their sources, or their use in connection with materials reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services. This metal-on-metal retrieval study was supported by the FDA contract on 'Volumetric assessment of wear & corrosion of conical head/stem taper junctions in explanted total hip replacements to provide regulatory guidance & better predict clinical success' (FDA-SOL 1134668). The findings of this article are not intended to reflect new guidance from the FDA.
- No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Conflict of interest statement

- D. J. Langton and S. Natu report consultancy fees for acting as expert witnesses for plaintiffs in metal-on-metal litigation. D. J. Langton and A. V. F. Nargol report personal litigation against DePuy Synthes and its parent company, Johnson & Johnson, regarding faulty manufacturing and fraudulent marketing.

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