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Microfocus study of metal distribution and speciation in tissue extracted from revised metal on metal hip implants

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Abstract. Unexplained tissue inflammation in metal-on-metal hip replacements is suspected to be caused by implant-derived nanoparticles. The aim of this study was to investigate the nature of the metal particles in tissue surrounding metal-on-metal (MOM) hips that has been extracted during revision. Mapping of tissue surrounding the failed MOM hips was performed using microfocus X-ray Fluorescence (XRF). This revealed mainly Cr which was localized to the cellular regions. There was co-localisation of Co, were present, to areas of high Cr abundance. XANES of the tissue and appropriate standards revealed that the most common species were Cr(III) and Co(II). EXAFS analysis of the tissue and various metal standards revealed that the most abundant implant-related species was Cr(III) phosphate. Different tissue preparation methods, including frozen sectioning, were examined but were found not to affect the distribution or speciation of the metals in the tissue.
1. Introduction

The clinical effects of poor biocompatibility of orthopaedic implants are of current international importance following a dramatic increase in the use of metal-on-metal (MOM) hip replacements since 1996 [1]. All types of MOM hip use ASTM F75 Cobalt-Chromium-Molybdenum (Co-Cr-Mo, in the ratio 60:30:7). In simulation studies, these implants generate 1 trillion cobalt-chromium-molybdenum nanoparticles from the two metal surfaces[1] per year of patient use (1 million particles per step walked times 1 million steps per year[2]). This technology has been shown to work well in the medium term[3], even for highly active patients, however, young patients require this device to work for up to 50 years and yet the device has to be removed prematurely in up to 10%[4,5] of patients, within 5 years of implantation, depending on type of prosthesis. The scale of the potential problem is large because since 1996, approximately 500,000 patients have had MOM hip replacements worldwide[4]. A better understanding of the mechanism of failure is also important to develop fully biocompatible implants, for which there has been a predicted soaring demand over the next twenty years[6].

The properties of wear species derived from ASTM F75 Co-Cr-Mo orthopaedic implants has been studied for many years and it has generally been found that the wear debris in the tissues is abundant in chromium and deficient in cobalt however little has been done with respect to studies of the speciation. In this work we report the use of synchrotron XRF and XANES/EXAFS to analyse the distribution, and chemical state of metal-derived wear debris in tissue surrounding MOM hips.

2. Experimental

Data were collected at the microfocus spectroscopy beamline (I18) at Diamond Light Source. The beamline uses a cryogenically cooled Si(111) monochromator and operates over a 2-20keV energy range producing a focused X-ray beam, typically 3x3µm in size. Data was collected using a 9-element Ortec Ge monolithic solid state detector with XSPRESS2 processing electronics (STFC). Two types of experiments were performed. X-ray Fluorescence (XRF) mapping of the sample, performed at 10 keV, was used to produce a 2-dimensional map of the distribution of elements in the samples with XAS performed at points of interest to determine speciation. XANES was recorded for the following standards for comparison: Cr (II) acetate, Cr2(III)O3, Cr(VI)O3, CrPO4·4H2O and Cr metal. XAS data were also collected from MOM hips samples (ASTM 75).

Samples of hip capsule from were fixed in 10% neutral buffered formalin and blocks were processed to paraffin wax and sequential sections were cut at 10 micrometers thick before dewaxing by immersion in xylene. For histological analysis 3-4 micron thick sections were stained with haematoxylin and eosin (H&E) using routine histological methods. The machine processing for histology involves vacuum impregnation with fixatives and dehydration solutions. The tissue blocks are contained in porous plastic cassettes which are arranged in metal baskets in the machine. There were concerns that the process of fixing and sectioning the tissue could contaminate the tissue or alter the distribution and chemistry of the implant-derived wear debris so tissues samples were also prepared using a procedure adapted from Collingwood et. al. [7], in the investigation of metal-based particles in brain tissue. Sections from 2 patients were prepared from snap frozen, unfixed, unprocessed tissue and sectioned using blades coated with PTFE to avoid contact with the blade metal. The PTFE was sprayed onto the cryostat blade and anti-roll plate. One section was cut at 5 micrometers thickness for H&E staining and sequential sections cut at 10 micrometers were picked up onto silica slides and brought to room temperature. Epoxy glue was spread around the sections and the slides were covered by 25 micron thick Kapton, cut to size using plastic scissors. The cryostat and blade were cleaned with absolute alcohol between specimens.

For all samples, areas of interest for XRF mapping were selected after histological analysis (AS) and the regions marked on H&E stained sections were used to guide the analysis of the dewaxed and frozen sections XRF mapping was performed on all patient samples, typically covering a
400x400 micron region in 4 micron steps. Based on points of interest on the XRF maps (typically a marked variation in composition, such as high Co/low Cr concentration or low Co/high Cr) XANES/EXAFS of the Co and Cr edges were measured where applicable. X-ray absorption spectra were typically collected to \( k = 10 \). At some points more than one spectrum was collected primarily to improve data quality but also to investigate any possible beam damage to the sample. Data reduction and XANES analysis were done using the programs Athena and PySpline, while EXAFS fitting was done using DL-EXCURVE[8-10].

3. Results

XRF maps of the Cr and Co distribution in fixed tissue along with the associated light microscopy image of the corresponding stained section, are displayed in Figure 1. Cr was the most abundant and widely distributed element in line with previous studies of the tissues surrounding hip replacements [11]. Co was found in discrete locations and the concentration levels with respect to Cr varied greatly across the samples but did not reflect the MOM alloy composition - (the Co-Cr ratio in these high Co pixels varied over the range Co:Cr 9:1 - 1:1 compared to the alloy composition of ca 2:1). As mentioned previously, to exclude processing and contamination artifacts, mapping was also performed on tissue prepared by frozen sectioning. Comparison of fixed and frozen tissue sections showed similar distributions and relative concentrations of Co and Cr indicating that, for this system, the fixing process does not appear to affect the location of metals.

In terms of particle size and location of the wear debris, Figure 1 shows that implant related debris is localized to the cell aggregates and there was no evidence for ‘background’ occurrence of implant debris in the intervening fatty connective tissue; however, the resolution, which is primarily, due to the beam size is not sufficient to determine if the metal is confined inside or between the cells. Previous
TEM studies by Shahgaldi showed that chromium-based particles, typically 40nm in size, were located intracellularly [11] whereas a recent study by Urban et. al. identified particles 1-200micon in size at intercellular locations[12]. The discrepancies between these studies may be due to particulate sizes present in the samples and further experiments are required to resolve the location of the metal.

XANES/EXAFS of the Cr spectra from different regions and on the fixed and frozen tissue was collected and two types of Cr spectra were observed. These spectra along with those of several standard Cr compounds are displayed in Figure 2.

Spectrum (g) from Figure 2 is representative of nearly all the Cr XANES spectra collected from all the tissue samples, fixed and frozen, irrespective of varying Cr and Co concentration across all samples.

Previous studies have pointed to the presence of Cr-orthophosphate[11,12] and a comparison of the XANES and EXAFS of spectrum (g) and CrPO$_4$·4H$_2$O (Figure 2) showed excellent agreement. Outside the body, CoCr alloy passivates with a thin layer of Cr$_2$O$_3$ which functions to reduce corrosive attack and as a result of wear it might have been expected that Cr found in the tissue would be of this form but examination of the XANES spectra show this is clearly not the case. While we have demonstrated the presence of Cr-phosphate this experiment does not indicate if the Cr is formed in the tissue from CoCr particulates or on the surface of the metal hip and subsequently deposited in the tissue. Spectrum (h) was observed at a single point of very high Co concentration on the tissue sample.

Using linear combination fitting the XANES spectra could be well approximated by 0.75:0.25 mix of Cr(CoCrMo) and CrPO$_4$·4H$_2$O however it is unclear if this is a result of a number of different Cr particles in the area illuminated by the beam or a single particle with both forms present.

EXAFS recorded from Co-containing regions in the fixed and frozen tissue samples (not shown) identified a metallic like Co along with what is an oxidized Co state. This oxidized state was observed...
to evolve from metallic Co with increased x-ray beam exposure and the speed of this oxidation process varied, which is most likely related to particle size. We suspect that any oxidized Co observed is a result of exposure of the metallic particles in the tissue to the x-ray beam. Co-Cr and Co metal have similar spectra and given that the Co spectra from the tissue evolves with beam exposure it is difficult to be certain of the exact form of Co in the tissue.

4. Conclusions

Synchrotron XRF of tissue surrounding current generation metal-on-metal hip replacements showed that while the implant material consists of 60% Co, 30% Cr and 7% Mo the body seems to metabolize the Mo and Co more efficiently (but that need not mean more safely) than the Cr which forms a much less soluble phase. The results of the frozen tissue study, (where care was also taken to eliminate possible metal contamination with the use of ceramic blades) were essentially the same as those tissue samples prepared using more conventional histological techniques, illustrating that for these sorts of tissues samples the histological preparation does not seem to affect the speciation of the metal present. When compared to data from other studies it appears that humans may have a common response to chromium-containing implants involving the deposition of chromium phosphate into the tissues which is influenced in only a minority by the alloying elements of molybdenum and cobalt. Our findings provide useful clues regarding the active metal species that can cause severe inflammation in human tissues, sufficient to "reject" a hip replacement and are relevant to many groups. Nearly all the Cr is in a Cr(III) phosphate phase. The rest of the Cr is associated with Co and in native cobalt chrome particles but metal particulate matter is generally much less commonly found than the chromium phosphates.

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