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Can Cobalt(II) and Chromium(III) Ions Released from Joint Prostheses Influence the Friction Coefficient?

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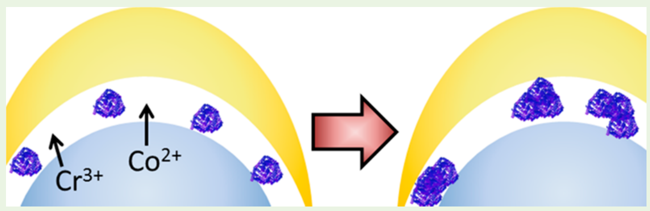
Supporting Information

ABSTRACT: Cobalt chromium molybdenum alloys (CoCr-Mo) are commonly used as articulating components in joint prostheses. In this tribocorrosive environment, wear debris and metal ionic species are released and interact with proteins, possibly resulting in protein aggregation. This study aimed to investigate whether this could have an effect on the friction coefficient in a typical material couple, namely CoCrMo-on-polyethylene. It was confirmed that both Co(II) and Cr(III) ions, and their combination, at concentrations relevant for the metal release situation, resulted in protein aggregation and its concomitant precipitation, which increased the friction coefficient. Future studies should identify the clinical importance of these findings.



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Since articulating components in joint prostheses must be both wear- and corrosion-resistant, cobalt chromium molybdenum alloys (CoCrMo) are commonly used. The possibility of release of Co and Cr species as well as wear debris has been widely debated due to the potentially adverse effects;[1] implications that depend on the loading situation,[2] other wear conditions (severity, rate, mode, and source),[3] and on the bearing size.[4] Although the oxidation state of released Cr in vivo is still a subject of debate,[1a,5] it is nonetheless known that Cr is released in its trivalent oxidation state and Co in its divalent state from CoCrMo alloys at simulated physiological conditions.[6] Both Cr(III) and Co(II) are known to bind to proteins such as albumin,[7] which is also a prerequisite for their relatively high sensitization potential.[8] This binding almost certainly changes the configuration of the albumin molecule,[7a,c,9] increases its effective molecular weight,[7a] and/or results in its aggregation or precipitation (sedimentation).[6,7d] We hypothesize that such aggregation processes could also influence the friction in articulating components of joint prostheses made of CoCrMo. There is, to the best of the authors' knowledge, no data available on the potential effect of protein aggregation on the friction coefficient in a (simulated) articulating contact. This study therefore investigates whether albumin aggregation takes place in the presence of Co(II) and/or Cr(III) ions in concentrations relevant for a release scenario, and whether this influences the friction in a CoCrMo-on-polyethylene couple in a simplified model of a joint prosthesis bearing couple.

Aggregation of albumin was studied continuously up to 9 h in terms of its size distribution in solution by means of photon-cross-correlation-spectroscopy (PCCS; Nanophox, Sympatec GmbH), at room temperature. Measurements were performed using 1 g/L bovine serum albumin (BSA) in phosphate buffered saline (PBS, pH 7.4) with (molar ratio of albumin:Co:Cr of 12:5:4), and without any addition of metal ions (reference solution; albumin:Co:Cr ratio of 1:0:0). In addition, aggregation studies were performed on the reference solution by means of PCCS at room temperature upon titration with both metal ions up to a ratio of 12:5:4 (albumin:Co:Cr). For comparison, two solutions (ratios of 1:0:0 and 12:5:4) were investigated by means of nanoparticle tracking analysis (NTA; NS300, Malvern) at room temperature. Experimental details are given in the Supporting Information text and Figure S1.

Friction was monitored using a pin-on-disc setup in a rotational motion, see Figure S2. A force of 1 N was applied to a nonirradiated polyethylene cylinder (UHMWPE; GUR 1050) with a diameter of 8 mm, corresponding to a contact pressure of approximately 20 MPa. This contact pressure was the lowest possible in the test equipment for that contact geometry. This

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is slightly higher than what has been reported for polyethylene-CoCr hip joint prostheses (up to 9 MPa),[10] but lower than observed in CoCr−CoCr hip joint prostheses (up to 70 MPa).[10] The pin was run against a cast CoCrMo alloy flat disc (ASTM F-75, polished by the manufacturer to an average surface roughness of 10−15 nm, Sandvik AB, Sweden) using a rotational motion. A diameter of 6 mm was used with a speed of 0.04 m/s, which can be considered a simulation of normal walking.[11] The alloy disc was fitted into a Teflon bath filled with 40 mL BSA-containing PBS (reference solution 1:0:0). Friction studies were run for 2 h (after a running-in time of 4 h) at room temperature. Subsequently, a solution (50 μL PBS; 10 μL of 1 g/L Cr(III); or 33.5 μL of 0.45 g/L Co(II)) was injected every 15 min a few mm from the contact to evaluate its effect on the friction coefficient. Each metal ion injection corresponded in the bulk solution to an albumin:Co:Cr molar ratio of 12:5:0 (for Co), 12:0:4 (for Cr), or 12:5:4 (for Co+Cr).

All measurements were conducted at a relatively low molar ratio of added metal at a ratio of albumin:Co(II):Cr(III) of up to 12:5:4. The selected ratio of the current study is considered relevant from a metal release perspective for CoCrMo joint prostheses under normal conditions. In fact, a molar ratio (albumin:Co) between 1:0.06 and 1:80 can be expected in joint prostheses (see Supporting Information for calculations and references).

Large aggregates were clearly present in the solution and visible to the naked eye after 48 h in solutions with an albumin:Co:Cr ratio of 12:5:4. No aggregation was observed in the reference solution (albumin:Co:Cr ratio of 1:0:0, data not shown).

Figure 1 illustrates that the addition of Co(II) and Cr(III) ions (at a molar ratio of albumin:Co:Cr of 12:5:4) results in

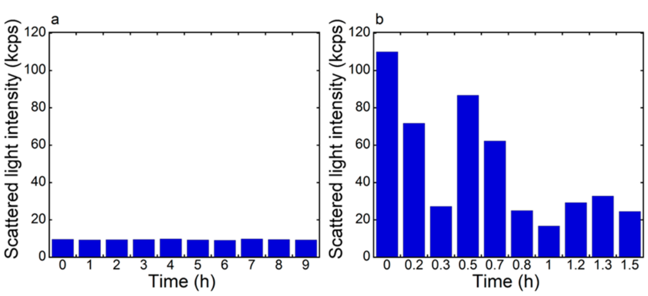

Figure 1. Time-dependent intensity measurements in PBS (a) without metal ions (an albumin:Co:Cr molar ratio of 12:0:0), and (b) with metal ions (albumin:Co:Cr ratio of 12:5:4) by means of PCCS showing reduced count rates with time due to precipitation (sedimentation) of large protein/metal aggregates. Only count rates, no size distributions, are shown, since the signal either was too low (without metal ions) or strong precipitation took place (with metal ions). Corresponding correlation functions are shown in Figure S1.

albumin aggregation and concomitant precipitation (sedimentation) of large aggregates outside (below) the volume probed by the laser, visible as reduced count rates with time (Figure 1b). Aggregation and precipitation of large aggregates is also indicated by the correlation functions (Supporting Information text and Figure S1).

NTA measurements confirmed a higher extent of protein aggregation in PBS with a molar ratio of albumin:Co:Cr equal to 12:5:4 compared with the 1:0:0 reference solution, as judged from significantly higher particle concentrations (Figure S3).

Figure 2 shows how added amounts of Co(II) and Cr(III) ions change the relative size of albumin in solution. It is evident

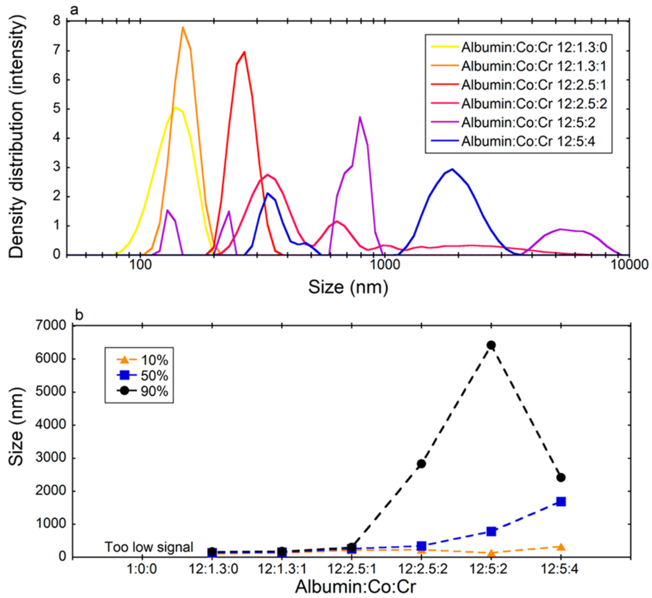

Figure 2. (a) Intensity distribution and corresponding (b) 10, 50, and 90% cutoff values of the size distribution during titration with Co(II) and Cr(III) ions from an albumin:Co:Cr molar ratio of 12:1.3:0 to 12:5:4. Because of the polydispersity and strong precipitation (sedimentation of large aggregates), only trends should be interpreted. The relative standard deviation of the 50% cutoff values of three subsequent measurements after each addition varied between 5 and 77%. The dotted lines are only guides for the eye.

that significant aggregation occurs when the molar ratio exceeds an albumin:Co:Cr ratio of 12:1.3:1, a level that is significantly lower than that reported by Yang and Black, who studied the metal-albumin binding by measuring free and bound metals in solution after dialysis.[7d] Their findings revealed in addition a stronger bonding between albumin and Co(II) compared with Cr(III), and an even stronger bonding for their combination. The latter case is highly relevant for CoCrMo alloys that predominantly release Co(II)-species, but also Cr(III)-species,[6] and should be further investigated.

The friction coefficient, μ, instantly increased when either Cr(III) or Co(II) ions, or both, were added to the contact area, an effect that was not seen for a solution without the metal ions (PBS), Figure 3. Injections at larger distances than a few mm from the contact did not show any effect on the friction coefficient (data not shown). The hypothesis is that protein aggregates of changed conformation, possibly denatured, increase the friction coefficient in the contact area. This would be in agreement with literature findings that show that protein denaturation (less hydrated proteins and hence a higher shear force) increases the friction coefficient.[12] The decay in friction coefficient after the injection of the protein/metal ion solution into the contact area can possibly be explained by the removal of aggregated proteins from the contact area (Figure S2), which was also suggested earlier.[13]

Future studies should investigate the effect of lower and higher albumin:metal molar ratios, and the effect of Mo ions, on the friction coefficient and estimate potential long-term effects. Current investigations have mainly been conducted at room temperature, with some exceptions at 37 °C, showing similar effects. Future studies should investigate whether a

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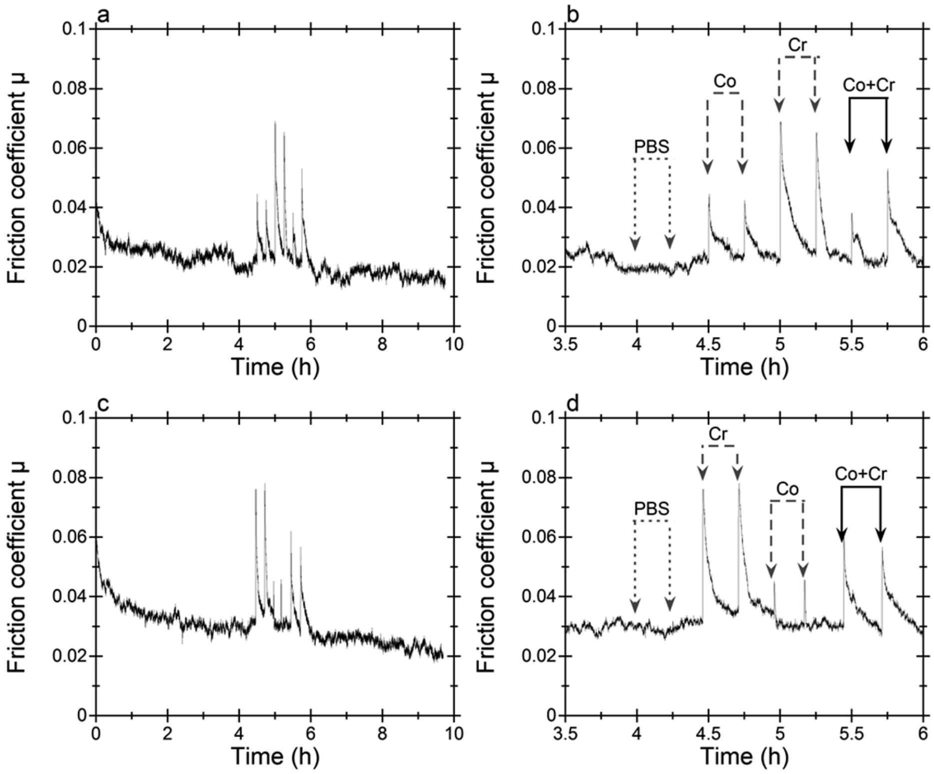

Figure 3. (a, b) Changes in the friction coefficient (μ) in a CoCrMo-on-polyethylene couple during sequential addition of PBS, Co(II) (albumin:Co:Cr ratio of 12:5:0), Cr(III) (albumin:Co:Cr ratio of 12:0:4), and both Co(II) and Cr(III) (albumin:Co:Cr ratio of 12:5:4). (c, d) The same sequence of metal ion addition as in a, but with the addition of Cr(III) before Co(II). The running-in time was 4 h, the solutions were added during 2 h, and finally 4 h were measured without additions. Panels b and d show magnified sections of panels a and c during solution addition.

higher temperature, e.g., 43−44 °C in the contact area of an artificial hip joint,[10] may further influence albumin aggregation or its possible denaturation.[14] Other factors known to influence the extent of aggregation and capacity to bind Co(II) to albumin are the solution pH[7a,c,15] and ionic strength of the solution,[15a] aspects that also influence the extent and proportion of released Co, Cr, and Mo species from CoCrMo alloys. Furthermore, it should be investigated whether released metal ions influence or induce, the nanocrystalline metal−carbon-containing layer reported to be present on the metal surface[16] and its importance for metal release, wear, particle release, or corrosion processes.

This study demonstrates that Co(II) and Cr(III) ions, known to be released from CoCrMo alloys in joint prostheses, interact with albumin in solution, which rapidly aggregates and precipitates from solution (sediment). These processes seem to result in a temporarily increased friction coefficient in a simplified model of a joint prosthesis contact of a CoCrMo-on-polyethylene couple. Future studies should identify whether these observations are of clinical importance for joint prostheses over their service life and investigate possible effects on their wear resistance and biocompatibility.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsbiomaterials.5b00183.

> Additional experimental details, calculations of expected molar ratios of albumin to Co(II) or Cr(III) ions based on literature findings, Figures S1−S3, and additional references (PDF)

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Notes

The authors declare no competing financial interest.

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