Can gamma irradiation during radiotherapy influence the metal release process for biomedical CoCrMo and 316L alloys?

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Received 19 August 2017; revised 19 December 2017; accepted 19 January 2018
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jbm.b.34084

Abstract: The extent of metal release from implant materials that are irradiated during radiotherapy may be influenced by irradiation-formed radicals. The influence of gamma irradiation, with a total dose of relevance for radiotherapy (e.g., for cancer treatments) on the extent of metal release from biomedical stainless steel AISI 316L and a cobalt-chromium alloy (CoCrMo) was investigated in physiological relevant solutions (phosphate buffered saline with and without 10 g/L bovine serum albumin) at pH 7.3. Directly after irradiation, the released amounts of metals were significantly higher for irradiated CoCrMo as compared to nonirradiated CoCrMo, resulting in an increased surface passivation (enhanced passive conditions) that hindered further release. A similar effect was observed for 316L showing lower nickel release after 1 h of initially irradiated samples as compared to nonirradiated samples. However, the effect of irradiation (total dose of 16.5 Gy) on metal release and surface oxide composition and thickness was generally small. Most metals were released initially (within seconds) upon immersion from CoCrMo but not from 316L. Albumin induced an increased amount of released metals from AISI 316L but not from CoCrMo. Albumin was not found to aggregate to any greater extent either upon gamma irradiation or in the presence of trace metal ions, as determined using different light scattering techniques. Further studies should elucidate the effect of repeated friction and fractionated low irradiation doses on the short- and long-term metal release process of biomedical materials. © 2018 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 008: 000–000, 2018.

Key Words: passivation, radicals, radiotherapy, BSA, implant

INTRODUCTION
CoCrMo alloys and stainless steel grade AISI 316L are biomedical alloys widely used for different dental implants, orthodontic appliances and devices, artificial joint prostheses or orthopedic temporary devices.1–4 They are therefore often present in patients that undergo a radiation cancer treatment (radiotherapy), and might be in the irradiated zone. A common example is radiotherapy of prostate cancer in the presence of artificial hip joints, which make radiotherapy and imaging by computed tomography more complicated due to shielding and perturbation effects.5,6 Reports and reviews on failed implants or insufficient osseointegration after/during radiotherapy for both hip joints7–9 and dental implants10–17 indicate risks of implant failure or loss of the implant upon irradiation, most probably due to tissue damage. These risks increase with increasing irradiation dose.10,11,15,18 This has been questioned in some recent reviews and studies,19,20 and patients that undergo radiotherapy have been recommended dental implant therapy if following some guidelines (e.g., strict monitoring).16,20–23 Pelvic irradiation of patients with gynecological cancer without implants did not result in a higher risk of hip replacement afterward.24 The reviews and studies that suggest an increased risk for failed implants or osseointegration caused by irradiation explained this risk to be related to damage of the bone or soft tissue, altered mechanical properties of the bone, and increased risks of infections. The metallic implant itself may also be affected by gamma irradiation radiotherapy. During radiotherapy, ionizing radiation, in particular gamma-radiation, will be absorbed and result in excitation and ionization of water and aqueous organic systems. These processes cause formation of oxidative and reductive

radicals and species, for example, \( \text{OH}^- \), \( \text{O}_2 \), \( \text{H}_2\text{O}_2 \), \( \text{HO}_2 \), \( \text{H}_2 \), \( \text{O}_2 \), \( \text{O}^- \), and \( \text{H}_2\text{O}^- \). These species may affect the metal release process, the surface oxide characteristics, and/or the corrosion behavior of the implant material. The amount of produced radicals depends on solution pH and is proportional to the total irradiation dose. Most studies that investigate metal release and corrosion of stainless steels or other metals and alloys have been performed at higher temperatures and irradiation doses as compared to what would be relevant for the human body and radiotherapy (37°C and 10–145 Gy total irradiation dose). An early study on stainless steel AISI 304 in the temperature range from 65 to 250°C in water of different pH and dissolved oxygen content observed a thicker surface oxide and transformation of released metals to insoluble corrosion products, but not an increased total amount of released metals upon exposure to gamma irradiation with a total dose of 120,000–225,000 Gy. An evident surface oxidation effect was also observed for a Ni-Cr-Fe Inconel 600 alloy in water (pH 6–10.6) at 150°C, exposed to gamma-irradiation with a total dose of 295,200 Gy. The study reported increased release of metals upon irradiation for solutions of the lower pH levels. A study on stainless steel AISI 316L at relatively harsh conditions (320°C, 3 weight parts per million H₂, neutral pH, a total proton irradiation dose up to \( 1.04 \times 10^9 \) Gy) revealed accelerated corrosion and depletion of chromium from the surface oxide upon irradiation.

To the best of our knowledge, no studies exist that investigate metal release from biomedical materials at conditions of relevance for radiotherapy. This is of interest, since elevated levels, possibly toxic, of released metals upon radiotherapy could detrimentally affect the clinical outcome of the cancer treatment and/or the implant biocompatibility. This might furthermore be of particular interest in high risk groups for implant complications and/or for the rare cases of metal-induced sarcoma.

The aim of this study was to investigate the extent of metal release from the biomedical materials stainless steel AISI 316L and cobalt-chromium-molybdenum alloy at simulated physiological conditions induced by gamma irradiation with a total dose of relevance for radiotherapy.

### Materials and Methods

#### Materials

Samples of a biomedical grade cobalt-chromium-molybdenum (CoCrMo) alloy with nitrogen addition in disk shape of 22 mm in diameter and 2 mm in thickness (a total surface area of 9.0 cm²) were supplied by Ionbond, Switzerland, and produced by Aubert & Duval, France, by means of vacuum induction melting followed by electroslag remelting and warm working. The material conforms to the ASTM F1537 Alloy 1 standard. Coupons from sheets of AISI 316L stainless steel (cold-rolled), sized approximately 1.5 \( \times \) 1.5 cm² (with a total surface area of 4.6–4.8 cm²), were supplied by Thyssen Krupp, Germany. Nominal bulk compositions are given in Table I.

### Metal release exposure and irradiation

All samples were ground by 1200 grit SiC, ultrasonically cleaned in acetone and isopropyl alcohol for 5 min, dried with cold nitrogen gas, and aged (desiccator, room temperature) for 24 h to enable a defined surface oxide. The samples were then entirely immersed into the solution of interest in acid-cleaned glass vessels. The solution volume was 20 or 30 mL to completely immerse the coupons or disks and enable solution sampling after different exposure times (in the case of CoCrMo disks). The sample area to solution volume ratio was approximately 0.3 cm²/mL and accounted for in the metal release results presented in the unit of µg/cm². In all cases, triplicate samples and one blank sample (without metal samples) were exposed in parallel into phosphate buffered saline (PBS), pH 7.3 ± 0.1, and also in PBS with bovine serum albumin (BSA), 10 g/L (A7906, Sigma Aldrich), denoted PBS + BSA, pH 7.3 ± 0.1. PBS was composed of 8.77 g/L NaCl, 1.28 g/L Na₂HPO₄, 1.36 g/L KH₂PO₄, adjusted with 50% NaOH, pH 7.2–7.4 (all at analytical grade, from VWR or Sigma Aldrich, Sweden), and ultrapure water (18.2 MΩ cm, Millipore, Solna, Sweden). The albumin concentration was lower than present in human blood (about 40 g/L), though higher than approximately 0.5–1 g/L that is necessary to adsorb a monolayer of BSA on stainless steel and to significantly enhance the metal release from 316L. The 10 g/L BSA concentration was hence chosen as it requires less sample preparation prior to trace metal analysis, as compared with higher concentrations. All samples were irradiated (a Gammacell 1000 Elite, MDS Nordion) for 2 min and 13 s at a gamma irradiation rate of 0.124 Gy/s, resulting in a total irradiation dose of 16.49 Gy. Four milliliter of the 20 mL (316L) or 30 mL (CoCrMo) solution was directly sampled at 0 min (a few seconds) prior to irradiation and another 4 mL directly after irradiation (denoted 2 min and 13 s, or 0.035 h). The exposure was thereafter continued without irradiation for another 58 min (total exposure time of 1 h), after which the metal coupon/disk was separated from the solution. Since no agitation or temperature control was possible inside the gamma cell, all exposures were performed at room temperature and without agitation. Parallel nonirradiated reference samples were treated in the same way outside of the irradiation cell. This resulted in 12 independent CoCrMo samples.

### Table I. Nominal Bulk Alloy Composition of AISI 316L and the CoCrMo Alloy (wt %)

<table>
<thead>
<tr>
<th></th>
<th>Co</th>
<th>Cr</th>
<th>Fe</th>
<th>Mn</th>
<th>Ni</th>
<th>Mo</th>
<th>C</th>
<th>P</th>
<th>Si</th>
<th>S</th>
<th>N</th>
<th>W</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoCrMo</td>
<td>Bal.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AISI316L</td>
<td>N/A</td>
<td>16.6</td>
<td>Bal.</td>
<td>1.0</td>
<td>10.6</td>
<td>2.1</td>
<td>0.03</td>
<td>0.02</td>
<td>0.4</td>
<td>0.001</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*a N/A, no data available; bal., balance.*
12 independent 316L samples and eight blank solution samples, all sampled at three time points (resulting in 96 solution samples). After the 60 min exposure time, the coupons/disks were rinsed with ultrapure water, dried with nitrogen gas, and stored in a desiccator for postsurface analysis. The solution was acidified to a pH < 2, and analyzed with graphite furnace atomic absorption spectroscopy (GF-AAS) on iron (Fe), chromium (Cr), and nickel (Ni) for the 316L samples, and on cobalt (Co), Cr, and molybdenum (Mo) for the CoCrMo samples. All chemicals were of at least analytical grade, and all equipment and vessels were acid-cleaned by 10% nitric acid for 24 h, and rinsed four times with ultrapure water.

**Trace metal analysis**
Solution metal analysis was performed using AAS (AAAnalyst 800 instrument, Perkin Elmer), with graphite furnace mode. Calibration curves were based on at least four calibration standards and quality control samples of known concentration were analyzed regularly. The limits of detection, as determined by three times the highest standard deviation of the blank samples, were approximately 1 μg/L for all elements. Some sample concentrations were lower than the corresponding blank concentrations, or lower than the limit of detection denoted “<LOD.” In all cases, the released and nonprecipitated amount of measured metals in solution in the unit μg/cm² is based on the average concentration of three independent replicate samples with the corresponding blank concentration subtracted, multiplied by the initial exposure volume (e.g., 0.03, 0.026, and 0.022 L for CoCrMo disks after 0 min, 2 min and 13 s, and 1 h), and divided by the exposed coupon/disk surface area. The error bars in the figures show the standard deviation of three independent samples.

**Analysis of albumin size by dynamic light scattering**
In order to investigate whether albumin aggregates or changes its size upon irradiation or due to released metal ions, independent duplicate solution samples of PBS + BSA were prepared with or without the addition of 150 μg/L Co (from CoCl₂) and 5 μg/L Cr (from chromium(III) oxalate trihydrate), concentrations that approximately correspond to observed metal concentrations released during 60 min from the CoCrMo disks. The solutions were filtered by 0.2 μm polytetrafluoroethylene Acrodisc CR 25 mm syringe filters prior to irradiation. Some filtered solution samples were irradiated (as described previously), while others remained as references, that is, eight independent solution samples in total. After treatment, all solution samples were investigated within 1–6 h by means of two different dynamic light scattering techniques: Photon-cross-correlation-spectroscopy (PCCS; Nanophox, Sympatec GmbH, Germany) with a 632.8 nm laser, and nanoparticle tracking analysis (NTA) using a Nanosight NS300 instrument (Malvern, Uppsala, Sweden) with a 405 nm laser. Both measurements were conducted at 25°C, with the viscosity of water as input value. For PCCS, a control measurement of 23-nm latex nanoparticles gave reliable results and measurement of ultrapure water revealed only minor particle contamination.

For each sample in Eppendorf cuvettes (Eppendorf AG, Germany, UVette Routine pack, LOT No. C153996Q), duplicate sequential readings were performed for 120 s each. A non-negative least squares algorithm was used by the instrumental to determine the intensity size distribution. All 16 correlation functions were found acceptable, except one (that measurement was excluded), and all count rates were significantly (5–46 kcps) exceeding background values (ultrapure water, 0.5 kcps). For NTA, triplicate measurements with 60 s captures were performed. The intensity and particle concentration of all samples (6.9 ± 2.1 particles/frame) were significantly exceeding the background value (ultrapure water), for which 0.25 particles per frame were observed. The NTA 3.2 software was employed to analyze the data.

**Analysis of surface composition by means of X-ray photoelectron spectroscopy**
X-ray photoelectron spectroscopy (XPS) was used for surface compositional analysis of the CoCrMo disks and 316L coupons, and a nonexposed (ground, cleaned, and aged) disk/coupon for comparison. Two different locations were analyzed on two independent disks/coupons for each condition. Wide spectra and detailed spectra (20 eV pass energy) on Co 2p, Cr 2p, Mo 3d, for CoCrMo disks, and on Fe 2p, Ni 2p, Mn 2p, and Cr 2p for 316L coupons, as well as 0 1 s of each test item including carbon (C 1s) and N 1s were run using a Kratos AXIS UltraDLD X-ray photoelectron spectrometer (Kratos Analytical) with a monochromatic Al X-ray source (150 W) on areas approximately sized 700 × 300 μm². The information depth is about 5–10 nm. Compositional findings of the outermost surface oxide are in the following presented as the relative mass ratio of oxidized metals only. For 2p metals (Co, Fe, Ni, Mn, and Cr), the 2p 3/2 peaks were resolved into their metallic and oxidic peaks (Table II). For Mo 3d, the distinct metallic 3d 5/2 peak (228.2 ± 0.2 eV) as well as the metallic 3d 3/2 (231.3 ± 0.2 eV) peak were subtracted from the 3d peaks in order to obtain the oxidic fraction. C1s at 285.0 eV (denoted C1) was used as internal standard. For the disks/coupons exposed in PBS + BSA, also the atomic fraction of the nitrogen peak (399.5 ± 0.9 eV) to the sum of the oxidized carbon peaks (denoted C2, at 286.7 ± 0.2 eV, and C3, at 288.5 ± 0.3 eV) was calculated.

**Statistics**
To identify the significance of differences, a Student’s t test of unpaired data with unequal variance (KaleidaGraph v. 4.0) was employed between two different data sets of independent samples. In the case of different time points for the same disks/coupons, a t test of paired data was used. Differences are counted as significant when p < 0.05, with higher significance for a smaller p values.

**RESULTS**
**Metal release**
For CoCrMo, the released and nonprecipitated amount of Co and Cr in solution increased 1.6–3-fold with exposure time
Statistical differences in solution concentrations of Co and Cr were observed between nonirradiated and irradiated disks after the irradiation period (2 min and 13 s), Figure 1(a), but not after 1 h of exposure. No significant difference was observed between PBS without and with BSA.

Differences could not be calculated for Mo, since the concentrations were below the limits of detection after 0 and 0.03 h, however, the trends were similar as for Co and Cr. In the case of 316L, one of the three coupons showed in several cases higher release compared to the other two coupons. This resulted in large error bars and disabled any

**TABLE II. X-Ray Photoelectron Spectroscopy (XPS) Binding Energies and Assignments**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Binding Energy (eV)</th>
<th>Assignment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co 2p3/2</td>
<td>778.8 ± 0.16</td>
<td>Co metal</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>782.3 ± 2.3</td>
<td>Oxidized Co</td>
<td></td>
</tr>
<tr>
<td>Fe 2p3/2</td>
<td>707.1 ± 0.13</td>
<td>Fe metal</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>712.3 ± 1.2</td>
<td>Oxidized Fe</td>
<td></td>
</tr>
<tr>
<td>Cr 2p3/2</td>
<td>574.6 ± 0.16</td>
<td>Cr metal</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>577.7 ± 0.8</td>
<td>Cr(III)</td>
<td></td>
</tr>
<tr>
<td>Mo 3d</td>
<td>228.2 ± 0.2, 231.3 ± 0.2</td>
<td>Mo metal</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>232.6 ± 0.3, 235.8 ± 0.1</td>
<td>MoO3</td>
<td></td>
</tr>
<tr>
<td>Ni 2p3/2</td>
<td>853.0 ± 0.14</td>
<td>Ni metal</td>
<td>51</td>
</tr>
<tr>
<td>Mn 2p3/2</td>
<td>641.3</td>
<td>Oxidized Mn</td>
<td>51</td>
</tr>
<tr>
<td>N 1s</td>
<td>394.4 ± 0.07 (if no BSA)</td>
<td>Oxidized Mn</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>399.5 ± 0.9</td>
<td>metal nitride</td>
<td>53</td>
</tr>
<tr>
<td>C 1s</td>
<td>285.0</td>
<td>C–C, C–H bonds</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>286.7 ± 0.2</td>
<td>C–N, C–O bonds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>288.5 ± 0.3</td>
<td>C=C–O, O=C– bonds</td>
<td></td>
</tr>
<tr>
<td>O 1s</td>
<td>530.7 ± 0.3</td>
<td>Lattice oxide</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>531.8 ± 0.3</td>
<td>Hydroxide, hydrated, or defective oxide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>533.2 ± 0.3</td>
<td>Water, organic oxide</td>
<td></td>
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All binding energies are normalized to C 1 s at 285.0 eV.

(\(p < 0.05\) for most cases comparing 0 and 1 h), Figure 1(a). Statistical differences were observed between nonirradiated and irradiated disks after the irradiation period (2 min and 13 s), Figure 1(a), but not after 1 h of exposure. No significant difference was observed between PBS without and with BSA.

**FIGURE 1.** Released and nonprecipitated amounts of Co, Cr, and Mo in solution (aq—aqueous) from the CoCrMo alloy (a), and of Fe, Cr, and Ni from the 316L alloy (b) after 0 (few seconds), 0.035 (2 min 13 s), and 1 h of exposure at room temperature with or without irradiation (during the time period 0–0.035 h) in PBS (pH 7.3) or PBS and 10 g/L BSA (pH 7.3). Statistical differences: \(*p < 0.05\), \(**p < 0.01\), \(***p < 0.001\). non, nonirradiated; irr, irradiated; <LOD, below limit of detection.
statistical comparison. However, the time dependence (increased release with time) was stronger as compared to CoCrMo, due to a very low release during the first seconds of immersion (0 h), Figure 1(a,b). For Ni, significantly lower amounts of Ni in solution were observed after 1 h of exposure for the irradiated coupons in PBS as compared to the nonirradiated coupons, despite similar amounts after 2 min and 13 s for the same coupons, Figure 1(b). After 1 h of exposure, released amounts in PBS + BSA were 3–32-fold larger as compared to PBS, however, these differences were not statistically significant. Co was the main released element quantified in solution for the CoCrMo disks and Fe the dominant element released from 316L, even when normalized to their corresponding bulk content in Table I. Cr was the least released element quantified in solution for 316L, and Mo the least released element for CoCrMo, Figure 1. Cr was detected to a smaller extent for AISI 316L as compared to CoCrMo, Figure 1.

**Surface characterization**

XPS revealed a surface oxide composition of oxidized cobalt (Co 2p3/2 line at 782.2 ± 2.3 eV), chromium (at 577.7 ± 0.8 eV, corresponding to trivalent chromium), and molybdenum (with two main peaks at 232.6 ± 0.3 and 235.8 ± 0.1 eV corresponding to MoO3) for CoCrMo, and of oxidized iron (712.3 ± 1.2 eV), chromium (at 577.3 ± 0.8 eV, corresponding to trivalent chromium), and manganese (641.3 eV, only for the abraded reference coupon) for 316L, Table II. The binding energy positions were independent of irradiation or exposure to PBS. The ratio of Co, Cr, and Mo in the surface oxide of the abraded reference disk corresponded nearly to the bulk composition, Figure 2(a). Upon immersion in all solutions for one hour, the surface oxide became enriched in Cr. This enrichment (coupled with a Co depletion) is expected from earlier studies. A small, but statistically significant Cr enrichment and Co depletion was also observed for disks exposed to PBS + BSA (nonirradiated) as compared to PBS (both nonirradiated and irradiated), Figure 2(a). This is also in agreement with previous observations. Mo was statistically significant enriched in PBS + BSA as compared to PBS (for irradiated disks), Figure 2(a). No difference in the ratio of metal peaks to oxidized metal peaks (0.4 by mass) was observed between the differently exposed CoCrMo disks. The ratio was though higher as compared to the abraded reference disks (0.3 by mass), which indicates a thinner oxide after exposure. Due to individual differences among the coupons, no statistical differences between the reference coupon and the exposed coupons, the irradiation conditions, or the solutions, were observed for 316L, Figure 2(b). However, calculated ratios of metal peaks to oxidized peaks indicated a statistically significant (p < 0.05) thicker oxide for 316L coupons exposed to PBS as compared to the abraded reference coupons (0.24 and 0.29 by mass as compared to 0.35 of the reference), while the oxide of coupons exposed to PBS + BSA seemed to be thinner (though not statistically different, 0.43 and 0.47 by mass). Small, but statistically significant (p < 0.05), differences were also observed for the irradiated coupons as compared to nonirradiated 316L coupons in both PBS and PBS + BSA. This indicates in both cases a thinner oxide in the case of irradiation.

The measured atomic ratio of N/(C2 + C3) was slightly lower compared with the theoretical ratio of 0.48 of BSA41 (0.41 ± 0.1 in nonirradiated and in irradiated PBS + BSA for rinsed CoCrMo disks, and 0.35 ± 0.04 in nonirradiated and in irradiated PBS + BSA for rinsed 316L coupons).

**Effects of gamma irradiation on the size of albumin**

PCCS and NTA measurements were conducted of filtered (0.2 μm) irradiated and nonirradiated PBS + BSA solutions in order to investigate whether the applied gamma irradiation induced albumin aggregation, which could influence the measured amount of released metals in solution or the metal release process. Since previous studies showed the ability of released metal ions in solution to cause albumin aggregation, the same conditions were investigated for
albumin solutions containing 150 μg/L Co and 5 μg/L Cr. These concentrations are similar to their corresponding released levels in solution after 1 h for the CoCrMo alloy. Figure 3 shows the hydrodynamic size distribution of albumin, measured by PCCS (a) and NTA (b). As seen in the figure, no significant difference in albumin size was observed either upon irradiation or in the absence or presence of these trace metal concentrations. A slight change in size, visible by an additional peak at 13 nm, was detected by both PCCS and NTA measurements for irradiated samples as compared to nonirradiated solution samples. However, this difference was not statistically significant. Albumin self-aggregates at all sizes below the cut-off value of the membrane filter (200 nm), Figure 3(b), but is mostly present as a monomer (theoretical triangular structure of 8 × 8 × 3 nm³), Figure 3(a).

**DISCUSSION**

Radiotherapy for cancer treatments is usually given at daily fractions up to 2 Gy, 3–5 times per week, with a total irradiation dose of 10–145 Gy. For high risk patients, radiotherapy at a total dose of 10–20 Gy may also be given to prevent heterotopic bone formation, a complication for hip arthroplasty, which treats the condition equally pre- and postoperatively. The total irradiation dose used in this study is hence highly relevant for such treatments, however, the dose rate is higher as compared to what is used in radiotherapy.

Irradiation-induced radicals can be both reductive and oxidative, and can therefore theoretically both result in reductive or oxidative dissolution of the surface oxides and oxidative dissolution (corrosion) of the metal beneath the (damaged) surface oxide. Despite the relatively low total irradiation dose, we observed that the radiation slightly influenced the extent of metal release from CoCrMo (increased directly after irradiation) and in the case of AISI 316L, both the extent of metal release (decreased Ni after 1 h) and oxide thickness (reduced upon irradiation). This can be interpreted as an effect of oxidation of the alloy surface caused by the gamma irradiation that may result in surface passivation (stabilization of surface oxide). Passivation means in this context a further stabilization of the barrier properties of the surface oxide even though the surface oxides of CoCrMo and 316L also were passive prior to irradiation, as indicated by generally very low amounts of released metals. This passivation effect is in agreement with an early study on AISI 304 where significantly higher irradiation doses and temperatures were investigated. Passivation is known to initially cause a higher release of the least stable elements of the surface oxide, Fe in the case of AISI 316L and Co in the case of CoCrMo, while it decreases the overall amount of metal release after improved passivation. Both joint prostheses and dental prostheses are partially exposed to friction, which may result in a partial or complete destruction of the surface oxide, similarly to the abrasion procedure in this study applied 24 h prior to the irradiation exposure. It can hence be assumed that the surface of implant parts exposed to friction would face a new passivation each time when irradiated, with an initially increased amount of metal release, while surfaces of implant parts that are not exposed to friction and therefore maintain their passive surface oxides would not experience any increased metal release upon irradiation treatments. Irradiation-induced metal release and passivation of implant parts that are exposed to friction requires further investigations—both directly after abrasion/friction and after long-term immersion, or their combination. Furthermore, implants that have a damaged surface oxide or on-going corrosion, for example, due to misalignment, galvanic corrosion (due to different metallic implant materials in contact), or an on-going infection or inflammation, might be at risk to release elevated amounts of metals upon irradiation treatments. This might be particularly important for patients with on-going or known hypersensitivity reactions to metals, and requires further investigations.

That albumin was able to increase the extent of metal release from AISI 316L and change the surface oxide composition (however, not statistically significant in this study), while no such effect was observed for CoCrMo, is in agreement with previous studies. It has been speculated...
whether the lack of increased metal release from CoCrMo in the presence of albumin is related to a different protein-surface interaction, as compared to AISI 316L, or due to an increased metal-induced protein aggregation that may result in an underestimation of the amount of released metals in solution from CoCrMo.\textsuperscript{30,62} However, for the low concentrations of released metals in this study and the short time period of exposure to gamma irradiation, no protein aggregation effect was discerned. This observation further suggests that the lower effect of irradiation on the metal release in albumin-containing solution as compared to PBS without albumin for AISI 316L most probably was not due to albumin aggregation.

The metal release rate from CoCrMo was highest during the first few seconds of immersion. A similar trend has for instance been shown for AISI 316L powder in physiological solutions.\textsuperscript{50} However, released amounts of metals after a few seconds from the 316L coupons of this study were not measurable. Decreased metal release rates with time further show the importance of a rapidly passivating surface oxide that adjusts to the new environment and results in lower extent of released metals. However, it could also mean that repeated destruction of the surface oxide (e.g., by friction due to joint movements or chewing) would result in relatively high amounts of released metals during the first seconds following the friction event.

Further studies should therefore investigate repeated friction in combination with fractionated irradiation treatments at conditions of relevance for radiotherapy (≤2 Gy per occasion).

CONCLUSION

The amount of released metals from biomedical stainless steel AISI 316L and CoCrMo in physiologically relevant fluids (PBS with and without 10 g/L BSA at pH 7.3) was investigated as a function of gamma irradiation with a total dose of 16.5 Gy as a measure of relevance for radiotherapy. The following main conclusions were drawn:

1. Generally, the effect of irradiation (total dose of 16.5 Gy) was small, but detectable in some cases. It is therefore expected to be only clinically relevant in cases where other factors such as friction and corrosion, possibly synergistically, exist.

2. Irradiated CoCrMo disks released higher amounts of metals directly after irradiation (during the first 2 min and 13 s) as compared to nonirradiated CoCrMo disks. No differences in released metals were observed during the concomitant nonirradiated exposure up to 60 min for the same disks. This was mainly probably related to an irradiation-accelerated surface passivation effect.

3. No significant differences in metal release among the different investigated conditions were observed for 316L due to individual differences among replicate coupons, except that nickel release was lower after 1 h of exposure in irradiated coupons in PBS as compared to nonirradiated coupons (despite similar or higher levels directly after irradiation, 2 min and 13 s, of the same coupons). This indicates an irradiation-accelerated surface passivation effect.

4. The presence of albumin in solution resulted in a reduced surface oxide thickness for 316L, coupled to nonsignificant increased amounts of released metals and a nonsignificant enrichment of chromium in the surface oxide. No such effects were observed for CoCrMo except for a slight enrichment of chromium in the surface oxide in the presence of albumin.

5. Most metals were released into solution from CoCrMo during the first seconds of immersion, independent of whether they were exposed to radiation or not.

6. No albumin aggregation in solution was observed at the conditions of this study either in the presence or absence of metal ions or irradiation.

ACKNOWLEDGMENTS

Docent Susanna Wold, previously at KTH, and Professor Carina Johansson, Gothenburg University, Sweden, are highly acknowledged for valuable discussions. Maria-Elisa Karlsson, Dr. Gunilla Herting, at Div. Surface and Corrosion Science, KTH, and Dr. Neda Mazinanian, previously at Div. Surface and Corrosion Science, KTH, are gratefully acknowledged for help in supervision and experiments

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