Cell-Induced Damage of Total Joint Implant Alloy Oxide Layers

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Abstract

Cobalt-Chromium alloy is commonly used in total joint arthroplasty (TJA). Several studies have investigated evidence of inflammatory-cell-induced-corrosion (ICIC) causing pitting in TJA retrieved implants. Others have determined that placing orthopedic alloys into lower pH solutions will increase the rate of corrosion. We have determined that electrochemical potential and corrosion rates of human knee synovial fluid show a variation greater than an order of magnitude. This means there is going to be a significant variation between a patient's local environment of the TJA implant and may affect how macrophages interact with alloy oxide layers. Knee disability can be quantified by using the Knee Injury and Osteoarthritis Outcome Score for Joint Replacement (KOOSJR). In order to determine predictive measures of patient outcomes, we plan to measure the electrochemical properties of patient implants and associate them with these KOOSJR scores. In addition, we plan to further investigate the effects and extent of macrophage-mediated damage to alloys when under inflammatory conditions. The current results are inconclusive, but suggest that there is a relationship between these parameters and patient outcomes and encourage further investigation of the mechanisms at play.

Introduction

Total knee arthroplasty (TKA) is one of the most common joint replacement procedures performed; however, complication rates are common and difficult to predict.

According to a meta-analysis performed by Shau et al. (2015), complications of TKA most commonly lead to difficulty navigating stairs, mobility concerns, and emotional distress. Finding clinically relevant indicators regarding whether a patient will respond appropriately to their implant material can prevent these complications in the long term. Additionally, this mitigates costly repair surgeries associated with implant corrosion and subsequent failure. The goal of this proposal is to investigate the electrochemical and cellular mechanisms causing changes to the oxide layer of implant alloys used in total knee arthroplasty implants. We hypothesize that a subset of these patients has a local inflammatory response to the implants generated by metal ions and macrophages and that a patient's synovial fluid electrochemical potential (Fig 1) plays a role in this reaction.

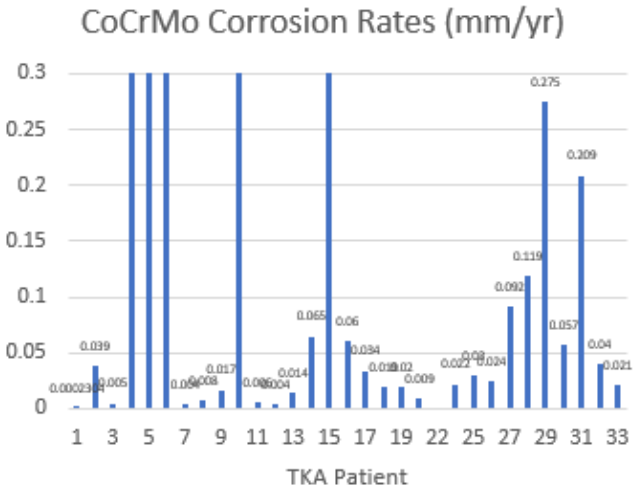

Figure 1. Comparison of corrosion rates of a set of 33 patients who received a CoCrMo TKA. Synovial fluid was taken at time of surgery.

We propose to measure the electrochemical potential and corrosion rate of 100 patients undergoing a primary TKA and follow them for one year after surgery comparing their outcome measures to their electrochemical profile to see if a difference in patient-reported outcome is determined. To further understand the cellular mechanism of inflammatory-

cell-induced-corrosion (ICIC) we also propose measuring the cellular uptake and surface damage of TKA implant alloy disks cultured with macrophages and lymphocytes for 30 days. Our lab's ICIC *in vitro* model has measured significant cellular uptake of cobalt and chromium (Fig 2) and surface damage to these disks (Fig 3) and believe a further study of ICIC damage with the addition of lymphocytes is needed to determine if these reactions are clinically significant.

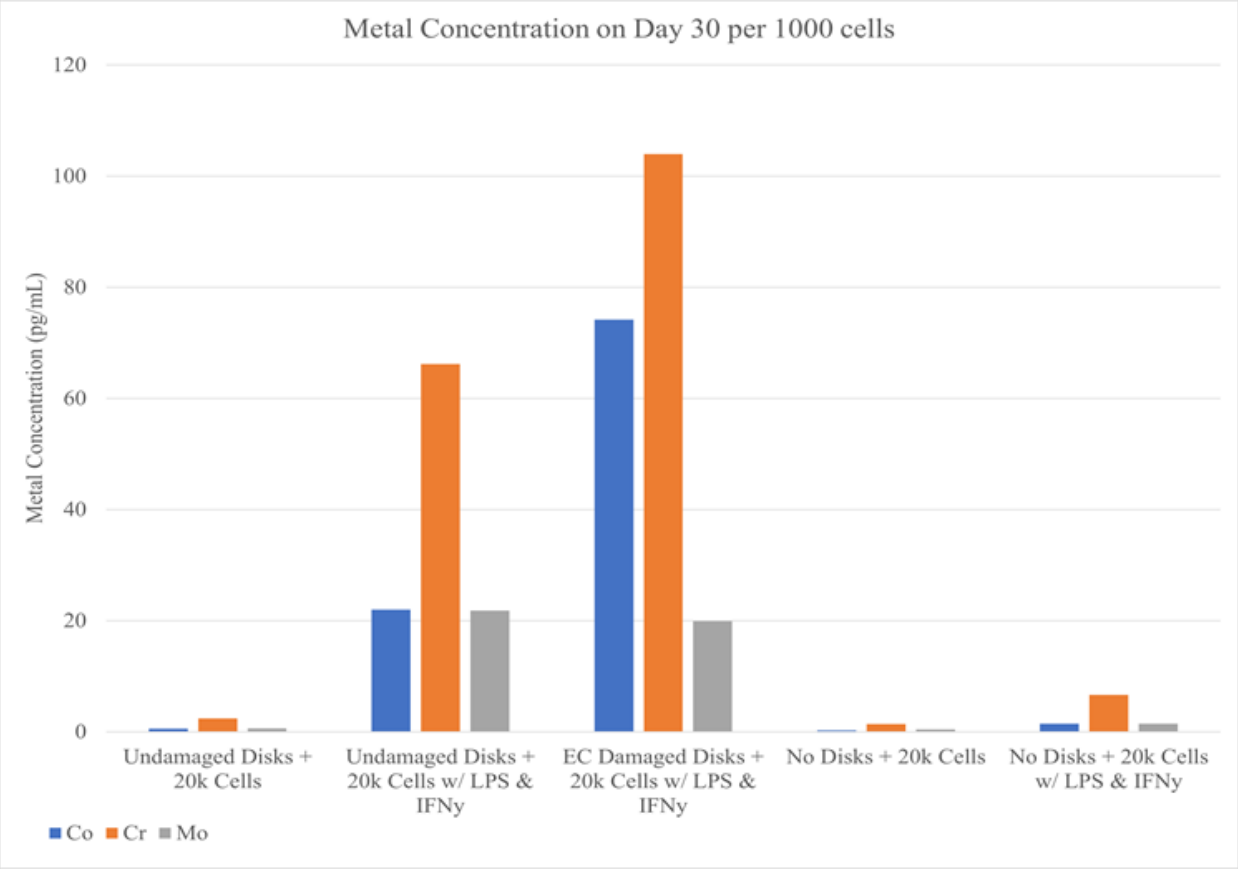

Figure 2. ICP Mass Spectrometry Analysis of digested cells with 100 cells per group. *EC = Electrocautery*

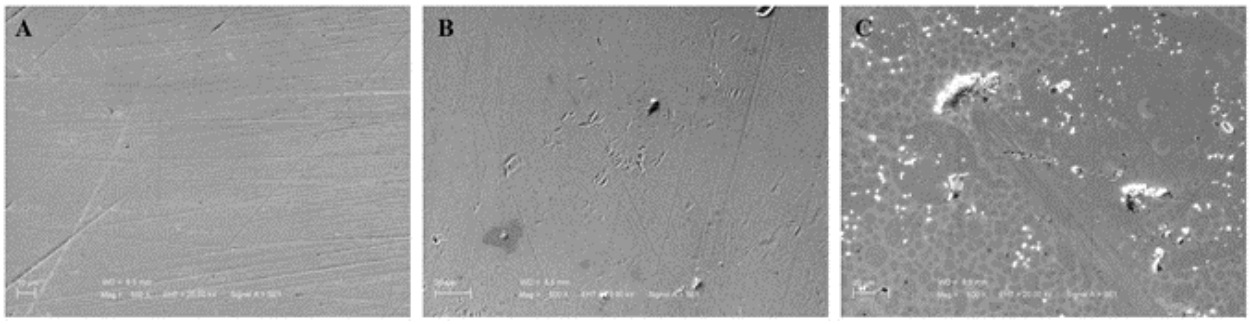

Figure 3. Microscopic imaging of CoCr disk surfaces which are (a) undamaged containing medium, (b) undamaged with standard cells, or (c) undamaged with activated cells showing multiple pits in the oxide layer.

Methods

The study is two-pronged, consisting of an electrochemical analysis and a cellular analysis. In order to study the electrochemical kinetics involved in corrosion of these metal alloy oxide layers, samples were taken from patients at time of their primary TKA, where up to ten milliliters of synovial fluid were extracted with a 16-gauge syringe. The syringe was stored in an incubating chamber at 37C and the studies were performed immediately to minimize the effects of oxidation from exposure to air. Approximately 500 microliters were pipetted into a small-volume electrochemical cell. In contact with the fluid was a 3-electrode system. A cylindrical rod of either titanium or cobalt chromium was selected for the working electrode, a double-junction silver-silver chloride electrode was selected as a reference, and a platinum wire was included as the auxiliary electrode to prevent charge buildup at the reference. The system was placed within a faraday cage and wired to a potentiostat in order to simulate *in vivo* electrical conditions. Open circuit potential (OCP) was first measured over the course of an hour and the steady-state potential was determined by extrapolation. Once the OCP is determined, a linear potentiometry experiment is conducted where the voltage is driven away from the OCP in either direction to induce either an anodic or cathodic current. The polarization resistance of the electrode was calculated as the inverse of the voltage-current plot as a method of determining corrosion rate. Patients were contacted three months post-operation to discuss their

outcomes, and the KOOSJR scores calculated from those conversations were correlated with the electrochemical results done previously.

To better understand how the chemical profiles of ECIC and ICIC differ on orthopedic implants, the implant alloy disks undergoing the in vitro study will be analyzed under Scanning Electron Microscopy (SEM) and Energy Dispersion X-ray Spectroscopy (EDS) to identify the differences in damage patterns and chemical makeup. To address these questions, in vitro methods will be performed using IC-21 murine peritoneal macrophages activated with LPS and IFN-y on disks made of CoCr and Ti6Al4V orthopedic implant materials (Heise, 2020). Select disks would also be intentionally damaged using fretting scratch on the surface of the disks to varying depths. Our hypothesis is that the addition of lymphocytes that direct macrophages will result in more metal particles from the CoCr and Ti6Al4V disks being taken up by cells than we found with macrophages alone. Given this hypothesis, our second specific aim will be: Evaluate the differences in the surface chemical profile and amount of metal ingestion by lymphocytes interacting with macrophages and cultured on CoCr and Ti6Al4V disks in a 24 well plate. The alloy disks will then be examined after 30 days to assess degrees of oxide layer fretting damage, using XPS and SEM.

Results

For each metal, the corrosion rates were calculated and compared to the KOOSJR scores determined 3-months to 1-year later. The patients showed a consistent range of corrosion rates with the exception of a small group of outliers in which the corrosion

kinetics were calculated to be one to two orders of magnitude larger than normal. These “outliers” for each type of metal were compared to the rest of the cohort to determine if their KOOSJR scores varied.

Surprisingly, there was a statistically-significant difference for titanium corrosion rates, but in the opposite direction to the original hypothesis. Patients with higher predicted corrosion rates actually reported better outcomes when compared to their counterparts. The implications of this are still not totally clear. Currently, about 50% of the necessary patients have been recruited and surveyed, and more will be needed to achieve appropriate power for the study.

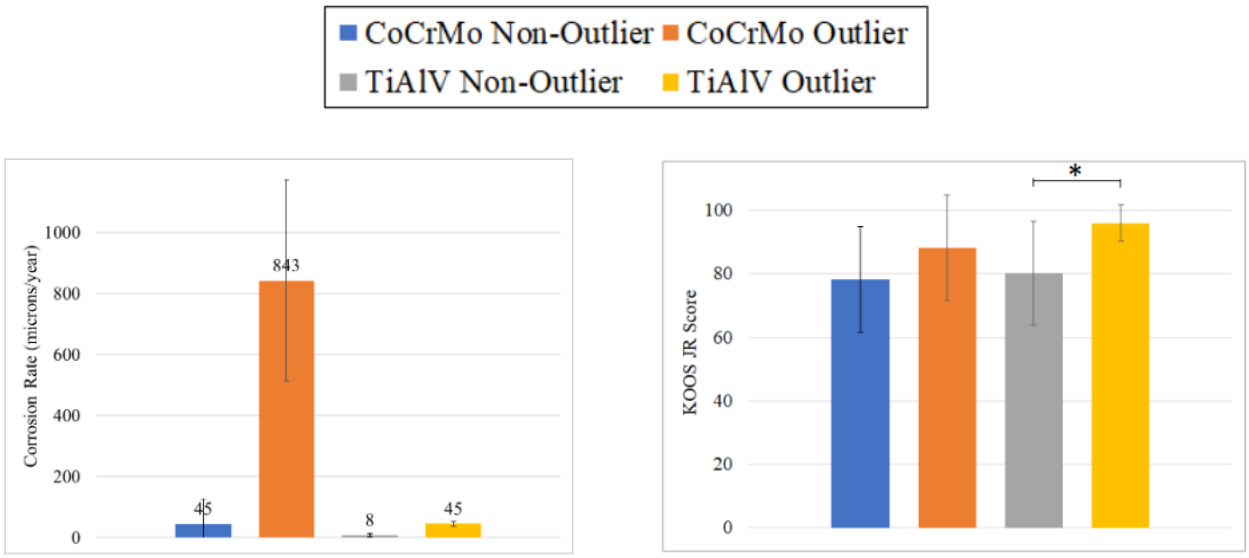

Figure 4. (left) the corrosion rates of outliers and non-outliers for each metal, and (right) the associated KOOSJR scores for those groups.

Discussion

In conclusion, we found that large variations exist between patients in regards to the electrochemical properties of their synovial fluid and confirmed that there is a relationship between those properties and patient outcomes. The results were in opposition to the original assumption that corrosion was predictive of poor outcomes and

more patients are needed in order to further elucidate the mechanism behind this relationship. An interesting relationship was also found as an aside, in which the volume of synovial fluid collected strongly correlated with a positive outcome several months later. This was only tangentially related to the study, but does warrant additional investigation to understand why such large variations in synovial fluid volume exist between patients.