Exploring Possible Adverse Effects on Cardiac Function Following Chronic Exposure to Metal Wear Debris from Total Hip Arthroplasty

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INTRODUCTION:

Total hip arthroplasty (THA) is an effective surgical treatment for end-stage osteoarthritis, with over 450,000 procedures performed annually in the U.S. While implant designs have evolved, most still rely on metal components that degrade over time. Degradation products (DPs), including cobalt ions (Co I), chromium ions (Cr I), and cobalt-chromium-molybdenum particles (CoCrMo P), have been implicated in adverse local tissue reactions; however, systemic deposition of wear particles remains an underappreciated clinical concern. In a previous postmortem study, cobalt and chromium wear debris were identified in the liver, spleen, and, critically, the myocardium of patients with orthopedic implants. Furthermore, a recent case report describes a patient requiring cardiac transplantation due to cobalt-induced cardiomyopathy stemming from a metal implant, with histological confirmation of cobalt in myocardial tissue. As such, it is hypothesized that implant DPs may potentially induce cardiac toxicity. This study investigates the cardiac impact of implant-derived DPs using four clinically translatable models: (1a) Static *in vitro* exposure using H9C2 myoblasts, (1b) dynamic *in vitro* exposure using a microfluidic perfusion system, (2a) human stem cell-derived cardiomyocytes, and (2b) an *in vivo* murine model simulating chronic systemic exposure.

METHODS:

The static (1a) H9C2 myoblast cells were exposed to Co I, Cr I, and CoCrMo P across concentrations ranging from 0.25 ppm to 50 ppm over 1, 3, 5, and 7 days. Cytotoxicity and inflammatory responses were assessed using viability and nuclear integrity assays, as well as gene expression profiling of metabolic and contractile markers. To replicate vascular perfusion (1b), myoblasts were seeded in a microfluidic chamber connected to a peristaltic pump, allowing continuous media flow. Cells were exposed to CoCrMo P to model chronic circulatory exposure to DPs. Human contractile cardiomyocytes (2a) were differentiated from human GM1-induced pluripotent stem cells (iPSCs) and then treated with Co I at 0.25–50 ppm to assess electrophysiologic changes, through contraction rate and calcium imaging. Adult mice (2b) received an intra-articular injection of 50 ppm CoCrMo P into the synovial joint to simulate particle generation from a THA implant. 45 days following exposure, myocardial tissue was collected for histopathologic assessment (H&E) and immunohistochemical staining to evaluate inflammatory infiltration and particle deposition.

RESULTS:

In static cultures (1a), myoblast viability declined from 93.18% at 0.25 ppm to 64.12% at 50 ppm following CoCrMo P exposure. After 7 days of exposure, even low concentrations reflective of clinically observed ion levels (0.25 ppm) resulted in reductions in cell viability of 86.02% for Cr I and 84.90% for Co I. Nuclear integrity and DNA damage were noted, particularly in CoCrMo P-treated cells. Gene expression analysis revealed downregulation of metabolic and contractile markers, Cox6a2 and PDE4A, respectively. In the microfluidic system (1b), dynamic exposure to CoCrMo P resulted in increased nuclear fragmentation and cellular toxicity. iPSC-derived cardiomyocytes (2a) demonstrated diminished spontaneous contraction rates, disrupted calcium signaling, and increased troponin concentration following metal exposure. *In vivo* mouse models (2b) injected with CoCrMo particles showed increased CD3-positive T-cell infiltration and potential indicators of particle deposition in cardiac tissues.

DISCUSSION AND CONCLUSION: Our findings suggest that implant-derived Co I, Cr I, and CoCrMo P may impair cardiac cell function. Elevated cytotoxicity in both static and dynamic models likely stems from oxidative stress initiated by reactive oxygen species (ROS), which disrupt metabolic pathways and impair DNA integrity. The downregulation of Cox6a2 and PDE4A implicates mitochondrial dysfunction and altered contractility. In iPSC-derived cardiomyocytes, disrupted calcium flux and diminished contraction rates further suggest interference with excitation-contraction coupling, possibly through ROS-mediated calcium dysregulation. Histologic evidence of CD3+ T-cell infiltration in murine myocardium points to an immunologic response to particle exposure. These findings advance the understanding of cardiotoxicity at a cellular and tissue level and support the use of stem cell and microfluidics models in implant toxicity research. Clinically, this work highlights the potential for subclinical myocardial injury in patients with metal implant components and supports incorporating cardiac monitoring and metal ion screening into long-term care protocols.

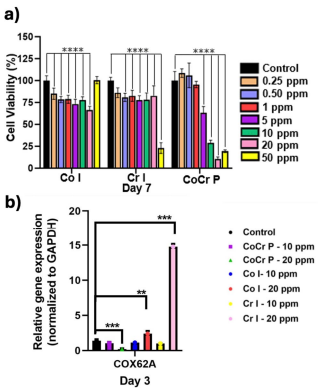

Figure 1. *In vitro* toxicity and gene expression: a) depicts cell viability for H9C2 myoblasts following 7-day treatment exposure. b) gene expression upregulation of the COX6A2 following 3-day treatment exposure

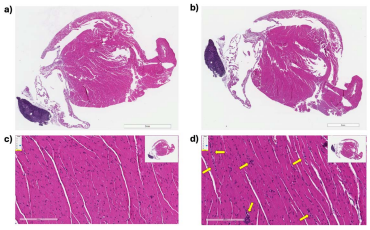

Figure 2. Mouse heart tissues - H&E stained: a) is the non-treated (control) mouse heart stained with H&E. b) is the 50 ppm CoCrMo P treated mouse heart, stained with H&E. c) depicts an H&E-stained control mouse heart biopsy taken at 20x magnification for further detail and analysis. d) H&E-stained 50 ppm CoCrMo P treated mouse heart tissue taken at 20x magnification. The yellow arrows point to concerning areas within the stained tissue.

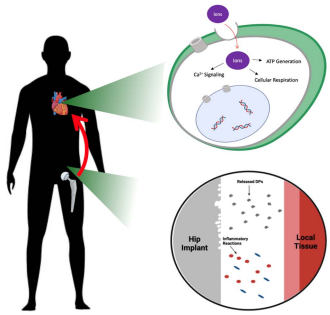

Figure 3. Mechanism: Implant degraded products (DPs) local to the prosthetic site are believed to travel systemically via vascular pathways to systemic organs such as cardiac tissue. DPs can cause cell toxicity and DNA damage, as well as cardiac-specific effects such as arrhythmia and gene dysregulation that may lead to cardiac injury.