Effects of implant-derived metal debris on the systemic local immune cell composition

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INTRODUCTION:

Modern implants enable painless mobility and thus a high degree of quality of life even in advanced age. Crucial for the long-term success of artificial joint reconstruction is the firm integration of the endoprosthesis into the surrounding mineralized tissue and requires continuous active bone remodeling [1]. Implant failure is often associated with impaired bone homeostasis, leading to aseptic loosening and revision surgery, which usually results in inferior outcome to the initial surgery. The mechanism behind implant failure could be triggered by local inflammatory responses to implant-related wear products and involves both bone marrow cells and surrounding bone marrow. Long-term metal exposure leads to inflammation mediated and maintained by bone marrow immune cells [2]. This chronic inflammatory response is representative of many immunological functions of the bone marrow. Our objective was to investigate the effects of implant-induced metal exposure on bone remodeling and bone marrow.

METHODS:

The study was approved by the local ethics committee (EA2/089/20); all donors provided written informed consent. Multi-metal quantification was performed by inductively coupled plasma mass spectrometry (ICP-MS) in whole blood, synovial fluid, and bone marrow samples from patients who underwent primary replacement (control patients) or revision knee or hip surgery (implant patients). In addition, spatially resolved multi-element quantification was performed in bone and bone marrow biopsies using synchrotron-based X-ray fluorescence (XRF) spectroscopy [3]. The effects of the degree of metal exposure on cytokine and immune cell profiles in the samples was performed using standardized multiplex ligand assays (human cytokine antibody array, G-Series, RayBiotech) and standardized 10-color panels (Duraclone™ basic phenotyping and T-cell subsets, Beckman Coulter), respectively [4]. In parallel, different scenarios of metal exposure were simulated in a microfluidic 3D bone-on-a-chip system [3] and the resulting biological effects were compared with the results of the ex vivo analyses.

RESULTS:

Multi-metal analyses detected increased systemic and local concentrations of at least one of the implant-related metals in biopsies from 57% of patients (without metal-on-metal joint surfaces). Spatially resolved XRF imaging showed that there is significant accumulation of cobalt, chromium, titanium, and zirconium particles in the peri-implant bone marrow, depending on the composition and design of the implant. Basic immune-phenotyping of the blood, synovial, and bone marrow samples showed a correlation between elevated local metal levels and a shift in B- and T-cell. Within the T-cell population, CD4+ T cells are significantly elevated in exposed bone marrow samples compared with controls, which may indicate a hypersensitivity reaction to the implant material in some patients. This characteristic distribution of implant metals accumulating in the bone marrow matrix and trabecular bone and its effects on immune cell composition could also be replicated in the human 3D in vitro model.

DISCUSSION AND CONCLUSION:

Using the unique combination of ICP-MS and spatially resolved synchrotron XRF analysis, we quantified the release of endoprosthesis metals in synovial fluid, bone and bone marrow behind the implant capsule and showed that these metals play a specific role in the pathogenesis of aseptic bone loss. Our findings suggest considering bone and bone marrow as the relevant tissues for pre-clinical testing and post-clinical risk-benefit evaluation of orthopedic biomaterials.