Correlation of the chemical signature of periprosthetic macrophages with the CoCr head wear rate in hip resurfacing

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Introduction

- The release of CoCrMo wear debris and/or corrosion products remains a major concern of total hip arthroplasty (THA) procedures, often leading to implant failure due to osteolysis or lymphocyte dominated adverse local tissue reactions (ALTRs). The pathways leading to ALTRs are not well understood.
- Our previous work has shown Fourier transform infrared micro-spectroscopy (FTIR) is a useful tool to add complementary chemical information to the investigation of histopathological features[2]. Most notably, we found particle laden macrophages can exhibit a variety of chemical signatures depending on the type of bearing material, presence of modular junctions, and extent of damage related to both.
- Using principal component analysis (PCA) we have shown that macrophages from tissue retrievals associated with metal-on-metal (MoM) hip resurfacings (HR) exhibit an entirely different Infrared (IR) signature with wide scattering compared to those associated with metal-on-polyethylene (MoP) THAs (see ORS 2021 recap below).

Study objective:

The goal of this work was to 1) characterize differences in the IR spectrum of periprosthetic tissue samples--specifically of particle laden macrophages--from patients with failed MoM-HR, and 2) determine the relationship between macrophage chemistry and CoCrMo alloy wear and wear rate.

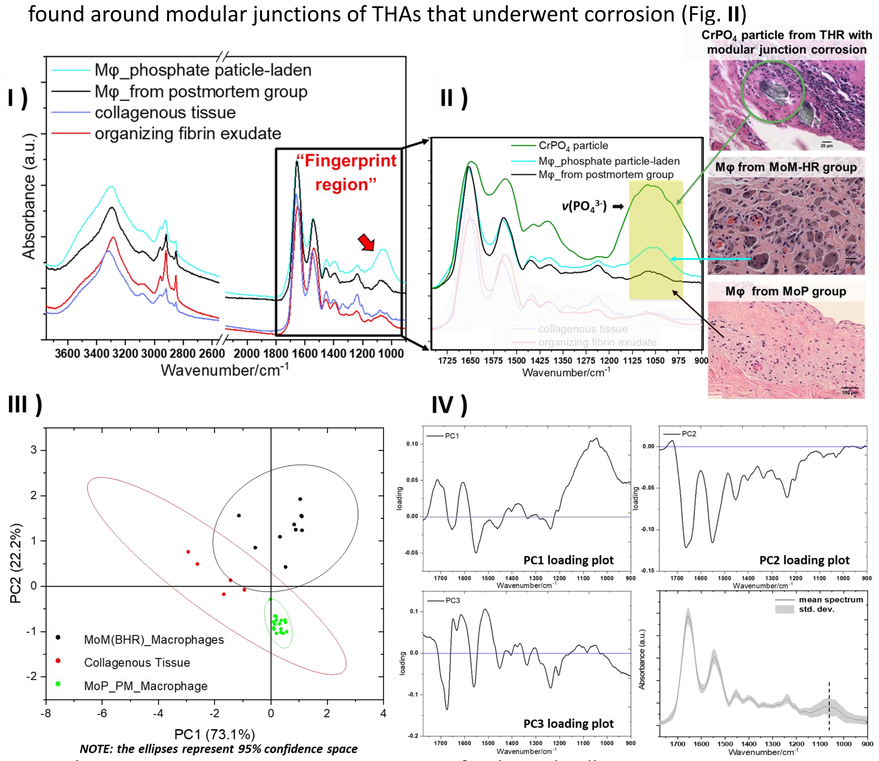
Methods

- Surgically retrieved hip pseudo-capsule tissue samples from 15 MoM-HR patients were analyzed. These samples were chosen to exclude the impact of corrosion products on macrophages due to the lack of modularity.
- Main reasons for revision were pain, elevated metal ions, ALTR, and aseptic loosening. The mean time in situ was 4.8 years (1.5, 10.4). Wear of the metal heads was assessed using an optical coordinate measuring machine (OrthoLux, RedLux). Acetabular liners were not available for the majority of cases. Thus, femoral head wear rate was used as a proxy-measure for total wear rate. Cases were categorized as well-functioning (<1mm^3/yr), high (1-10mm^3/yr), and excessively (>10mm^3/yr) wearing.
- Two serial, 5-µm sections of formalin-fixed, paraffin-embedded tissue were made. One section was stained with H&E for histological evaluation. The second section was analyzed using an Agilent Cary 670/620 FTIR imaging system.
- FTIR data were collected at a spectral resolution of 4 cm^{-1} with a spectral range of 3750-850 cm^{-1}. Transmission mode was used with an aperture size ~25 µm. For each single point measurement, 64 interferograms were collected, and ratioed against a 128 co-added scans of reference background.
- Three to four macrophage spectra and one connective tissue spectrum were recorded from each sample. Finally, data were vector normalized within the 1725-1596 cm^{-1} range, and the extended multiplicative signal correction was performed on the entire spectral dataset[3]. The calculated value of wear rate and total wear volume were incorporated to the spectral datasets to perform PCA and further data visualization using Python-based custom-made programs.

Results

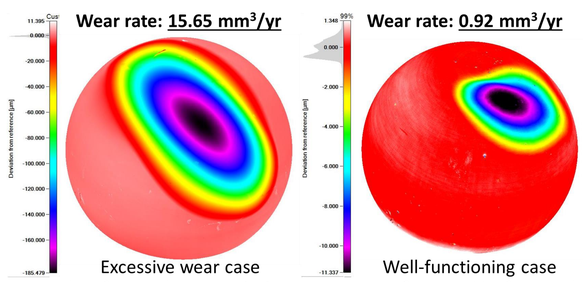
Recap from What We've Learned from ORS 2021

- Previously, we analyzed periprosthetic tissue of two groups: *1)* surgically retrieved MoM HR, and *2)* postmortem retrieved MoP THA.
- The MoM HR group by design exhibited only CoCrMo wear, and no corrosion due to the lack of modularity, while the postmortem retrieved THA group can be considered as well-functioning, and additionally only cases with no modular junction corrosion were chosen (thus, only negligible CoCrMo release).
- The MoM HR group exhibited a pronounced presence of greyish particle-laden macrophages within the tissue.
- In both groups, the most affected IR spectral region is associated with nucleic acids, carbohydrates as well as different types of phosphates (i.e., 1145-950 cm^{-1}).
- Clusters from HCA have been assigned solely based on their spectral signatures, particularly from the 'fingerprint region', where most of the biochemical information is encoded (Fig. **I**&**II**).
- Particle-laden macrophages/foreign body giant cells in all MoM tissue samples (N=5) exhibited a strong absorbance in the phosphate region ($\nu(PO_4^{3-})$) compared to macrophages with minimum metallic particle burden in the MoP group (N=5).
- This peak occurred with different intensities depending on specific cases and cells.
- The intensity of this "dome-shaped" characteristic peak was highest in the two MoM cases with the highest wear rates.
- In fact, this peak indicated a similar chemical signature compared to $CrPO_4$ flakes often found around modular junctions of THAs that underwent corrosion (Fig. **II**)



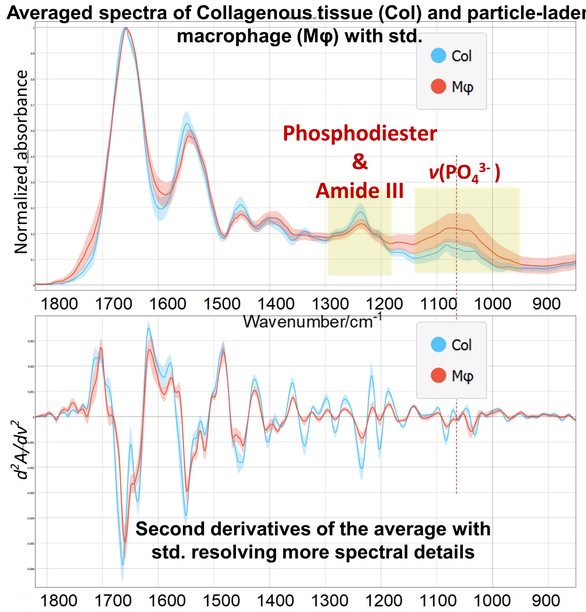
- A preliminary group comparison on spectra of Mφs and collagenous tissue using PCA showed that the average spectra of Mφs extracted from the postmortem MoP group form a dense cluster, while Mφs of the MoM group exhibited **wide scattering**, but were still distinct from MoP group(Fig. **III**).
- Scattering likely occurred due to the variation of **particle burden in the MoM group**. The first two principal components (PCs) explain more than 95% of the variance. PC1 presented a strong weight in the nucleic acid area, and PC2 appeared to be negatively corelated to chemical changes of the collagen matrix (Fig. **IV**).

1)



➢ Example of two characteristic wear scars of MoM-HR femoral heads: The elongated scar suggests *edge loading*, and the smaller round wear scar indicates *normal wearing conditions*.

2) **Averaged spectra of Collagenous tissue (Col) and particle-laden macrophage (Mφ) with std.**



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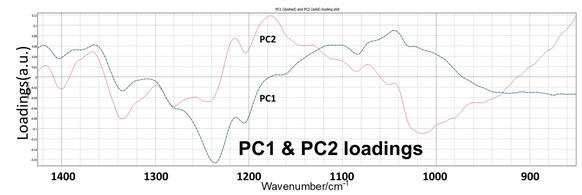
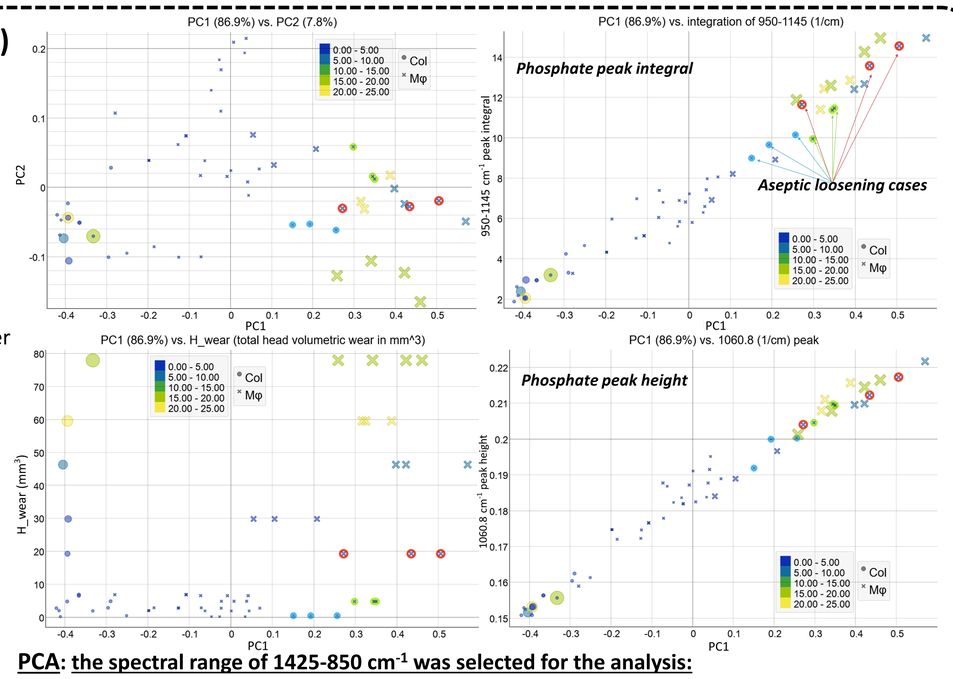


High PC1 score suggest higher absorbance in nucleic acids/ phosphates, while lower in amide III/phosphodiester region

4)

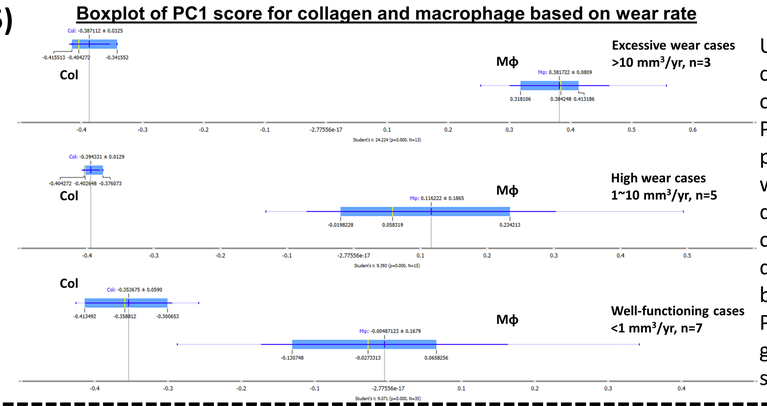


PCA: the spectral range of 1425-850 cm^{-1} was selected for the analysis:

➢ The scatterplots (**Fig.4**) are **color-coded, size-coded,** and **shape-coded. The lighter the color the higher the wear rate, and the bigger the symbol size the higher the total volumetric head wear.**

➢ **PC1 & PC2 explain 94.6% of variance**. **PC1** is well correlated with phosphate peak height and integrated area, as well as wear rate and total wear. **Red**, **green**, **blue** **circled cases** exhibited many bone fragments due to femoral loosening. Bone particles add another source of phosphate debris up-taken by macrophages, thereby obscuring the IR peak in the phosphate region.

5) **Boxplot of PC1 score for collagen and macrophage based on wear rate**



Using wear rate to categorize subgroups clearly shows that the PC1 scores are positively correlated with the wear rate. A decreasing wear rate correlated with a degreasing gap between Mφ and Col PC1 scores, yet two groups are still significantly different.

Discussion and Conclusions

- The chemical signature of periprosthetic macrophages associated with MoM HRs correlated with the femoral head wear rate
- Particle-laden macrophages exhibited a strong absorbance in the phosphate region ($\nu(PO_4^{3-})$ and exhibited a similar **dome-shaped** peak as previously described for $CrPO_4$[2]
- It is known that under well-functioning conditions MoM bearings predominately produce Cr_2O_3 nanoparticles (<100nm). High and excessively wear components are usually the result of edge loading (wear mechanism shifts from mild surface fatigue to abrasion), resulting in the release of large CoCrMo alloy particles (100nm to µm-range) [4,5].
- It appears likely that higher wearing HRs are also associated with the formation of $CrPO_4$ within macrophages, which is likely the result of phagocytosis of large cobalt containing particles as evidenced by large dome shaped $\nu(PO_4^{3-})$ peaks.
- Low wearing HRs are associated with lesser pronounced peaks which can likely be explained by the mostly inert nature of Cr_2O_3 debris
- There are a few outliers that can be seen (circled in Red, green, blue) which include a low wearing HR clustered with the highest wearing HRs. These specific cases exhibited gross implant loosening and numerous necrotic bone particles within macrophages that have obscured the phosphate related spectra.
- The absence of cup wear in this study is a major limitation. We expect that an even better correlation would have been achieved if the total wear volume would have been available for all cases.
- In conclusion, this study strongly indicates that chromium-phosphate is the dominant byproduct of the phagocytosis process of CoCrMo particles. Also, we demonstrated how FTIR can complement the semi-quantitative ALVAL assessment with specific chemical information.

References:

[1] Campbell, P et al. Clin Orthop Relat Res (2010) 468. [2] Liu, S et al. ORS Annual meeting, Virtual (2021); [3] Tafintseva, V et al. J Biophotonics. 2020 Mar;13(3) [4] Pourzal, R et al. Wear 271 (2011). [5] Gill, H et al. Trends Mol Med. 2012 Mar;18(3).

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