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Off-Resonance Based Assessment of Metallic Wear Debris Near Total Hip Arthroplasty

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Abstract

Purpose—The presence of metallic debris near total hip arthroplasty can have a significant impact on longitudinal patient management. Methods for MRI-based quantification of metallic debris near painful total hip replacements are described and applied to cohorts of symptomatic and control subject cases.

Methods—A combination of metal artifact reduction, off-resonance mapping, off-resonance background removal, and spatial clustering methods are utilized to quantify off-resonance signatures in cases of suspected metallosis. These methods are applied to a cohort of symptomatic hip arthroplasties composed of cobalt-chromium alloys. Magnetostatic simulations and theoretical principles are used to illuminate the potential sources of the measured off-resonance effects. Reported metrics from histological tissue assays extracted during surgical revision procedures are also correlated with the proposed MRI-based quantification results.

Results—The presented methods identified quantifiable metallosis signatures in more than 70% of the symptomatic and none of the control cases. Preliminary correlations of the MR data with direct histological evaluation of retrieved tissue samples indicate that the observed off-resonance effect may be related to tissue necrosis.

Conclusions—Magnetostatic simulations, theoretical principles, and preliminary histological trends suggest that disassociated cobalt is the source of the observed off-resonance signature.

Keywords

Susceptibility quantification; metallosis; total hip arthroplasty; metal implants

INTRODUCTION

In 2013, more than 320,000 total hip arthroplasty (THA) procedures were performed in the United States (1). These procedures have failure rates of 6% and 13% at five and ten years respectively (2), which resulted in nearly 45,000 revision THA procedures within the United States in 2013 and generated more than \$4.5 billion of healthcare costs (1). The public health impact of THA revision is accelerating, and revisions in the United States are projected to double from 2013 levels within the next 15 years (3).

Historically, the most common bearing surfaces used in THA are composed of an ultrahigh molecular weight polyethylene (UHMWPE) acetabular component articulating against a cobalt-chromium (CoCr) alloy femoral head. Although this metal-on-polyethylene (MOP) combination generally yields excellent results (4), polymeric debris from the articular surface can initiate a host-dependent inflammatory reaction. These reactions often cause bone resorption (osteolysis) and subsequent implant loosening, which is a common cause for THA failure (5, 6).

Metal-on-metal (MOM) bearing THAs were introduced, in part, to allow the use of larger femoral heads that are associated with a lower incidence of dislocation. MOM devices are composed primarily of cobalt-chromium alloy and have annual linear wear rates that are more than 20 times less than MOP articulations and generate smaller (7, 8) but significantly more (9, 10) wear particles. Observation of substantial metallic debris on imaging in peri-implant tissues can confirm the generation of wear debris at articular surfaces related to edge loading (11), misalignment (12), or electrochemical corrosion (7). Debris deposition into the surrounding soft tissue envelope, which is often described as “metallosis,” leads to tissue necrosis of important structures, such as hip abductors, resulting in patient morbidity with altered gait mechanics and pain. As few noninvasive methods exist to quantify metallosis, whole blood or serum ion levels are often used as an index of implant wear and tissue metal content (13). Serum ion levels may correlate with implant wear (12, 14), but this methodology lacks spatial information about the sources of ion generation and has been shown to be less accurate than magnetic resonance imaging (MRI) in determining the extent of soft tissue pathology according to histologic samples from extracted tissues (15).

In this work, we present and utilize an imaging-based mechanism for quantifying the severity of metal particle deposits in the immediate vicinity of THA. Though pockets of dense particulate debris (metallic or UHMWPE) can be crudely identified using magnitude MRI data, where they present as hypointense regions in proton-density weighted acquisitions (16), the methods presented here offer a quantitative and specific assessment of metallic particle deposition. This approach leverages the magnetism of metallic debris products and the sensitivity of MRI to local changes in effective bulk material magnetization. The presented methods could further lend support to the use of MRI as a biomarker for tissue necrosis due to metallic corrosion after THA.

THEORY

Static variations in bulk tissue magnetic susceptibility are the foundation of widely adopted susceptibility-weighted imaging (SWI) (17) and quantitative susceptibility mapping (QSM) (18) techniques.

Conventional SWI and QSM techniques utilize gradient echo acquisitions collected with multiple echo times to estimate phase evolution and, by extension, Larmor frequency offset maps. When imaging near metallic implants, gradient-echo imaging techniques suffer substantial signal loss and do not provide useful off-resonance information in the vicinity of the implant (19). Spin echo acquisitions utilizing asymmetric readout windows can be utilized to provide phase-based off-resonance information without substantial signal loss. However, these maps will suffer from severe spatial phase wraps and image distortions (20).

Multi-spectral imaging (MSI) methods collect a series of three-dimensionally encoded spectral volumes, or “bins” (21, 22). When spectral bins are acquired with substantial overlap, the measured spectral bin responses at each voxel can be utilized to construct off-resonance maps (23).

To date, most multi-spectral maps have been constructed using a center-of-mass (COM) computational assumption. This assumption allows for computation of local off-resonance values according to

$$\Delta v_o(\vec{x}) = \sum_{b=1}^{N_b} v_b \frac{S_b(\vec{x})}{|S(\vec{x})|} \quad (0.1)$$

where N_b is the number of spectral bins, v_b is the applied center frequency of the b^{th} spectral bin, and $S_b(\vec{x})$ is the magnitude intensity of this spectral bin at the voxel position $\vec{x}$.

This COM approach is susceptible to slight inaccuracies due to noise or ghosting (due to limited signal-to-noise ratio [SNR]) in far off-resonant MSI bins. Therefore, in this work, an alternative MSI off-resonant mapping technique is utilized.

The Multi-Acquisition with Variable Resonance Image Combination (MAVRIC) 3D-MSI implementation utilizes overlapping Gaussian spectral windows. Typically, a conventional MAVRIC dataset will provide three to five spectral data points per image voxel that characterize this spectral windowing function. These spectral profiles can be approximated by the Gaussian model,

$$S_b(A, \Delta\nu, \sigma) = A e^{-\frac{(\Delta\nu - \nu_b)^2}{2\sigma^2}}. \quad (0.2)$$

For each voxel in the image, the acquired bin data can be fit to Eqn. 0.2 so as to identify the parameters A , ν , and σ . This spectral profile is analytically differentiable, which readily

enables parameter optimization at each voxel using iterative steepest descent approaches. Since this generalized approach performs a fit to an anticipated model within the MSI spectral domain, it eliminates the aforementioned sensitivity to off-resonant bin noise and ghosting.

Background Field Removal

Off-resonance maps estimated using MSI methods near metal implants are dominated by the field perturbation induced by the implant itself. For CoCr alloyed hip replacements at 1.5T, this induced off-resonance distribution spans 10–20 kHz. Furthermore, this wide spectral dispersion shows substantial spatial variation near the implant interfaces, often in locations that overlap with regions of suspected metallic deposits. As a result, the implant-induced “background” field must be removed from the measured map so as to expose the “tissue” field that contains information that can be used to identify metallosis deposits.

Background field removal is a crucial step in established QSM algorithms (18), which have typically been applied to neuroimaging where background fields can be decomposed into relatively low-order spatial harmonics. Though a wide variety of background removal methods exist, here we utilize the Projection onto Dipole Fields (PDF) (24) technique.

Briefly, the PDF technique performs an inversion of dipolar field “sources” within voxels labeled as “non-tissue” across the analyzed volume of interest. For the present purposes, this method is well-suited to identify and remove the implant-induced field. This is because the implant can be well-approximated as a sum of high susceptibility source dipoles that characterize the implant-induced perturbation field.

Metallic Particulate Debris

The metallic particles of interest near total hip replacements are derived from CoCr alloy wear debris. Individual CoCr metallic debris particles have been well-characterized using electron microscopy and were found to range from 20 nm to nearly 200 nm in maximal cross-sectional length (25). More recent work has produced exquisite ultrastructural images showing corrosion and metallic particles that confirm earlier estimates of debris composition (26). Individual metal particles can crudely be identified with light microscopy. However, only very large particles or clusters of smaller particles can be identified, often within macrophages (27). CoCr particles less than roughly 200 μm or individual Co and Cr ion components cannot be visualized using conventional optical methods.

Co and Cr levels are typically quantified using inductively coupled plasma mass spectrometry (ICPMS) (28). Sampson et al. (29) performed ICPMS on samples from subjects with symptomatic total hip replacements, where Co and Cr levels were measured in the blood and synovial fluid collected near symptomatic implants. As expected, in some case studies, the level of Co found in the synovial fluid were orders of magnitude higher than that in the blood. Scharf et al. (26) further demonstrated the presence of Co and Cr ions in soft tissue near symptomatic hip replacements, with increased deposition near devices with MOM articulating surfaces. Bench testing by Scharf et al. also led to the conclusion that the observed metal ions in soft tissues are produced from phagocytosed CoCr nanoparticles that

have been absorbed by macrophages. To date, no in vivo imaging methods have been shown capable of quantitatively identifying Co or Cr particulate matter.

METHODS

Off-Resonance Simulations

In this work, we consider the potential off-resonance effects of both large inhomogeneous clusters of CoCr particles and homogeneous distributions of disassociated metallic by-products. While the treatment of homogeneously distributed materials can be handled analytically, the effects of larger, inhomogeneously distributed particles must be numerically simulated. Following the empirical observations of Scharf et al. (26), a magnetostatic computational phantom was developed to estimate off-resonance signatures within a cubic volume of 10 μm edge length for a variety of potential macroscopic CoCr particle distribution densities with 150 nm granulation at 1.5T. These particles are on the large end of the metallic debris spectrum and represent particles that may be detected using light microscopy in histological assessments.

A magnetic susceptibility of 1000 ppm was utilized for the CoCr debris, which was passed through a forward-dipole model that predicts MR-observable off-resonance fields (30, 31). The simulation was run in Monte Carlo fashion for 1000 iterations for particle densities ranging from 5% to 45% by volume. A final off-resonance signature for the voxel was estimated by taking the mean of all off-resonance in regions not occupied by the particles themselves, followed by mean and standard deviations for all iterations performed within the Monte Carlo analysis.

Image Acquisition, Analysis, and Processing

This study was approved by the local institutional review board, and all subjects provided written informed consent prior to participating in the study. Off-resonance analysis was performed on 27 subjects undergoing revision for total hip arthroplasty (12 males, 15 females, age: 57.3 ± 14.7 years). For symptomatic cohort analysis, a single THA was analyzed for each subject. For control analysis, opposing non-instrumented joints were analyzed in unilateral arthroplasty cases. In bilateral cases, a region of unlikely metallic particle deposition near the unsymptomatic instrumented joint was used for control analysis.

Prior to revision surgery, enrolled subjects underwent an MRI exam including MAVRIC SL 3D-MSI. Image acquisition parameters were as follows: coronal scan plane, 36–40 cm field of view (FOV), 7 ms echo time (TE), 4 s repetition time (TR), echo train length (ETL) of 20, 5 mm slice thickness, $(512 \times 256 \times 24\text{--}32)$ in-plane data matrix, 24 spectral bins, spectral width of 2.25 kHz (full-width-half maximum), and a 1 kHz spectral bin separation, with a receiver bandwidth of ± 125 kHz (500 Hz/pixel).

For each subject, a region of suspected metallosis was identified on a MAVRIC SL image by a board certified musculoskeletal radiologist with more than 20 years experience interpreting MR images of arthroplasty. This regional identification used to guide extraction of a 1 cm^3 tissue sample during the surgical revision procedure. These regions were denoted as areas of low signal intensity within the synovial envelope on the MAVRIC SL images. Extracted

samples were fixed in formalin and processed for routine histology; representative sections were then graded by a board-certified pathologist with more than 30 years experience specializing in orthopaedic pathology and biomaterials. The utilized histological metallosis metrics were previously described by Fujishiro (32) and Willert et al (33). Briefly, these evaluation methods semi-quantitatively grade the presence and extent of histiocytes, particle types, and tissue particle load under high magnification (400). Tissues were also evaluated using Campbell's aseptic lymphocytic vasculitis associated lesion (ALVAL) score (34).

3D-MSI spectral model-based field maps were computed for each subject using an analytic steepest-descent iterative approach implemented in GE Healthcare's Orchestra C++ reconstruction environment. The solver was initialized with physical estimates for each spectral parameter (maximum bin amplitude, COM frequency, and designed profile width), utilized a minimum-norm pseudoinverse solution within each iteration, and performed five iterations at each voxel.

Off-resonance metallosis scores, or "mScores," were initiated on each subject by manually selecting a 120 cm³ cuboid encompassing the indicated region of suspected metallosis. Regions were selected using a manually constructed user interface in MATLABTM (Natick, MA, USA).

Implant masks were determined for each volume by examining the 3D-MSI spectral integrity at each voxel. As previously described, a given voxel in the dataset was expected to have three to five dominant spectral bin contributions, depending on the severity of the local induction field gradients (35). With this knowledge, spectral integrity was quantified by computing the ratio of the cumulative three highest magnitude spectral bin signals to the sum of the remaining spectral bins. A ratio of 3.0 was empirically found to provide the most reliable masking for the present purposes. The implant region was identified in this integrity mask as the largest contiguous region of poor spectral integrity (<3.0) in the volume. This "implant" volume was then dilated by an additional 3 mm to ensure that high-quality spectral signal was utilized in the analysis of the remaining volume (which is nominally the "tissue" compartment). The cumulative goal of these preprocessing steps was to remove voxels with poor MRI signal integrity from the off-resonance analysis.

Following the volumetric off-resonance mask generation, background field removal was performed on each selected volume using the PDF algorithm, which was implemented in MATLAB using scripts provided by the MEDI Toolbox (36). Inputs to the PDF algorithm were (a) the computed spectral model-based field map and (b) the spectral integrity mask. For the current purposes, the PDF algorithm was implemented using 100 conjugate gradient iterations as the terminating criterion.

A fundamental limit of particulate detection stems from local fat-water chemical shifts, which are present in MSI-derived off-resonance maps. Though Dixon-based fat-water separation approaches to MSI have been proposed, these methods remain in early investigative stages (37). The presence of chemical shift contamination establishes an off-

resonance detection threshold, below which particulate deposits cannot be distinguished from normal fat-water tissue transitions (225 Hz at 1.5T).

Considering this theoretical detection limit, mScores were computed using off-resonance thresholds of $T_i = [350\ 400\ 450\ 500\ 550\ 600]$ Hz and cluster size thresholds of $S_j = [0.3\ 0.6\ 1.2\ 1.8\ 2.4]$ cm³. The choice of a minimum off-resonance threshold of 350 Hz provides a conservative buffer above the chemical shift threshold, so as to reduce false positive detection. Clusters were identified using the spatially correlated 3dclust algorithm provided by the AFNI toolbox (38), which was implemented using a rudimentary face-connected nearest neighbor algorithm.

Given a cluster volume array C_{ij} , which represents the volume of a cluster computed using a volume threshold of S_j at an off-resonance threshold of T_i , mScores were computed according to

$$mScore = \sum_{i,j} e^{\left(\frac{1}{T_i} + \frac{1}{\alpha S_j}\right)} C_{i,j} \quad (0.3)$$

where α can be used to balance the weighting between T_i and S_j . The exponential term provides a multi-parametric nonlinear weighting at each data point, based on the off-resonance and cluster volume thresholds used to compute each data point. This weighting slightly amplifies scores with smaller clusters at lower off-resonance values. Without this weighting, computed mScores in the symptomatic cohort were found to have a very large dynamic range that complicated group analyses. This is because larger pockets of debris deposition tended to have higher off-resonance values. Data shown in this work used an empirically chosen value of $\alpha = 160$. In addition to regions of suspected metallosis, mScore analysis was also performed for 16 of the 27 subjects in soft tissue regions where no metallosis would reasonably be expected. For subjects with unilateral hip replacements, these regions were identified on the opposing hip joint. Subjects with bilateral hip replacements had control volumes identified from lower regions on the distal femoral stem outside of the femoral cortex, where metallosis is less likely to be identified. This control analysis served as a false positive assessment of the presented method. In this context, a “false positive” is considered to be a nonzero mScore in a control region where no particulate deposition is physically feasible.

Linear regression statistics were computed using computed mScore values and quantitative histological features of generalized particle load, tissue necrosis, lymphocyte density, ALVAL score, and metal particle density.

Results

The results of one iteration within the Monte Carlo simulation, utilizing a particle density of 15% by volume, is shown in Figure 1A. The resulting off-resonance field (with metal voxels masked) is shown in (B). Average off-resonance values averaged across the analysis volume

and the Monte Carlo iterations are plotted for a range of particle densities in (C). Error bars indicate the standard deviation of the average off-resonance and are derived from the Monte Carlo analysis. While the variance of the volume-averaged off-resonance measurement is clearly correlated with particle density, the mean value does not change. These computational results indicate that large inhomogeneously distributed CoCr particles, such as those that have been measured using light microscopy, cannot be the source of the bulk Larmor off-resonance frequency signature that is detected using MRI methods.

Figure 2 illustrates the process of computing and processing local tissue off-resonance maps near total hip replacements. Starting with the large FOV MSI (A), the indicated region is extracted (B) whereby voxelwise 3D-MSI spectral data are used to construct an off-resonance map (E). Background extraction using the PDF method (F) exposes the local tissue off-resonance distribution. Finally, thresholded cluster analysis allows for definition of a suspected metallosis pocket (C).

Figure 3 shows localized background-removed off-resonance maps (bottom row) and correlated magnitude MAVRIC SL 3D-MSI images (top row) for six cases, with computed mScores for each case. Clear regions of locally isolated positive off-resonance are seen in all cases, which translates to mScores of various amplitudes depending on the 3-dimensional size and off-resonance amplitude of the pockets.

The importance of model-based 3D-MSI off-resonance mapping is exemplified in Figure 4. The selected 3D-MSI shows a region of suspected metallosis. A background-removed off-resonance map computed with the conventional COM method (23) indicates a large region of potential metallosis. However, the presented model-based residual map shows a far muted off-resonance signature. When examining the MSI spectral profile in the indicated position (X in COM map), a region of unanticipated elevated signal is seen in far off-resonant bins (arrow). This elevated signal, which is suspected to be caused by image ghosting artifacts in the off-resonant bins, slightly shifts the COM off-resonance estimate. When the model-based algorithm is utilized, the computed model is not impacted by the false magnitude elevations of the distant off-resonant bins. In this case, the ghosting artifacts of off-resonant bins in the lower signal region of suspected metallosis would have generated a false positive mScore using the COM field map. The model-based approach clearly reduces this risk of false positive findings.

The choice of field mapping algorithm proved crucial in the elimination of false positive mScores across the control analysis cohort. Using the COM off-resonance mapping method, 25% of the 16 control cases yielded significant false positives (mean mScore = 1.79). When applying the presented spectral modeling approach, all 16 control cases properly yielded null mScores.

Figure 5A provides a histogram of the mScores computed across the symptomatic cohort. Within this group, non zero mScores were computed in suspected regions of metallosis for 19 of the 27 (70%) subjects. Statistical analysis (unpaired, unequal-variance, two-tailed t-test) of the symptomatic (mean = 4.4, standard deviation = 8.8) and control (mean = 0.0, standard deviation = 0.0) mScore groups yielded a significant correlation with regions of

suspected pathology ($p=0.008$). The variety of scores in the symptomatic group is substantially distributed, with a mean of 4.4 and standard deviation of 8.8. While variations of magnetic susceptibility in different alloys of CoCr could explain some of this variation, the different CoCr alloys used by implant manufacturers can vary by only roughly 30% (39, 40). The far more extreme variation seen in this preliminary clinical mScore analysis is therefore likely representative of different in vivo concentrations and volumes of metallic wear products.

Table 0.1 provides linear regression p-values analysis of variance (ANOVA) correlating measured mScores with histological scores for a variety of metrics. Figure 5B presents a scatter plot relating mScores and necrosis histology scores for the symptomatic analysis cohort.

To further probe the correlation of necrosis with off-resonance effects, we also independently interrogated the correlation of histological necrosis score with cluster size for the lowest off-resonance threshold (350 Hz) and the mean off-resonance value within these clusters. The results of this linear regression (ANOVA) were $p = 0.08$ and 0.64 for the correlations with cluster size and off-resonance values, respectively.

Discussion

A 3D-MSI off-resonance mapping mechanism for identifying and quantifying metallic debris has been presented and applied to control and symptomatic clinical cohorts.

The observed off-resonance signatures in this preliminary study are spatially focused and cannot easily be attributed to alternative sources of susceptibility offsets. Furthermore, a control analysis of the presented methods yielded no false positives in 16 analyzed cases. This excellent control performance is attributed to a spectral model-based off-resonance mapping approach and boosts the confidence of true positive mScore findings in the symptomatic cohort. Given the strong resistance of the proposed algorithms to false positives, a group-wise statistical analysis of the suspected regions of metallosis ($n = 27$) in our symptomatic cohort and the control regions ($n = 16$) yielded an excellent statistical correlation ($p = 0.008$).

Computational modeling results presented in this work have shown that collections of large CoCr particles, which can be observed via histological examination, are not likely to be the source of the observed off-resonance effect.

The theory of MR observations of paramagnetic material distributions was established by Chu et al. (41). This theory describes the off-resonance effects expected from paramagnetic contrast agents, and defines both inhomogeneous (T_2^*) and homogeneous (measured off-resonance) bulk magnetization shifts (BMS). Within this formalism, a magnetized material that is non-uniformly distributed within a given compartment of NMR sensitive nuclei will not generate an observable bulk-off-resonance shift, which is confirmed by the simulation results displayed in Figure 1. However, such a distribution can and will generate an inhomogeneous effect, impacting T_2^* relaxation times. In the present context, where spin

echo techniques are required to capture sufficient signal around metallic implants, only the homogeneous BMS effect is of consequence.

When a magnetic material is more homogeneously distributed within a background medium, a homogeneous BMS can be detected by probing the local Larmor frequency of spins. As outlined by Chu et al., if compartment geometries are neglected, a homogeneous distribution of material will yield a bulk Larmor frequency offset that is scaled by a factor of 1/3. This adjusted estimate of a BMS off-resonance observable is driven by the Lorentz sphere concept (42), whereby diffusing MR-visible nuclei are modeled with random motion throughout a spherical cavity within the homogeneous magnetization medium.

In the present context, these fundamental principles dictate that any bulk off-resonance effect observed in a given tissue must be driven by a collection of magnetized sources that have a net homogeneous distribution component.

We now focus on the potential products of implant wear that fall into this category. First, we consider the smallest of CoCr particles, which must be far smaller than the levels detected via light microscopy (100–200 nm) and homogeneously distributed. To our knowledge, the molar susceptibility of CoCr has not been reported. Therefore, here we approximate this value through a density scaling operation, whereby 100% by mass of CoCr registers to a bulk susceptibility of 1000 ppm. We then consider an effective 9 ppm bulk susceptibility, which would yield a Lorentz sphere corrected shift of 3 ppm, or roughly 200 Hz for protons at 1.5T. Within our crude scaling approximation, this yields a mass density of roughly 1%. Utilizing the molar mass of CoCr and elemental Co, this would yield a Co density of roughly 4500 µg/mL within soft tissue. The aforementioned mass spectroscopy results of Scharf et al. found Co densities of roughly 0.20 µg/mL in soft tissue compartments near MOM devices using extracted tissue samples that were not conclusively targeting focused deposition regions (26). This measured Co amount is substantially less than the maximal Co density found by Sampson et al in synovial fluid (12 µg/mL) (29). However, both of these measurements are orders of magnitude less than the 4500 µg/mL our estimates predict would be required to produce a 200 Hz off-resonance shift. Therefore, we propose that homogeneously distributed CoCr nanoparticles are not responsible for the shifts observed in this work, which are well beyond 200 Hz.

Given the lack of a viable direct off-resonance response from CoCr nanoparticles, we now consider disassociated metallic particles derived from these larger particle sources. It is well known that Co and Cr disassociate corrosion processes, which is the motivating principle for blood serum ion testing in patients with symptomatic total hip replacements. This provides another mechanism for generating off-resonance contrast in regions of metallosis and provides an advantage of direct in situ localization of these deposits relative to clinically relevant surrounding soft tissue structures at risk for corrosion-related necrosis and destruction.

While both Co and Cr are products of corrosion processes, relative to Cr, Co has a dominating magnetic contribution in both its elemental, ionic, and molecular byproduct forms. We therefore consider the effect of Co particulate debris pathways on potential MRI

off-resonance observables. Atomic Co has a very high magnetic moment and in a solid lattice is the second most ferromagnetic element (behind iron). Biochemically, CoCr alloys disassociate into bivalent and trivalent states of Co, which can combine to form compounds such as cobalt-oxides, cobalt-chloride, cobalt-phosphates (43, 44). In addition, further dissociation of Co can result in the hexaaquacobalt ion $\text{Co}(\text{H}_2\text{O})_6^{2+}$. Cobalt salts, oxides, and phosphates are highly paramagnetic (45). However, like the CoCr nano particles, utilizing the known molar susceptibilities of these compounds in conjunction with mass spectroscopy results, we arrive at off-resonance estimates that are well below the values found in our results (>350 Hz).

To our knowledge, the bulk susceptibility (or chemical shift effect) of $\text{Co}(\text{H}_2\text{O})_6^{2+}$ has not been published. A comprehensive analysis of the BMS and chemical shifts induced by bound $\text{Co}(\text{H}_2\text{O})_6^{2+}$ or free Co^{2+} ions requires substantial physical chemistry and fundamental imaging experiments that are well beyond the scope of the current study. Our computational estimates suggest that the net molar susceptibility of any Co by-products required to generate our observed off-resonance effect be roughly $3.4 \text{ cm}^3/\text{mole}$. This is a very high molar susceptibility, roughly 20 times that of gadolinium (Gd) at room temperature. However, we note that elemental solid-state Gd is no longer ferrous at room temperature, whereas solid-state Co lattice is still ferrous. Therefore, it is not inconceivable that disassociated Co in solution can have a molar susceptibility that is greater than that of Gd.

The notion of highly magnetic metals generating BMS shifts is not an unfamiliar concept in the MR community. In particular, we can point to recent studies of Gd in brain tissues (46). Multiple groups have performed experiments verifying this Gd deposition (46, 47) using the same mass spectroscopy tools previously mentioned for assessing Co and Cr levels. In addition, other groups have used QSM to detect Gd deposition in various brain tissues via net BMS shifts in groups with serial Gd contrast injections (48). Though the deposition rates and chemical processes are different, it is plausible that both Gd and Co, in possessing high levels of atomic magnetism, could have similar impacts on observable BMS and chemical shifts.

If disassociated Co is the source of observed MR off-resonance signatures, it may provide valuable information on the presence or likelihood of adverse local tissue reactions near hip arthroplasty prior to discernible damage noted on MRI evaluation with artifact-reduction sequences. This could allow for earlier intervention with revision before macroscopic tissue destruction ensues.

In correlating the mScores and histological metrics within the symptomatic cohort, we found the strongest correlation between mScore and necrosis severity. Though this correlation ($p = 0.09$) does not reach statistical significance ($p < 0.05$), it is an encouraging trend that lends support to the proposed hypothesis. This observed trend is supported in the literature by biochemical studies that have correlated ionized Co with tissue necrosis (49–51). It is difficult to hypothesize whether mScores should correlate with histological particle load assessments. Since increased mScores are hypothesized to result from increased disassociated cobalt, one might expect regions with larger optically visible “source” particles

to show higher mScores. On the contrary, if the disassociated Co products are migrating away from the larger particles, then the histology particulate observations may not track with off-resonance observables.

Our preliminary statistical analysis also suggests that off-resonance cluster sizes (deposition expanse, $p = 0.08$), rather than off-resonance levels (deposition density, $p = 0.64$), correlate stronger with off-resonance. Though neither trend reaches statistical significance, this preliminary analysis indicates that histologically identified necrosis is more related to material expanse than deposition density.

None of the reported metrics reached statistical significance ($p < 0.05$), which may be attributed to a variety of factors. First, we do not expect mScores to correlate with all histological metrics. Second, there is some inherent subjectivity and variability in histological scoring, particularly in measures of particulate matter. Third, histological scoring accuracy can be impacted by the removal of regions of nonviable cells from tissue samples prior to analysis. Finally, the ability to precisely extract the histological sample from the indicated regions is extremely limited due to inaccuracies of tissue sampling at the time of implant revision. Therefore, our mScore analysis interrogates a much larger region that is assumed to encompass the histologically sampled region. As a result, it is expected that particle deposition heterogeneity will cause disagreement between mScores and histological findings. This is suspected to be the dominant confounding factor in correlating mScore values with histological findings.

In light of the systematic variance between histological sample retrieval and mScore volumetric analysis regions, more statistical power will be required to connect mScores with histological findings. Further studies will seek to perform mScore comparisons with histological metrics in larger cohorts of symptomatic subjects.

Future work will also explore the physical connection between off-resonance measurements near total hip replacements and disassociated Co products. These bench experiments could include mass spectrometry analysis and histomorphometry of tissue samples acquired from revision surgeries to correlate Co compound concentrations, inflammation, and MR-observed off-resonance effects. In addition, physical-chemistry-guided MR experiments could be useful in experimentally validating the off-resonance signature from specific groups and concentrations of Co by-products.

The quantification approaches in this work are not direct measurements of local effective tissue susceptibility. Since conventional QSM algorithms have been optimized for natural tissue and fluid variations within the brain, they are not well optimized for the inversion required to perform QSM in the present context. In particular, the sharp variations between off-resonance pockets and surrounding tissue add instability to the already precarious QSM inversion process. The result of this instability can vary from heavy streaking along the magic angles of the magnet coordinate system to extreme inaccuracy of susceptibility estimates. Future work will investigate alternative QSM inversion approaches that are better suited for the quantification of metallosis debris pockets.

Conclusions

A method for off-resonance detection of metal particle debris near total hip replacements has been presented. This approach could enable both visualization and quantification of metallic debris severity in cases of symptomatic hip replacements. The method was applied to a cohort of symptomatic subjects with total hip replacements and yielded no false positives in a control group analysis. Through magnetostatic simulations, the source of off-resonance tissue signature has been shown not to be derived from groupings of large CoCr particles. Rather, a hypothesis is presented that suggests the effect is related to pooling of end products containing disassociated Co ions. The clinical significance of this biomarker could be substantial, as these Co ion by-products are directly related to disease progression and allow for detection prior to macroscopic tissue destruction. Though further studies with larger symptomatic cohorts will be required to build statistical confidence, preliminary trends in histological correlations support this proposed hypothesis.

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Figure 1.

Results from one iteration of Monte Carlo particle off-resonance simulation for CoCr particulate matter with 150 nm resolution spread across a cubic volume of 10 μm edge-length at 1.5T. (A) displays the distribution of particles, while (B) presents the off-resonance values induced in non-particulate (i.e., tissue) grid positions. The results of the Monte Carlo simulation, run with 1000 iterations, is shown in (C). It is clear that the mean of the expected Larmor frequency offset is negligible

Figure 2.

Demonstration of MRI mScore computation process. Large field of view MAVRIC SL image (A), indicated analysis region (B), identified off-resonance cluster superimposed on magnitude image (C). Full field of view (D) and zoomed (E) 3D-MSI off-resonance maps. Background extracted off-resonance field in the analysis region (F).

Figure 3.

Case studies of six symptomatic subjects with suspected metallosis. Localized background-removed off-resonance maps (bottom row) and correlated magnitude MAVRIC SL 3D-MSI images (top row) are displayed. Computed mScores are also displayed for each case.

Figure 4.

Importance of off-resonance mapping method. The conventional center of mass approach is prone to ghosting artifacts in far off-resonant bins, which displaces the off-resonance center frequency estimate for a given voxel (dashed line). The spectral model suppresses these bins from the center frequency estimate (solid line) and provides a map without false positive off-resonance pockets. Application of the center of mass approach yielded a 25% false positive rate in the control analysis, whereas the spectral modeling approach resulted in no false positives.

Figure 5.

(A) Distribution of mScores computed for cohort of subjects with symptomatic total hip replacements. (B) Plot of histological necrosis score (Natu) versus mScore. Linear regression analysis of the relationship yields $p = 0.08$. Though the trend does not reach statistical significance ($p < 0.05$), as indicated in Table 0.1, it shows the best correlation of all measured histology metrics.

Table 0.1

Table of linear regression correlations (ANOVA p value) between MRI-based mScore quantification and a set of histological metrics for n=27 symptomatic total hip replacements. mScores were computed over 120 cm³ volumes surrounding the location of the 1 cm³ tissue extraction regions. Though none of the metrics had statistically significant correlations ($p < 0.05$), the necrosis and ALVAL metrics were the most promising.

Histology Metric	p value
Particle Load	0.76
Metal Particle Load	0.36
Lymphocyte Load	0.35
ALVAL Score	0.12
Necrosis Score	0.09