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CORR Insights®: Periprosthetic UHMWPE Wear Debris Induces Inflammation, Vascularization, and Innervation After Total Disc Replacement in the Lumbar Spine

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Where Are We Now?

Total disc replacements (TDRs) for the lumbar spine are intended to restore and preserve motion while eliminating pain in patients suffering from degenerative disc disease. Five-year results in randomized clinical trials versus fusion show that lumbar disc replacements generally reach these goals, with pain relief equal to or better than fusion, maintenance of motion at the replaced joint, and less adjacent level degeneration than observed adjacent to a fusion [1, 11, 13, 14]. However, as is true of any joint replacement, motion between the contacting surfaces while under load causes wear with an associated release of debris that can vary in size, shape, and chemical composition depending on the materials used for the bearing surfaces, the design of the joint articulation, and the tendency for wear to occur due to unintended mechanical damage such as impingement.

The local and systemic effects of the biological reactions elicited by wear debris have been studied extensively in replacements for synovial joints such as the hip and knee, but have garnered less attention for replacing a cartilaginous joint such as between the vertebral bodies [12]. Still, reports of osteolysis and adverse local tissue reactions (ALTRs) similar to those seen around hip and knee replacements have emerged [3], substantiating the continuing concern that the biological reaction to debris may be an important factor limiting the longevity of disc replacements. Veruva and colleagues have provided additional compelling evidence that these concerns are warranted, and have begun to explore the hypothesis that a link exists between the presence of debris in local tissues and evidence of biological responses consistent with increased pain.

This CORR Insights® *is a commentary on the article* "UHMWPE Wear Debris and Tissue Reactions Are Reduced for Contemporary Designs of Lumbar Total Disc Replacements" *by Veruva and colleagues available at:* DOI: 10.1007/s11999-016-4996-8.

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Where Do We Need To Go?

Much work remains to be done in integrating data from clinical examinations, radiographic imaging, histology, implant retrieval analysis, and cellular and molecular markers to better understand the mechanisms responsible for adverse tissue reactions around total joint implants. The goals of these investigations must be to develop predictive tools, such as imaging markers or biomarkers for early diagnosis, and to use mechanistic explanations to develop potential treatments. Multidisciplinary studies aimed at such integration are hampered by many limitations. Chief among these limitations are the subjective nature of many of the tools currently in use (such as patient-reported outcomes, histology scoring systems, and retrieved implant wear and damage analyses), and the difficulty in obtaining sufficient tissue samples from appropriate locations around the joint to accurately assess key aspects of the biological reaction.

Despite these restrictions, no substitute exists for expanding studies of adverse biological reactions to include more patients (and more tissue samples) from around failed TDRs. Analyses of abundant sections through affected tissues increases the probability of accurately and precisely describing and quantifying the type and severity of the reaction. High-powered histological examinations, though limiting the area that can be examined, will reveal more evidence of smaller debris particles of both polyethylene and metal. This might better reveal not only small-wear particles, but also corrosion products, such as might be released from metal-on-metal articulations. Veruva and colleagues acknowledged the magnification of their histologic examinations as a limitation to their study. Debris particles smaller than 0.35 microns could not be detected by their methods of analysis. Smaller particles are known to be present in these tissues and are more biologically active [5]. Since wear particles generated by TDRs can cover a spectrum of size and shapes, it is difficult to attribute a biological reaction in the tissues to one particle type or size. Large debris particles (> 35 microns) may be visible in a location with a soft tissue reaction, but smaller particles that are invisible with light microscopy may also be contributing to the biological response around TDRs.

The complexity of TDRs for both the cervical and lumbar spine encompasses a wide array of design concepts and bearing material combinations. Results like those from Veruva and colleagues, which stem from only two commercially available designs of lumbar disc replacement, may not reflect those that would be found for other TDR devices on the market. Similar studies that include other designs of both cervical and lumbar TDRs are warranted to provide a more complete assessment of how differences in design and bearing materials affect in vivo wear and wear-related biological reactions.

The pursuit of the suggestion that two components of the biologic reaction to debris around the spine are vascularization and innervation is an intriguing one. The difficulty, as is evident from the study by Veruva and colleagues, is providing a direct link between the reaction, the innervation, and the patient's complaint of pain. Further muddying the waters, especially in studying failed TDRs, is that many of the failures have a mechanical component, component subsidence or loosening, that might itself be the cause of pain. Similarly, previous case studies [3] in humans and experiments using animal models have demonstrated that the pain is more likely due to the inflammation that is part of the biologic reaction to debris and not a neuropathic effect.

How Do We Get There?

Addressing the problem of adverse tissue reactions around TDRs requires a three-pronged approach. The first

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prong is continued clinical monitoring of TDR patients, which will serve to further elucidate the prevalence of wear and corrosion related problems. Given that osteolysis and other forms of ALTRs often do not cause symptoms until they progress to disastrous levels, longitudinal monitoring with imaging modalities such as ultrasound, CT, and MRI are warranted [7]. MRI studies around total hip replacements and hip resurfacing implants have detected adverse reactions in asymptomatic patients, and relationships between the presence of an adverse reaction and synovial volume and synovial thickening suggest that they may be valuable markers in the longitudinal assessment of asymptomatic patients [8, 9]. Furthermore, monitoring of serum metal levels in patients with metal-on-metal TDRs may prove beneficial. Case reports exist of failed TDRs secondary with ALTRs consistent with metallosis [2], though the systemic levels of metals might be low given the smaller wear areas of TDR surfaces compared to those in total hip replacements.

The second prong is continued integration of clinical, retrieval, imaging, and histologic studies. Despite the limitations in techniques discussed above, the search for correlations among data from such integrated studies is the best chance for describing the natural history of TDR failure from wear and wear-related phenomenon. Imaging studies can help in this second prong by providing improved sampling protocols so that the most appropriate biological specimens, those at the heart of the adverse reaction, can be obtained at revision surgery from around failed TDRs. The same approach could be applied to longitudinal, prospective studies of TDR patients in which guided biopsies could be performed of suspicious areas of adverse reaction; such studies could further our understanding of the natural history of TDR failure and would strengthen links between early adverse responses to debris and clinical symptoms like pain.

The correlations that emerge from such approaches to study the clinical problem of TDR will also serve to generate theories about specific mechanisms that can be explored in more controlled laboratory and animal experiments, which would be the third prong in my suggested approach. Much work has been done in studying wear of disc replacements experimentally in joint simulators [4, 6] and computationally using finite element stress analysis [10]. Similarly, research on in vitro and animal studies of biologic reactions to debris is quite extensive, yet few if any studies have been guided by clinical and retrieval results from TDR patients. Given the unique nature of the local environment around TDRs, guidance from such data would ensure the most relevant, useful findings would emerge as investigators plan basic and translational science studies in this area.

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