

UC San Diego

Independent Study Projects

Title

[The immunological profile of intrarticular fluid is different in patients with metal-on-metal compared to those with osteoarthritis controls, with several cytokine markers showing impressive elevations]

Permalink

<https://escholarship.org/uc/item/4dt6w3s8>

Author

Nagle, D.

Publication Date

2016

Introduction

More than 500,000 joint replacements are performed in the United States each year and this is expected to increase by at least 50% over the next 10 years [1]. Along with this increasing volume of joint replacements, the rate of revisions for failed hip and knee replacements is expected to increase at a similar rate over time. With all 'failures' it is important to carefully analyze the cause of failure in a continual effort to improve patient outcomes. The broad purpose of this study was to allow and facilitate ongoing research at UC San Diego into the mechanisms of failure of joint replacements in general.

More specifically, there is a particular mode of failure for metal-on-metal (MM) total hip replacements which can be a diagnostic dilemma and although the actual prevalence is currently unknown, it appears to be more common than previously anticipated. Epidemiological estimates show that MM accounts for up to 30% of bearing surface choices for all total hips performed in the United States. Therefore, these adverse local tissue reactions (ALTR) after metal-on-metal (MM) hip replacement may have a large impact on our health system.

There is a spectrum of severity, clinical presentation and pathologic findings in these cases. Symptomatic fluid collections may develop leading to local pain, tightness, obvious swelling, tissue necrosis and even nerve palsy. Osteolysis may be seen. Additionally, 'pseudotumors' or 'bursas' have been reported in association with MM implants [2,3,4,5,6]. To date, studies have focused on the histologic and pathologic features but have not focused on elucidating the underlying inflammatory response. Currently, the only definitive diagnostic criteria are based on soft tissue specimens that are obtained at the time of revision surgery. This means that the definitive diagnosis is made *after* the surgical treatment has been rendered. Furthermore, despite the spectrum of disease severity, there are no substantial prognosticating criteria to guide the urgency of treatment. An evolving clinical question is what to do with the patient with an asymptomatic fluid collection around an otherwise well-functioning MM hip.

Materials and Methods

This study is a prospective, case control study. A collaboration with several orthopaedic surgeons in a large, populous city was created in order to identify suspected cases of ALTR. Through this effort, 42 cases were identified. Current diagnostic criteria included symptomatic patients with discomfort, pain, fullness about the hip or overt, noticeable swelling, stiffness, or generally deteriorating function. When a patient presented with such complaints, the potential for infection is ruled out with screening inflammatory labs (complete blood count with differential, C-reactive protein and erythrocyte sedimentation rate).

Imaging studies were obtained including standard radiographs to assess implant position and evidence of loosening and/or osteolysis. Additionally, either MRI or ultrasound was used to assess for peri-articular fluid collections or masses. In most cases, an aspiration of the hip was performed pre-operatively in order to definitively rule out infection. When a suspected case of ALTR has been identified, the patient was consented according to IRB protocol. At the time of

revision surgery, peri-articular fluid, peri-articular tissues and explanted prostheses are collected and analyzed.

For each ALTR case, clinical data was recorded including prosthesis type and implant position, patient age and sex, time from index procedure to revision, and pertinent laboratory data. Additionally, intra-operative data is recorded including extent of soft tissue destruction, presence and size of fluid collection and/or bursa/pseudotumor, color and quality of fluid, evidence of metallosis and status of fixation of implants.

Patients with osteoarthritis of the hip served as a baseline control. Any evidence of inflammatory arthritis (such as rheumatoid arthritis, ankylosing spondylitis, etc.) or any history of infection of the involved joint are exclusion criteria for both control groups.

After the fluid samples from the ALTR cases and osteoarthritis controls are obtained and processed as described above, the fluid was then analyzed by Luminex bead-analysis assays to measure IL-1ra (receptor antagonist), IL-6, IL-8, IL-10, IP-10, TNF- α , VEGF, Rantes, and MCP-1 levels.

In addition, surgically removed capsule, membrane or joint mass tissues were stained with hematoxylin and eosin and evaluated with light microscopy. A 10-point histologic scoring system (ALVAL score) has been developed in order to semi-quantitatively assess and classify ALTR cases⁴. An ALVAL score of 1 to 4 is interpreted as a low level of tissue response, comparable to that seen in surgically or mechanically damaged tissues, or those with minimal reaction to wear debris; a score of 5 to 8 is a moderate response and indicates marked changes in tissue structure and either macrophage and/or lymphocytic inflammation; the highest scores are indicative of severe and extensive tissue damage and a prominent lymphocyte-dominated response, which have been associated with an allergy response. Tissues that have a low ALVAL score have few macrophages or lymphocytes. Conversely, the tissues found to have a high ALVAL score demonstrate a predominance of macrophages and lymphocytes. Pro-inflammatory cytokines are primarily produced by these cell types (macrophages and lymphocytes).

For statistical analysis, we fit linear mixed models for each biomarker, with covariates being fluid type, ALTR and ALVAL, respectively. A log transformation was used here in order to meet the assumption of normally distributed errors. We tested the hypothesis that there is no relationship between fluid type, ALTR, or ALVAL and each cytokine biomarker with a Likelihood ratio test. In addition, we investigated individual contrasts within each level of categorical covariate and the reference level with a Tukey's HSD test to control for multiple comparisons. In all of the following, we consider p-values < .05 to indicate statistical significance

Results

Of the 42 cases of metal-on-metal implants undergoing revision, 39 showed identifiable intra-operative ALTR (ALTR \geq 1), two had isolated mechanical failure of the implant (ALTR = 0), and

one patient was not assigned an ALTR score (Table 1). Twenty-four of the 41 scored cases were found to have a moderate reaction (ALTR = 1) and fifteen cases were found to have a severe reaction (ALTR 2-3). The periarticular fluid in the ALTR cases was compared with that of 11 osteoarthritis patients, which served as controls.

Using the two sample t-test, eight of the nine biomarkers tested showed significantly elevated levels in patients with metal-on-metal reactions (ALTR≥1) compared to osteoarthritis controls, including IL-1ra, IL-6, IL-8, IL-10, IP-10, MCP-1, RANTES, and TNF-alpha (Table 2). VEGF did not significantly differ between groups.

42 biopsies were submitted for gold standard histopathological analysis via ALVAL scoring. Eight samples had a low (1-4), 30 samples had a moderate (5-8), and four samples had a high (9-10) ALVAL score (table 1). A statistically significant association was found between continuous ALVAL score and four fluid biomarkers, including IL-6, IL-8, IP-10, and VEGF (table 3). For each unit increase of ALVAL, IL-6 increases by 60%, IL-8 by 28%, IP-10 by 43%, and VEGF increases by 23%. These four cytokines are tightly associated with degree of articular damage directly assessed by ALVAL. Levels of IL-1ra, IL-10, MCP-1, RANTES, and TNFalpha showed no significant association with ALVAL score.

| Fluid Type | N | % |
|----------------------------------|----|---------|
| Metal on Metal | 42 | 100.00% |
| ALTR Score | 41 | 97.62% |
| ALTR = 0 (Mechanical Failure) | 2 | 4.88% |
| ALTR = 1 | 24 | 58.54% |
| ALTR = 2 | 10 | 24.39% |
| ALTR = 3 | 5 | 12.20% |
| Gender | | |
| Male | 16 | 38.10% |
| Female | 26 | 63.41% |
| Age (Mean) | 60 | |
| ALVAL | 42 | |
| Mild (1-4) | 8 | 19.05% |
| Moderate (5-8) | 30 | 71.43% |
| Severe (9-10) | 4 | 9.52% |
| Osteoarthritis | 11 | |

Table 1 – Clinical Characteristics of Patients Undergoing Revision of Metal-on-Metal Joint Replacement - *one patient no ALTR

| Fluid Type | IL-1ra | IL-6 | IL-8 | IL-10 | IP-10 | MCP-1 | RANTES | TNFa | VEGF |
|----------------|--------|-------|-------|-------|-------|-------|--------|------|------|
| Metal on Metal | 16287 | 14886 | 44752 | 16 | 62210 | 32802 | 2425 | 31 | 5090 |

| | | | | | | | | | |
|------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| <i>Standard Deviation</i> | 18238 | 23668 | 48237 | 11 | 86491 | 35281 | 3102 | 58 | 4487 |
| Osteoarthritis | 5538 | 1102 | 75 | 5 | 2162 | 450 | 9512 | 4 | 3772 |
| <i>Standard Deviation</i> | 17516 | 1212 | 109 | 5 | 2193 | 303 | 10511 | 2 | 3641 |
| <i>p (two sample t-test)</i> | <.001 | 0.001 | <.001 | <.001 | <.001 | <.001 | 0.028 | <.001 | 0.540 |

Table 2 – Mean Levels of Cytokines in Patients with Metal-on-Metal Revisions and Osteoarthritis Controls

| Biomarker | Estimate | Std.Error | z value | p value |
|-----------|----------|-----------|---------|---------|
| IL-1ra | 0.0381 | 0.0735 | 0.518 | 0.604 |
| IL-6 | 0.468 | 0.1312 | 3.5669 | <.001 |
| IL-8 | 0.2486 | 0.1047 | 2.3754 | 0.018 |
| IL-10 | 0.0281 | 0.0643 | 0.4374 | 0.662 |
| IP-10 | 0.3598 | 0.0886 | 4.0587 | <.001 |
| MCP-1 | 0.0797 | 0.0926 | 0.8608 | 0.389 |
| RANTES | -0.06 | 0.0835 | -0.7191 | 0.472 |
| TNFa | 0.0601 | 0.1131 | 0.5311 | 0.595 |
| VEGF | 0.211 | 0.0763 | 2.7666 | 0.006 |

Table 3 - ALVAL Regression – levels of IL-6, IP-10, and VEGF were found to be significantly higher in patients with higher degrees of ALVAL

Discussion

Adverse local tissue reaction after metal on metal hip replacement and hip resurfacing are proving to be more common than previously anticipated. These reactions can be quite severe with significant soft tissue damage being reported in some cases. The reactions may result in large fluid collections, tissue necrosis, pseudotumors/masses and there have been isolated case reports of nerve palsy in some patients. Clearly, this spectrum of findings is a different clinical entity than the body's normal immune response to osteoarthritis.

The findings of the current study demonstrate definite differences between the synovial fluid in osteoarthritis and ALTR. In particular, levels of IP-10, IL-9, IL-8, IL-6, TNF- α , MCP-1, and IL-1ra were found to be markedly elevated in patients with ALTR. Interestingly, in a study published by Shanbhag et al exploring cytokine levels in patients with polyethylene induced osteolysis using protein chips, the authors found a mild elevation in expression of IL-6, IL-8 and IP-10 when compared to osteoarthritic controls. This mirrors the present study. We found that the osteoarthritis controls had the lowest levels of these select cytokines, and the cases of metal hips without ALTR had more mild (though not significantly lower) elevations in comparison. However, the cytokine expression in the ALTR group is markedly elevated when compared to the other 2 groups.

The primary immune cells present in the peri-articular tissues in patients with ALVAL (which is a distinct histologic diagnosis related to ALTR) are lymphocytes and macrophages. The lymphocytes suggest a hypersensitivity type response. Macrophages tend to appear in response to increasing levels of wear debris. Both of these cell types are the primary producers of the cytokines seen in the peri-articular fluid. The predominance of these cell types which we

have observed in the peri-articular tissues histologically, helps to explain the high levels of cytokines and chemokines which we have reported here.

As shown in table 3, several of the aforementioned biomarkers demonstrated significant associations with histopathological damage as measured by ALVAL score. Intra-articular levels of IL-6, IL-8, IP-10, and VEGF correlated well with the degree of tissue damage seen on pathological specimens. These findings have potential for diagnostic value in patients for whom revision surgery is not obvious.

The primary limitation on this study is a lack of ALVAL score in a small subset of the ALTR patients (18 out of 60 patients with ALTR > 1). In addition, it would be valuable to compare the cytokine levels in our ALTR patients to those of patients with non MM hip implant such as the polyethylene currently used in a majority of cases.

Conclusion:

The immunological profile of intrarticular fluid is different in patients with metal-on-metal compared to those with osteoarthritis controls, with several cytokine markers showing impressive elevations. Further, many of those same cytokines have a significant correlative relationship with actual tissue damage as measured by the gold standard of histopathological ALVAL score. These data and results can help to empower the clinician struggling with the decision to revise a metal-o

Citations

1. Bozic K, Kurtz S, Lau E, Ong K, Chiu V, Vail TP, Rubash HE, Berry D. The epidemiology of bearing surface usage in total hip arthroplasty in the United States. *J. Bone Joint Surg. Am.*, July 1, 2009; 91(7): 1614 - 1620.
2. Campbell P, Ebrahimzadeh E, Nelson S, Takamura K, De Smet K, Amstutz HC. Histological features of pseudotumor-like tissues from metal-on-metal hips. *Clin Orthop Relat Res.* 2010 May 11. [Epub ahead of print]
3. Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP. An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. *J Bone Joint Surg Am.* 2005 Jan;87(1):18-27.
4. Glyn-Jones S, Pandit H, Kwon YM, Doll H, Gill HS, Murray DW Risk factors for inflammatory pseudotumour formation following hip resurfacing. *J Bone Joint Surg Br.* 2009 Dec;91(12):1566-74.
5. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natsu S, Nargol AV. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. *J Bone Joint Surg Br.* 2010 Jan;92(1):38-46.