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Metal Hypersensitivity:

Pathophysiology and Diagnostic Tools

Editorial

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From The Editor

Metal Release and Hypersensitivity in Total Joint Arthroplasty

William M. Mihalko MD, PhD
JR Hyde Chair and Professor
Joint Graduate Program Chair
in Biomedical Engineering
University of Tennessee
Health Science Center
Campbell Clinic Orthopaedics
Memphis TN USA

The disparity between total knee arthroplasty (TKA) and total hip arthroplasty (THA) patient-perceived outcomes is concerning, with TKA patients being satisfied (80-90%) at a much lower rate than their THA counterparts. (94-97%). In many cases the TKA patients have vague subjective complaints about residual pain and swelling, an aching joint, or an inability to kneel or squat. Other more objective complaints may include a skin rash or constant or recurrent effusions in a joint. After infection has been ruled out along with implant suboptimal alignment, instability, and other causes of residual pain, a metal hypersensitivity reaction must be considered.

While TKA largely has seen decades of successful outcomes, as clinicians we should focus on improving the number of patients who are satisfied after their TKA. Over the last two to three decades a focus on patient-perceived outcomes has spotlighted that nearly 1 out of 5 patients may not be satisfied with their TKA result. About 15 years ago, dermatologists suggested that orthopedic surgeons begin skin-patch testing (SPT) of patients before insertion of metal implants. It was then suggested that the patients with poorer outcomes could be suffering from a metal hypersensitivity reaction. Over the last two decades, dermatologists have noted that nickel allergy in patients continues to climb when skin-patch testing results are compared over time.

In North America, such sensitivity has been reported in over 18% of individuals. But several authors in this publication point out the inherent issues with relying on SPT when applied to the presence of an implant in deep tissue. (In 2011, along with Drs. Josh Jacobs and Stuart Goodman, we published a rebuttal to the first dermatology suggestion of SPT for all orthopedic patients in *AAOS Now*). Today, there is still not enough data to suggest that this recommendation should be followed. In this issue of CeraNews, experts point out that SPT reactions rely on langerhan cells which are dendritic-derived cells, whereas deep-tissue reactions are driven by lymphocytes, monocytes, local cytokines, and antibodies. There also have been multiple reports where a SPT has converted after an implant was placed in a patient and cases where a patient with a nickel-positive SPT experienced a good clinical outcome after undergoing a primary TKA that had trace nickel in its alloy.

Many orthopedic surgeons still consider metal hypersensitivity as a cause for pain and dissatisfaction after a TKA as a diagnosis of exclusion. When a metal hypersensitivity reaction is suspected, surgeons should rule out all other common causes (i.e., infection, arthrofibrosis, suboptimal implant alignment) before going down the metal hypersensitivity pathway. Complaints of recurrent or constant effusion, continued pain, and never having a period of satisfaction also are common symptoms of a septic low-level infection, which is why it is imperative that infection first be ruled out. In the U.S., we are limited in the tests that we can order. While a lymphocyte transformation test (LTT) is available in most laboratories, not all insurance companies will cover its cost and not all labs have consistent protocols, which makes it difficult to rely on some results. Dermatologists can perform a SPT, but these typically cost well over $1,000. MELISA tests are not readily available and

William M. Mihalko MD, PhD

genetic testing has not become available or approved in the USA. (As you will read in this issue, the test has had promising results and is being used in other countries.)

Genetic testing is the newest diagnostic test on the scene, based mostly on the ALVAL determinants from our metal-on-metal (MoM) hip arthroplasty bearing surface experiences. ALVAL is now looking like a scenario that occurs more often in TKA revisions than previously thought, with up to 30% of TKA revision surgeries showing evidence of ALVAL. Taking into account the number of revisions in the first five years after primary TKA and then the fact that 30% of patients may show signs of ALVAL, this may represent a more true numerator of hypersensitivity reactions after TKA surgery. While a number of publications have shown improvements of metal hypersensitivity-diagnosed patients after undergoing revision TKA surgery with an alternative implant material (ceramic coatings, ceramicized metals, BIOLOX®*delta* or alumina-based implants), there also have been reports of patients who have not seen improvements after exchanging their implants for ones made of a nickel/cobalt chrome-free biomaterial.

Dr. Summer, from the Munich Implant Allergy group, reports in this edition that they advocate a multifaceted approach to diagnosis of implant hypersensitivity. Using SPT along with LTT results as well as IL-1α and IL-1β stimulation testing and genetic testing is beneficial. Their genetic testing focuses on identifying single nucleotide polymorphisms (SNP) of IL1RN. They think that by identifying these variants they can help predict which implants may be best on an individual basis.

Dr. Caicedo, in this edition, discusses the fact that genetic testing is in its early stages. He says utilizing human leukocyte antigen (HLA) haplotypes in patients who had ALVAL reactions might help some patients, but that specific clinical outcomes based on these results may be challenging.

We performed a single nucleotide polymorphism study on 44 patients with symptomatic pain and high cobalt and chrome levels after MoM THA and could not find a correlation with any SNPs that were identified. (Mihalko et al ISTA 2015) There was a weak association with an SNP for IL-15 in some patients with high cobalt and chrome circulating blood levels, but it was found to not be consistent.

Sensitization of the host: Is Nickel the Foremost Culprit?

For decades now, the literature has focused on nickel. **Dr. Langton**, in this edition, discusses how nickel allergy in orthopaedics has been ill defined as a cause of arthroplasty failure. While there are trace amounts of nickel in the grain boundaries of cobalt-chrome alloys, we know that cobalt-chrome alloys have been used for decades in a very successful manner. Dr. Langton's group also reports on how many ALVAL patients from MoM hip-bearing cases were found to have positive LTT results for nickel.

We know that these cobalt-chrome alloys have been labeled as the cause of hypersensitivity reactions, based on our experiences with MoM and taper-corrosion issues in total hip arthroplasty with ALVAL reactions. In the European Union, cobalt-containing implants are now labeled as carcinogenic. This has alerted the U.S. Food and Drug Administration (FDA) to focus on the possibility of cobalt-chrome alloys in TKA being an issue in a subset of patients. A research focus group (ARCTIC-Arthroplasty Retrieval and Cellular Tissue Investigation Consortium) was established after supporting a multi-center retrieval study by the FDA. Some preliminary results from revision and necropsy-retrieved synovial tissues around TKA implants showed that no nickel has been detectable, but larger amounts of chromium compared with cobalt are consistently being found in the synovium adjacent to CoCr TKA implants. In comparing bilateral synovial tissue in necropsy specimens where one side has a TKA and the other a native knee, there are significantly higher cobalt and chrome levels on the TKA side. Another recent report

has linked the amount of Co and Cr found in the synovium via inductively coupled mass spectrometry (ICPMS) analysis was to be correlated to time of implantation. (Kurtz et al 2024)

These preliminary findings suggest that the presence of the cobalt chrome implant has a local and systemic effect on the body with time; this might be one of the avenues of hypersensitization in a subset of TKA patients. We have also found necropsy specimens where a significant amount of metal- laden synovium was visually present, making no question that a patient could get sensitized to the metal alloy byproducts (Figure 1).

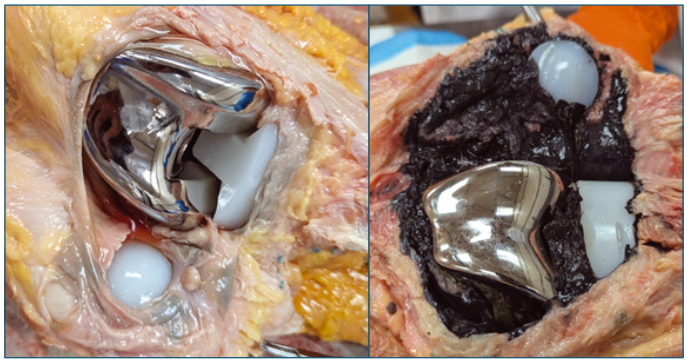

Figure 1A and B: Two examples of necropsy retrievals. A (left) shows mild synovial gray metal staining where B (right) shows severe metallosis of the entire surrounding synovial layer. Neither example showed any evidence of metal contact between the bearing or non-bearing surfaces, but the one on the right did have a periprosthetic femur fracture fixed with a side plate. Again, there was no evidence of implant metal contact

Other biomaterial byproducts, however, also have been found in the synovial tissue at much higher rates in our repository study. Polymethyl-methacrylate (PMMA) has been found in histology-prepared samples from this study group far more often than other metals (Figure 2).(ORS podium presentation 2025)

A recent 2025 report on 50 nickel-allergy patients undergoing TKA found no correlation with poor outcomes and severity of nickel allergy (Chimento et al 2025). However, a recent meta-analysis that included eight articles and over 33,000 TKA patients

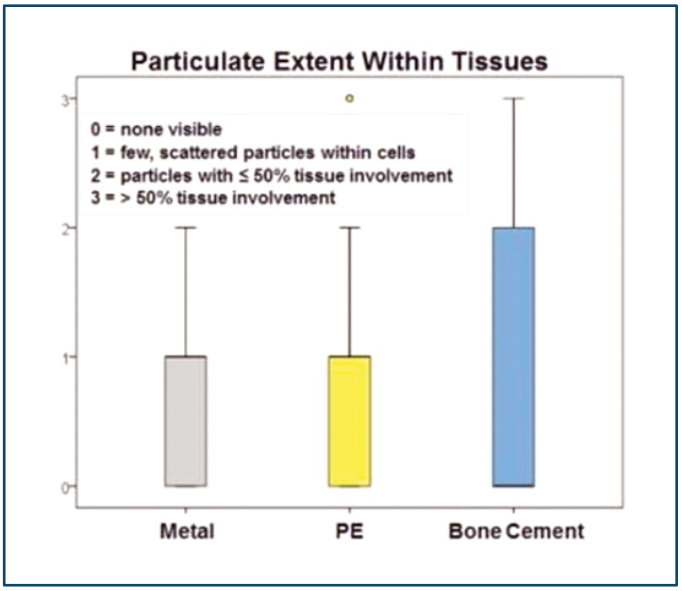

Figure 2: Extent of particles visualized under histologic analysis from synovial samples from revision TKA cases. Metal and polyethylene were seen at a one-to-one ratio, but bone cement particles were significantly found in larger number.

found that metal-allergy patients had poorer reported outcomes (Soler et al 2024). Siljander et al just reported on 287 patients who had a self-reported nickel allergy and compared them with a large cohort of patients without a self-reported allergy and found no difference in revision rates or with outcomes (Siljander et al 2024). Clearly, the literature shows mixed results when it comes to nickel allergy and TKA outcomes.

Revision is not always the answer

While newer diagnostic tools, such as genetic testing, have been developed from what we learned during the MoM ALVAL reactions, a perfect correlation to TKA may not be evident. Also, the ALVAL reactions and circulating metal levels may not show a correlation with genetic testing. The Mayo Clinic in 2016 reported on 161 primary TKAs (127 patients, 56 SPT positive) after SPT compared with a matched control group of 161 TKAs and found no difference in failures at 5 years or in outcomes. Clearly this study determined a positive SPT may not

be consequential and revision may not always make a difference. I personally have seen patients in my practice with a painful and chronic effusion after a primary TKA with a diagnosis of exclusion and a positive SPT and LTT for nickel that had no improvement with revision surgery. Therefore, I inform patients that revision surgery cannot always be relied on for improved results.

The problem remains and more data is necessary

While SPT, LTT, and lymphocyte proliferation testing have all been used for diagnosing metal allergy in TKA patients, there has not been a reported good correlation between these tests in the literature. (Dennis 2022, Malihias 2023) Careful assessment of genetic results should be taken into consideration. As has been explained above, a hypersensitivity reaction requires a pre-sensitized host. Previous exposure to the metal antigen triggers an initial immune cascade, and when re-exposed an exaggerated immunological reaction can occur. Sometimes it takes repeated exposure to an antigen before a true reaction occurs. Environmental and geographical location also have been shown to affect the patients' sensitization to metals. Many reports in the literature have shown good outcomes after TKA in patients with self-reported or positive SPT, so there may not be a perfect correlation with a significant false positive rate of results. According to SPT results, metal sensitivity in the general population is approximately 18% nickel, 7% cobalt (cobalt chloride), 3% chromium (dichromate), and cross-reactivity between nickel and cobalt is thought to be common. That being said, I do not believe that surgeons feel that we are seeing 20% or higher rates of orthopedic-implant patients with a metal hypersensitivity diagnosis. Clearly, the issue is more complicated and deep-tissue reactions may not be as prevalent. This brings up another issue with SPT, because as mentioned above, the metal byproducts utilized in SPT are not the same as those produced in the deep joint tissues from cobalt chrome or other orthopedic implant alloys.

Continued research

Local physiological environment around the implant may also have an impact on metal release around a femoral component after a TKA. We have hypothesized in my lab that inflammatory cell-induced corrosion (ICIC) may contribute to metal release of Co and Cr in a subset of individuals. While the pits on retrievals from revision THA/TKA have been reported at a high incidence (up to 60% in some retrieval archives), we have found in our necropsy-retrieval archive that the evidence was much lower (17%). This was most likely due to the fact that necropsy-retrieved implants are much less likely to be exposed to electrocautery effects (which has been proven to cause these pits found on implants). During revision surgery, most surgeons utilize electrocautery around the implant to aid in extraction. We have also found that in a small percentage of OA synovial fluid samples obtained during TKA surgery there was a significantly higher corrosion rate against CoCr (an order of magnitude greater corrosion rate in 5% of patients).

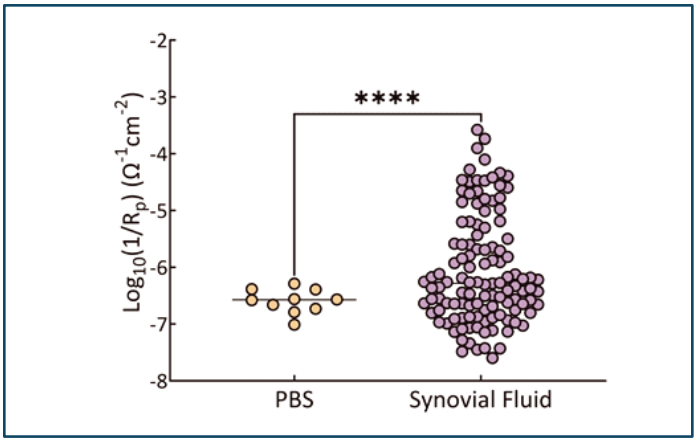

Figure 3: Log scale range of corrosion rates for phosphate buffered saline compared with osteoarthritis synovial fluid obtained at time of primary TKA. More than an order of magnitude variation against CoCr was seen for OA synovial fluid. This variation could accelerate corrosion by-products being released after implantation of a CoCr femoral component adding to sensitization of the host.

So local physiology combined with environmental exposure could be sensitizing patients after their TKA, which might cause local inflammatory response and a poor patient-reported outcome. We continue to follow these patients with high synovial fluid corrosion rates longitudinally to determine if there is a correlation with Knee Injury Osteoarthritis Outcome Score Joint Replacement (KOOSJR) scores. To date, the parameters found to correlate with outcome scores are higher volume of synovial fluid at the time of surgery and pH.
There is clearly a void in that data we need to analyze to determine who truly has and who may develop a metal hypersensitivity reaction.

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I also want to acknowledge the ARCTIC study group for the insights reported above concerning metal release around TKA implants.

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Implant Allergy Testing Possibilities: Insights from the LMU Munich

Introduction

Implant allergy testing has emerged as a crucial tool in addressing the increasing number of patients presenting with adverse reactions to implanted medical devices. As the use of implants in medical practice continues to grow, so too does the need for precise diagnostic methods to identify and address potential allergic reactions and to distinguish them from other inflammatory reactions. These reactions can range from localized inflammation to systemic immune responses, underscoring the importance of accurate and timely testing to mitigate complications and ensure patient safety.

The causes of implant allergies are multifaceted. Common triggers include hypersensitivity to metals such as nickel, cobalt, and chromium, which are often used in orthopedic and dental implants. Non-metal components, such as polymers, ceramics, and adhesives, can also provoke allergic responses in susceptible individuals. These reactions are typically mediated by antigen-specific T cells in the form of the so called delayed-type hypersensitivity. Factors such as a patient's genetic predisposition, history of allergies or atopic diseases, and the specific materials used in the implant play significant roles in the development of these reactions.

Symptoms of implant allergies vary widely and can affect both the implant site and the patient's overall health. Localized symptoms may include redness, swelling, warmth, pain, and delayed wound healing, often mimicking signs of infection. Systemic symptoms, though less common, can include fatigue, joint pain and skin rashes. These symptoms can significantly impact a patient's quality of life, making timely and accurate diagnosis crucial.

The Munich Implant Allergy Research Group in the Clinic of Dermatology and Allergology at the Ludwig-Maximilians-University has been running a special implant allergy consultation for many years and has seen over 4000 patients with a suspected implant allergy during this period. With this clinical and diagnostic experience we are able to explore, to develop, and to refine testing methodologies to ensure patient safety and optimal outcomes. Our mission is to bridge the gap between clinical practice and cutting-edge research, enabling healthcare providers to make informed decisions based on robust diagnostic tools. Our multidisciplinary approach combines dermatology, immunology, orthopedics, and laboratory medicine, creating a comprehensive framework for diagnosing and managing implant allergies.

This article delves into four primary testing modalities:

- patch testing,
- lymphocyte transformation assay (LTT),
- IL-1α/IL-1β stimulation test, and
- genetic testing.

Each method offers unique insights and can play a special role in a cohesive diagnostic strategy. By sharing our perspectives and experiences, we aim to shed light on the potential and challenges of these techniques, contributing to the broader understanding and advancement of implant allergy testing.

PD Dr. Burkhard Summer

Patch Testing: The Traditional Cornerstone

Patch testing is often the first diagnostic step when an implant allergy is suspected. This method involves applying small quantities of suspected allergens, such as metals or chemicals commonly used in implants, to the patient's skin under occlusive patches. After 48-72 hours, the skin is examined for signs of an allergic reaction (Figure 1).

Importantly, a late reading, performed after 96 hours or later, can significantly enhance the test's diagnostic accuracy. Delayed-type hypersensitivity reactions often require more time to manifest, and a late reading ensures that subtle or slow-developing responses are not missed.

factors such as individual skin reactivity and the potential for irritant reactions can complicate interpretation.

To mitigate these limitations, we have adopted a meticulous approach to patient history-taking and use a standardized panel of allergens. When possible, we also consider environmental and occupational exposures that might influence the results.
For example, we employ advanced testing panels tailored to specific implant materials, which include not only metals but also polymers, ceramics, and composite materials.
Despite its constraints, patch testing remains a cornerstone for initial screening due to its accessibility and established methodology.

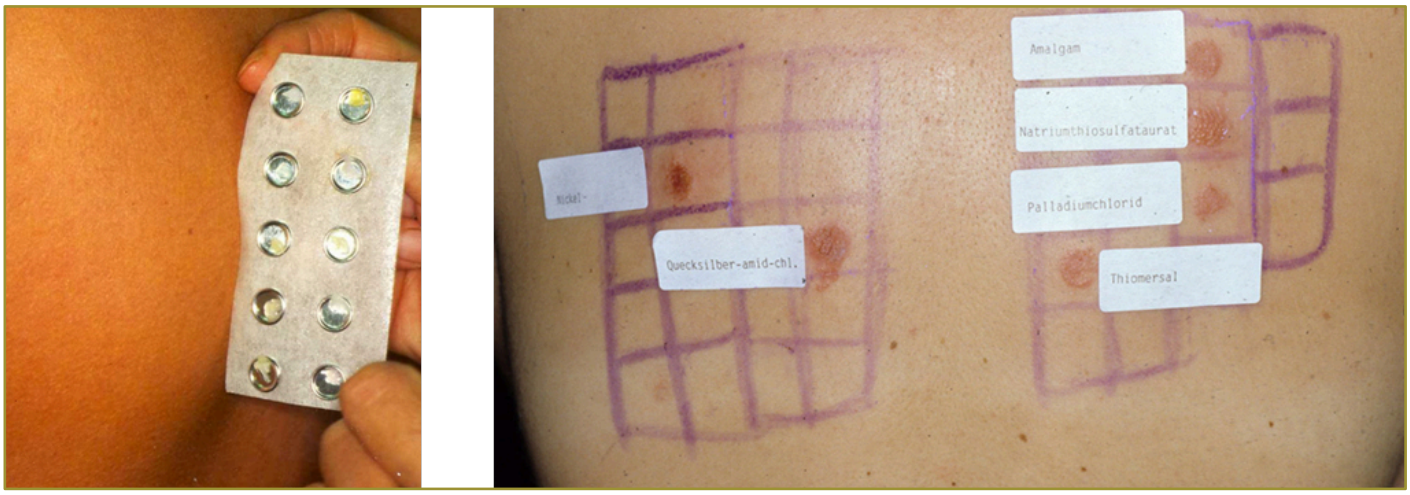

Fig 1: Application of patch test on patients back (above) and reading on day 3

This practice reduces the risk of false-negative results and provides a more comprehensive assessment of the patient's reactivity.

From our perspective, patch testing is particularly valuable for identifying delayed hypersensitivity reactions, especially to metals like nickel, cobalt, and chromium. However, its limitations cannot be overlooked. The results are not always predictive of systemic reactions, particularly those that occur deep within tissues around the implant. Furthermore,

Lymphocyte Transformation Assay: A Dynamic Assessment

For our patients in the special implant allergy consultation, we supplement the epicutaneous test with the lymphocyte transformation assay (LTT). This blood-based test evaluates whether a patient's lymphocytes react to specific allergens by measuring cell proliferation in response to the suspected substances.

Our experience with LTT has highlighted its superior sensitivity for detecting systemic immune responses compared to patch testing. For example, we have identified a quite high number of patients with positive LTT tests to nickel, cobalt or chromium when patch tests to these substances were negative.

The test itself involves isolating lymphocytes from the patient's blood and exposing them to potential allergens in a controlled laboratory environment. Proliferation rates are then quantified using advanced markers, such as incorporation of fluorescent dyes. These techniques allow us to measure even subtle immune responses, providing invaluable data for complex cases.

However, LTT is not without challenges. It requires specialized laboratory equipment and expertise, and its cost can be a barrier for some patients. The interpretation of results also demands caution, as not all lymphocyte proliferation correlates directly with clinical symptoms. To overcome these hurdles, we are evaluating our LTT tests in larger studies and also on large groups of healthy control blood donors and perform continuous training to ensure that LTT is applied judiciously and interpreted accurately (Figure 2).

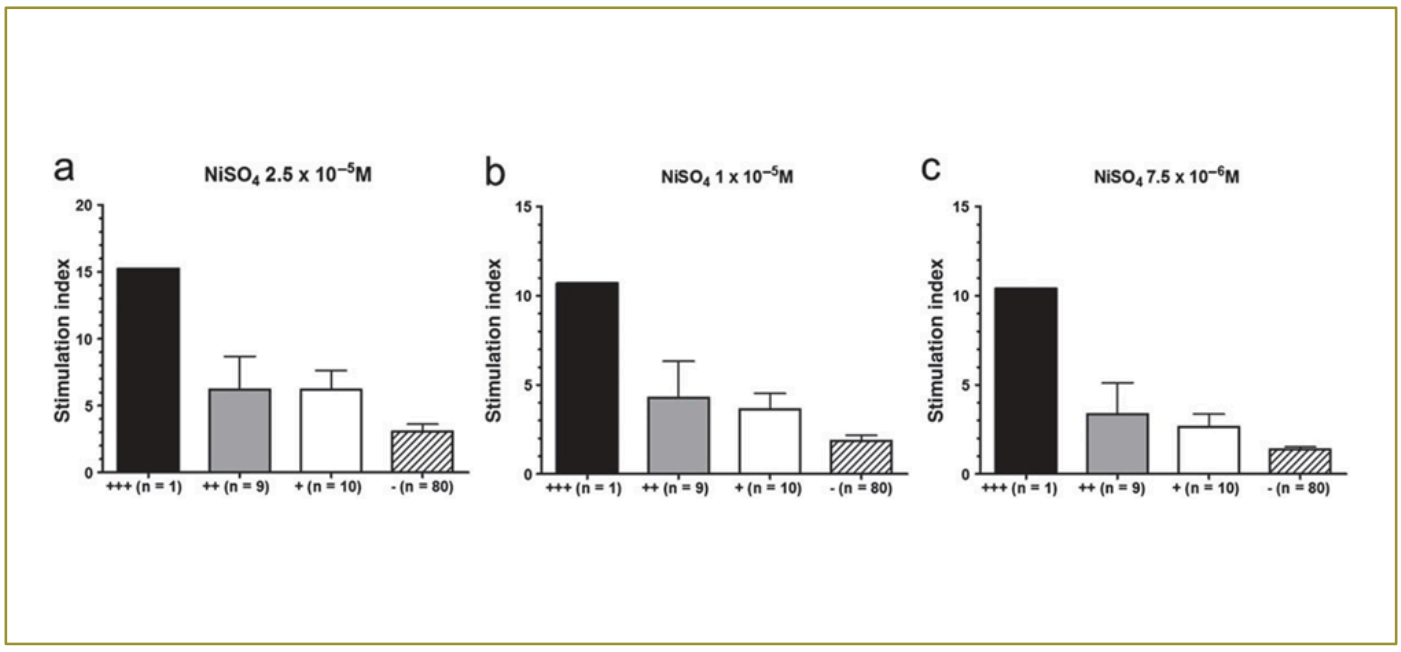

Fig 2: Lymphocyte transformation test reactivity to 3 Nickel concentrations [(a) NiSO4 2.5x10-5M, (b) NiSO4 1x10-5M, and (c) NiSO4 7.5x10-6M] in patch test-positive and patch test-negative individuals (in total, 100 individuals) irrespective of history (from Ständer et al. 2017)

IL-1α/IL-1β Stimulation Test: A marker for hypersensitivity?

The IL-1α/IL-1β stimulation test is an emerging method for assessing implant allergies by measuring the inflammatory response to specific materials. This test evaluates the release of interleukin-1α and interleukin-1β, two key cytokines involved in inflammation and immune regulation, when patient cells are exposed to implant materials.

This method provides valuable insights into the pro-inflammatory potential of implants, especially in cases where conventional tests yield inconclusive results. The IL-1α/IL-1β stimulation test can in special cases be useful for assessing materials considered biocompatible, such as titanium or certain polymers, as it can detect low-grade inflammation that may contribute to implant failure or chronic symptoms.

However, the test is not without its limitations. While it offers a more direct measurement of inflammatory potential, it is still a laboratory-based test requiring sophisticated equipment and technical expertise. Moreover, the clinical relevance of elevated IL-1α/IL-1β levels is not fully understood, as inflammation can result from non-specific stimuli or unrelated conditions.

Interpretation of results must therefore be done cautiously and in conjunction with other diagnostic findings.To address these challenges, we advocate for standardized protocols and further research into the clinical significance of IL-1α/IL-1β measurements in larger and especially prospective studies.

Genetic Testing: The Frontier of Personalized Medicine

The advent of genetic testing has opened new possibilities for predicting implant adverse reactions, particularly in the pre-implantation phase. Variants in genes related to immune function, such as HLA (human leukocyte antigen) alleles, have been associated with an increased risk of hypersensitivity reactions to certain materials.

Among the genetic tests, the detection of IL1RN polymorphisms stands out as a significant advancement in implant allergy diagnostics. IL1RN encodes the interleukin-1 receptor antagonist, a critical regulator of inflammatory responses. Specific polymorphisms in this gene can influence the balance between pro-inflammatory and anti-inflammatory signals, predisposing individuals to exaggerated immune responses when exposed to implant materials (Figure 3). By identifying these genetic variants, we can better predict a patient's likelihood of developing implant-related inflammation or allergy. This predictive capacity represents a crucial advantage, allowing for preemptive measures, such as selecting alternative materials or enhancing postoperative monitoring.

Our approach to genetic testing involves analyzing patient DNA for specific polymorphisms associated with immune response. For example variations in cytokine-producing genes may predict inflammatory responses to polymers or ceramics. By integrating these findings with clinical data, we aim to create a comprehensive risk assessment model.

However, this approach also raises ethical and practical questions. How should genetic information be communicated to patients? What safeguards are needed to prevent misuse of genetic data? These are questions we grapple with as we navigate the integration of genetic testing into routine clinical practice.

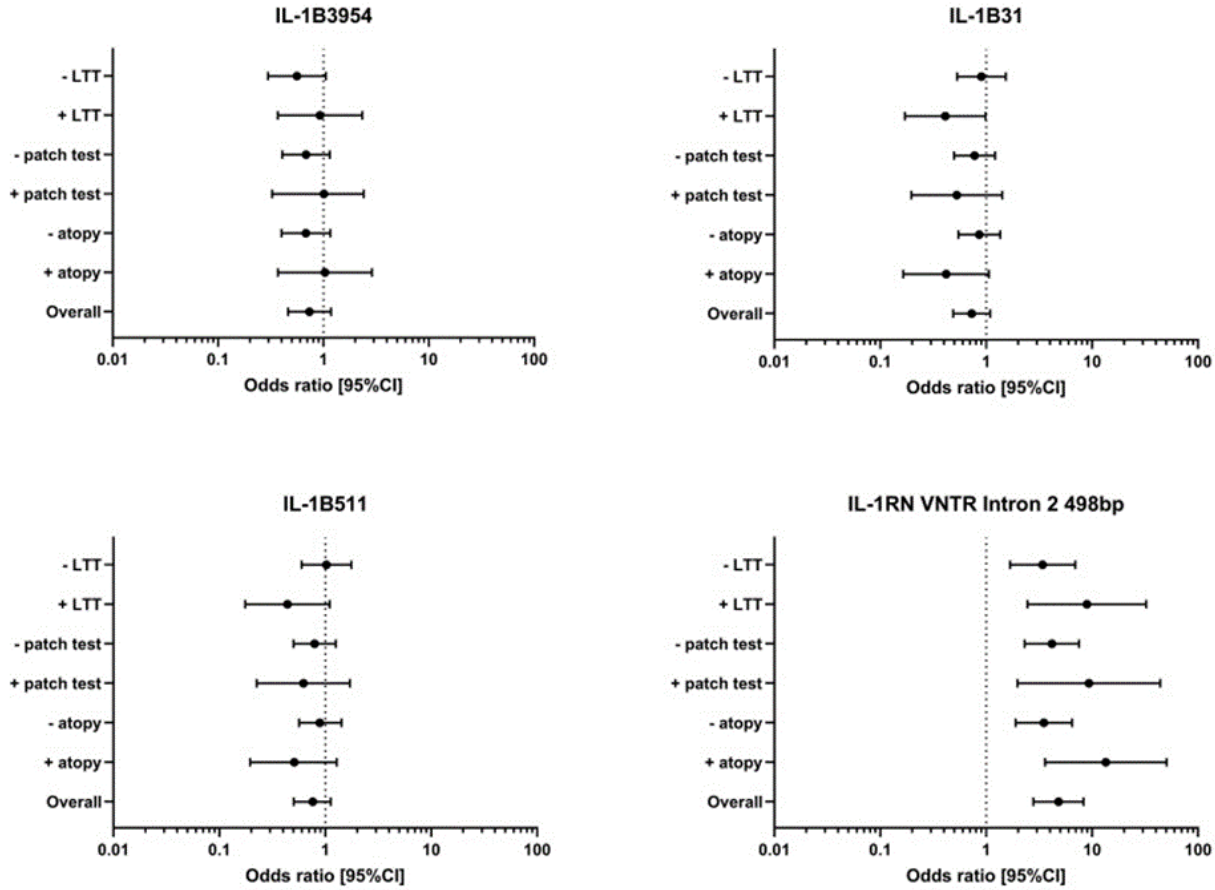

Fig 3 Odds ratio (and 95%confidence interval CI) of the IL-1B polymorphism IL-1B 3954, IL-1B 31, IL-1B 511 and the IL-!RN VNTR Intron 2 498bp allele are given for the risk analysis of the symptomatic arthroplasty paitent group against the control group overall and also for the subgroups atopy (yes/no), patch test to metal (positive/negative) and LTT to metal (positive/negative) (from Summer et al 2022)

Combining Testing Modalities: A Comprehensive Approach

While each of these testing methods has its strengths, their true potential lies in their combined application. For instance, a patient with suspected implant allergy might undergo patch testing to identify surface allergens, followed by LTT for systemic validation, and genetic testing for predictive insights. By integrating these modalities, we can achieve a more accurate and holistic understanding of the patient's immune response.

Additionally, we are explored the use of emerging technologies, such as proteomic and metabolomic analyses, to complement traditional testing. These advanced techniques will perhaps allow us in the future to identify biomarkers that will provide further insight into immune activation and inflammation.

The Munich Implant Allergy Research Group's Vision

As a group deeply invested in the field of implant allergy, we strive to combine the strengths of the three modalities—patch testing, LTT, and genetic testing—into a cohesive diagnostic strategy. Our vision is to create a patient-centric approach that emphasizes early detection, accurate diagnosis, and tailored interventions.

We advocate for multidisciplinary collaboration, involving dermatologists, immunologists, orthopedic surgeons, and laboratory specialists. Through such collaboration, we can provide comprehensive care and advance our understanding of implant allergies.
Looking forward, we see a future where genetic testing becomes a routine part of pre-implantation assessment, and innovative biomarkers further enhance the sensitivity and specificity of tests like LTT. Meanwhile, patch testing will likely retain its role as a practical, first-line diagnostic tool.

Conclusion

Implant allergy testing is a dynamic and evolving field. Our Munich Implant Allergy Research Group remains committed to refining and advancing testing methodologies to ensure that patients receive the best possible care. By combining traditional approaches like patch testing with cutting-edge techniques like LTT, and genetic testing, we aim to set a gold standard in implant allergy diagnostics and management.

Corresponding Author:
PD Dr. rer. biol. hum. Burkhard Summer
AG Allergomat
Ludwig Maximilian University Hospital
Department of Dermatology and Allergology
Frauenlobstr. 9-11
Munich - Germany

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Understanding the Pathophysiology of Metal Hypersensitivity

Metal hypersensitivity is a complex and often debated topic in orthopedics, especially concerning its impact on implant failure. Despite extensive research spanning over four decades, delayed-type hypersensitivity (DTH) responses to orthopedic implant degradation products remain challenging to predict and manage.

Metal hypersensitivity is a complex and often debated topic in orthopedics, especially concerning its impact on implant failure. Despite extensive research spanning over four decades, delayed-type hypersensitivity (DTH) responses to orthopedic implant degradation products remain challenging to predict and manage. It is well established that DTH responses to implant metals are associated with specific pro-inflammatory cytokine activity, histological markers of cell migration, and clinical symptoms, making the diagnosis of metal hypersensitivity relevant in the context of implant performance and patient outcomes [1-4]. Preoperative metal sensitivity testing has shown to improve outcomes when considered in surgical planning of implant revision surgeries, though the inconsistent link between pre-existing metal sensitivity and implant failure has sometimes limited its clinical application [5-7]. Notably, over 10% of orthopedic patients exhibit metal sensitivity pre-operatively, underscoring its importance in patient management.

The pathophysiology of metal hypersensitivity primarily involves a cell-mediated immune reaction distinct from particle-induced osteolysis, also known as "particle disease."

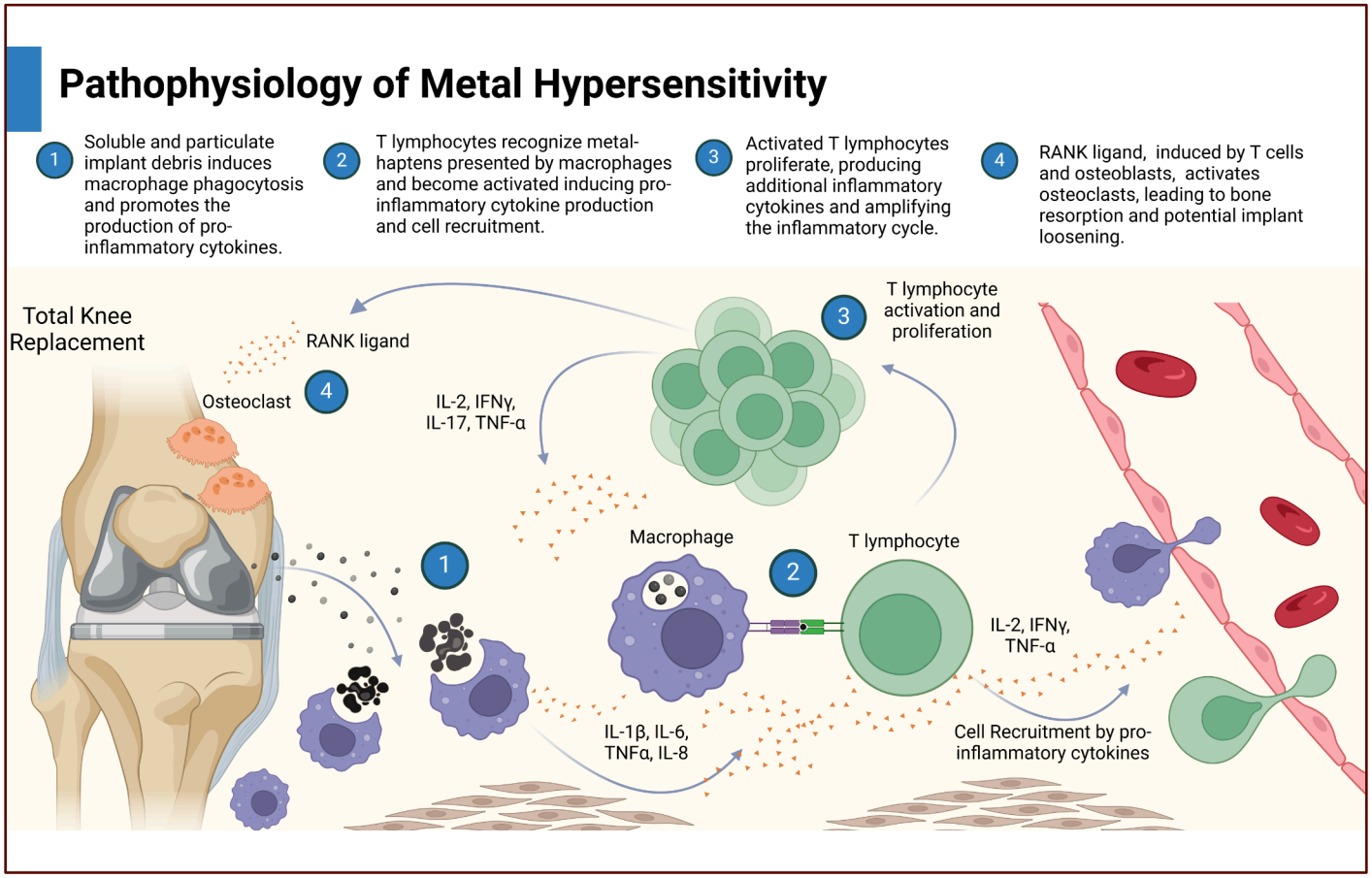
Particle disease is a chronic inflammatory response driven by macrophage interaction with implant debris over many years. In contrast, DTH responses, typically triggered by lymphocytes in response to metal haptens, are associated with worsening symptoms and earlier implant failure. These adaptive immune reactions are specific; lymphocytes recognize and respond to metal ions released from the implant, setting DTH responses apart from the general innate inflammatory responses observed in particle disease [8-10].

The immunological mechanisms behind metal sensitivity are initiated by the generation of metal ions due to implant wear and corrosion degradation products. Released metal ions interact with serum proteins, forming hapten-protein complexes that alter protein structure and activate the immune system. These metal-altered proteins are then processed by antigen-presenting cells (APCs), which present them to T-cells, prompting activation, proliferation and thus a hypersensitivity reaction [1;4]. This reaction, also known as a Type IV T-cell-mediated response, leads to symptoms such as aseptic pain and swelling around the implant and, in some instances, dermal manifestations like hives or redness, although such skin reactions are less common [2;11;12].

Metal hypersensitivity prevalence varies across populations, with about 10-15% of the general population demonstrating sensitivity, predominantly to nickel followed by chromium and cobalt. Among patients with metal implants, sensitivity is even more prevalent: approximately 25% of those with functioning implants and up to 60% of patients with painful or failing implants show sensitivity to metal ions[4]. The prevalence of hypersensitivity reaches as high as 76% in some cases of failing metal-on-metal implants, indicating a strong mechanistic relationship between metal exposure and the immune response [13;14].

A metal hypersensitivity response is primarily mediated by Th1 T-helper lymphocytes, which produce pro-inflammatory cytokines, such as interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), RANK ligand and interleukins (IL-2, Lt-α) upon activation [3;15;16]. Other studies have found an involvement of IL-17 producing Th17 lymphocytes in metal contact dermatitis[17]. These cytokines recruit and activate other immune cells like macrophages, monocytes, neutrophils and osteoclasts, leading to

Marco Caicedo, PhD



sustained inflammation. This ongoing immune activation can establish a self-perpetuating cycle of cytokine release and immune cell recruitment, causing long-term tissue damage and bone resorption similar to autoimmune conditions in which the immune response is chronically active and dysregulated [8;18-20].

While hypersensitivity to metal debris is relatively uncommon, contributing to only 1-3% of aseptic implant failures among traditional metal-on-polymer type total joint replacement designs [2;4;21], the immune response is influenced by the specific characteristics of the implant debris (i.e. particles and soluble ions) that come off the implant surface. This suggests that implant material design and type play a significant role in managing hypersensitivity risk. Reducing metal debris can decrease hypersensitivity incidence, underscoring the importance of selecting appropriate materials for implant designs [2;4;21].

Understanding the pathophysiology of metal hypersensitivity and its role in joint replacement is crucial for optimizing patient outcomes and minimizing implant failure. Advances in pre-operative testing, surgical planning, and implant material design hold promise for better management of this complex immune response, ultimately enhancing the longevity and performance of joint replacements.

Exploring the Currently Available Testing Methods for Metal Allergies

Current available diagnostic methods for metal allergy in humans primarily includes dermal (patch) testing and in vitro lymphocyte transformation testing (LTT). Both assess immune response to metals, although each has distinct mechanisms and limitations for evaluating sensitivity in orthopedic implant contexts[22].

Dermal (Patch) Testing: Patch testing involves applying metal-containing agents to the skin to identify contact sensitivity after 48-96 hours. However, its applicability to deep tissue implant-related metal sensitivity is debated. This test engages unique skin antigen-presenting cells (APCs), particularly Langerhans cells, which differ from peri-implant APCs such as macrophages[1;18-20]. Dermal APCs contain Birbeck granules—specialized organelles for antigen processing—that are not present in peri-implant macrophages[23].

Also, T regulatory cells (Tregs) make up about 20% of CD4* T cells in skin, while in peripheral blood they constitute around 5–10%. This higher proportion in the skin highlights Tregs' crucial role in controlling inflammation and maintaining immune balance, suggesting that the immune response observed in the skin may not replicate that in a less regulated peri-implant environment [24].

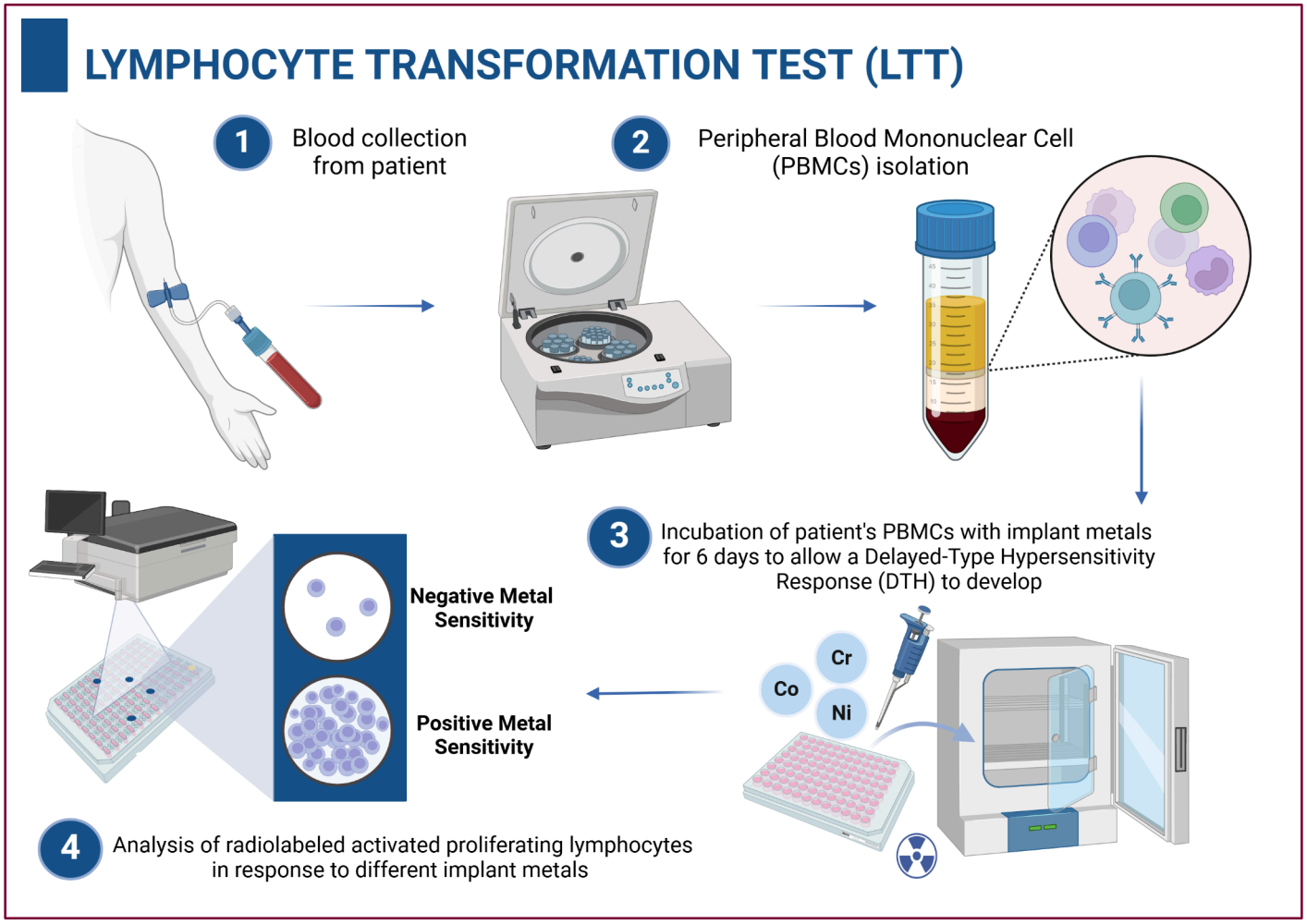
Several issues complicate patch testing's reliability for implant-related metal sensitivity. First, the subjective, operator specific nature of grading skin reactions (i.e. 0 to +3) leads to inconsistent standards, with interpretations varying among clinicians [25.] Additionally, skin-specific tolerance may suppress reactivity, potentially underestimating implant-related sensitivity[23]. Variability in host immune responses, influenced by environmental factors such as medications can also impact test accuracy[26]. Furthermore, patch testing carries a risk of sensitization in a previously non-sensitive individual[27] . Testing environments are also non-standardized and inconsistent, with patches applied on skin for 48-96 hours under variable uncontrolled cleanliness conditions. Lastly, commercially available patch tests lack standardized concentrations for important orthopedic metal alloys.

Lymphocyte Transformation Testing (LTT): LTT, a blood-based test, offers a more direct approach to assessing metal hypersensitivity by measuring lymphocyte proliferation in response to specific metals. This method involves isolating blood lymphocytes, exposing them to metal challenge agents in vitro, and using radioactive thymidine to quantify lymphocyte proliferation upon activation. The test produces a proliferation index that indicates immune reactivity to metal, allowing for a precise assessment of hypersensitivity [28;29].

LTT has significant advantages over patch testing for detecting implant metal-related sensitivity. Its higher sensitivity reduces false negatives, allowing for improved detection of immune responses to metal implants[22;28-29]. The quantitative data from LTT also enables dose-dependent analysis, as different concentrations can be tested to identify individuals who may respond to lower or higher levels of metal exposure[1]. Furthermore, the mixed mononuclear cells used in LTT—including T-cells and B-cells from the patient's blood—offer a closer mimicry to in vivo immune responses than patch testing, enhancing the test's relevance for peri-implant environments[30]. By testing across various metal concentrations, LTT enables clinicians to capture individual variability in immune response, which is critical for precise sensitivity assessments[11].

The objective quantitative nature of LTT eliminates operator dependency, producing consistency in test interpretations and reducing subjectivity [2]. Further, recent well-established studies suggests that LTT may have greater clinical relevance than patchtesting for detecting implant-related metal sensitivity[5;22;33-35]. This is evidenced by specific case and group studies where metal sensitivity diagnosis by LTT influenced the surgeon's implant choice resulting in a positive outcome for their patients after revision surgery[5;31-33].

LTT also offers a significant advantage over genetic predisposition testing by detecting a downstream, phenotypic immune response. This functional lymphocyte activation accounts for both genetic and epigenetic patient-specific factors by measuring



actual immune reactivity to metal haptens after all regulatory mechanisms at the gene, protein, and cellular levels have occurred[3;28]. As a result, the LTT provides a more comprehensive assessment of the immune system's functional response, capturing end-point phenotypic immune activation through cell surface activation markers (e.g., costimulatory molecules), cytokine/chemokine production, and resulting lymphocyte proliferation[15;30;36]. This approach goes beyond detecting specific alleles associated with a potential predisposition for metal sensitivity, which may not necessarily manifest as an actual immune response to metals given the wide array of genes and epigenetic factors associated with immunity[37].

Although LTT's high sensitivity may increase the risk of false positives, avoiding reactive metals is generally safer, as alternative materials are often available. In contrast, missing a metal sensitivity diagnosis with less sensitive methods could result in early implant failure and necessitate revision surgery. Consequently, LTT serves as the most reliable and effective diagnostic tool for assessing metal sensitivity, guiding implant selection, and managing patient care.

MELISA Test: The MELISA (Memory Lymphocyte Immuno-stimulation Assay) test is a variation of the LTT designed to detect metal hypersensitivity by similarly measuring lymphocyte proliferative reactivity in a modified population of peripheral blood

mononuclear cells (PBMCs)[38]. The test's deviation from using a standard PBMC population, combined with its reliance on microscopy for confirming lymphocyte reactivity, introduces technician dependent interpretative variability, thus questions about the utility of depleting antigen presenting cell in vitro may compromise clinical utility for implant-related metal hypersensitivity.

Genetic Testing: Although still in its early stages, the genetic sequencing of specific human leukocyte antigen (HLA) haplotypes has been proposed as a method for assessing a patient's risk of developing Adverse Local Tissue Reaction (ALTR) and aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL), as observed in patients with metal-on-metal cobalt-chrome (CoCr) implants[39;40]. Certain HLA class II alleles have been reported in a limited metal-on-metal total hip arthroplasty series to be associated with susceptibility to ALVAL, particularly when HLA genotypes are considered alongside factors such as age, gender, and metal exposure levels in recipients of metal-on-metal hip replacements[39]. However, it is important to recognize that predicting specific clinical outcomes based on genetic markers alone remains challenging, especially given the adaptability of immune responses and allele-disease associations, which vary greatly amongst ethnic populations[37;-41]. Conditions like DTH typically involve complex exposure interactions among multiple genetic and epigenetic factors. While specific HLA alleles may be associated with an increased propensity for T cell antigen recognition, genetic predisposition rarely operates in isolation and particularly in the case of DTH immune responses, e.g. vaccine efficacy[37;-41]. Epigenetic influences, such as DNA methylation, histone modification, non-coding RNA interactions, and environmental factors (i.e. overall immune status, diet, microbiome composition, medications, physical activity, etc.) play significant roles in modulating immune function in ways that single-gene testing cannot fully capture[37;42;43]. Consequently, comprehensive multi-gene analyses and consideration of epigenetic and patient-specific environmental factors are essential for accurate risk prediction of phenotypic immune responses.

Addressing the Relevance of Metal Allergy Testing in Diagnosis and Management of Patients Undergoing Joint Replacement

Metal allergy testing plays a critical role in diagnosing and managing patients undergoing joint replacement, particularly given the evidence linking metal hypersensitivity to implant performance. Retrospective studies have shown that patients with elevated metal exposure and functioning implants exhibit a 25% rate of metal sensitivity, approximately twice that of the general population. This sensitivity rate further escalates to 60% among patients with painful or failing implants, demonstrating a strong association between metal hypersensitivity and adverse implant outcomes[1;2;4]. Such data underscore the importance of metal sensitivity testing as a diagnostic tool for identifying patients at higher risk of implant-related complications.

Certain implants, especially those with metal-on-metal surfaces, are more likely to release metal particles and ions, increasing the likelihood of hypersensitivity responses. Metal-on-metal hip prostheses are associated with higher rates of metal sensitivity, with cases showing as high as 76% to 100% positive sensitivity results among symptomatic patients[13-14]. Even asymptomatic patients can develop metal sensitivity over time; for instance, one study found sensitivity rates increased from 5% pre-operation to 56% within 1-4 years post-operation in patients with metal-on-metal implants[13;44]. Elevated circulating metal ion levels have also been correlated with increased sensitivity and specific pathologies, such as pseudotumors, in metal-on-metal implant recipients. Patients with pseudotumors exhibited significantly higher metal sensitivity (80% versus 45%) and serum ion levels, suggesting that metal sensitivity may impact implant longevity and contribute to complications[45].

Moreover, self-reported pain levels often correlate with higher lymphocyte transformation test (LTT) responses, indicating that lymphocyte reactivity to implant degradation products may be linked to patient discomfort and reduced implant performance[11]. Given these findings, metal sensitivity testing is clinically relevant, particularly for two primary patient groups:

(1) those with a documented history of metal sensitivity and

(2) those experiencing implant-related pain where infection and mechanical problems have been excluded through extensive evaluation.

While evidence remains largely indirect, metal sensitivity testing provides a direct measure of immune cell reactivity to implant metals, representing a significant immune response rather than a mere correlational biomarker. Immune reactivity to metal is well-documented as being associated with implant performance, and a reproducible and quantifiable immune response to metal indicates a clinically significant finding that may impact treatment and management decisions.

Evidence from numerous studies supports the clinical value of metal sensitivity testing for individuals receiving total joint implants, highlighting its potential to improve implant outcomes by guiding material selection based on a patient's immune reactivity. Although the exact incidence of metal sensitivity leading to implant failure is unknown, around 1% to 3% of joint replacement recipients are highly susceptible to excessive immune reactions triggered by metal ions released from implants. Among metal sensitivity tests, the Lymphocyte Transformation Test (LTT) may offer greater sensitivity than patch testing, though larger clinical studies are needed to validate its specificity and overall efficacy[1;2;13;45]. Because metal sensitivity testing involves complex immunological assessments, facilities conducting these tests should maintain transparent testing protocols and be certified under strict quality and compliance protocols for immunological testing. For example, this includes Clinical Laboratory Improvement Amendments (CLIA) certification in the United States. Given that fewer than 1% of the million-plus annual joint replacement recipients in the U.S. tested for metal sensitivity pre-operatively, it is likely that implant-related metal sensitivity has been largely underreported[4;21].

Larger longitudinal studies are needed to build consensus on the clinical utility of pre- or post-operative testing by comparing outcomes of patients whose treatment plans are adjusted based on sensitivity findings. As the scientific community increasingly recognizes the impact of metal sensitivity, surgeons are factoring this into implant selection to reduce the likelihood of immune-related complications. Optimizing implant materials to match patients' immune profiles could not only improve outcomes for millions of people projected to require joint replacements[46] but also reduce mortality associated with revision surgeries in high-risk populations over age 75, where mortality can exceed 10%.

Corresponding Author:
Marco Caicedo, Ph.D
COO / Senior Scientist
Orthopedic Analysis, LLC
Adjunct Assistant Professor
Rush University Medical Center
Dept of Orthopedic Surgery
Chicago, IL - USA

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The Influence of Metal Exposure and Patient Genetics on the Development of metal Hypersensitivity

We live in an era where developments in DNA sequencing and proteomics are allowing researchers to make rapid advances in the understanding of complex disease processes[1]. But this technology has not replaced the fundamentals of medical practice. The diagnoses of the most common diseases still rely upon history taking, clinical examination, basic blood tests and imaging. The ability of doctors to understand disease processes, classify them - and thus diagnose them clinically - has to a large extent been developed through the histopathological assessment of diseased tissues. Even in modern medicine, histopathology remains a cornerstone of correctly identifying – and therefore managing - diseases.[2]

Once a disease process is described and hallmark macro- and microscopic features well defined, then further, more specific tests can be developed – either to make it easier for clinicians to diagnose a condition, to identify specific disease features associated with disease progression, or to direct specific treatments. Why is this relevant to the subject of metal allergy following arthroplasty?

Nickel allergy in orthopaedics is ill-defined

Nickel has long been the focus when it comes to discussing metal allergy as a potential cause of arthroplasty failure.[3] The diagnosis of nickel allergy has historically been made through the use of skin patch testing[4] or lymphocyte transformation tests (LTTs)[5]. But, to date, there remains no clear understanding of how nickel allergy relates to periprosthetic tissue responses at a microscopic (in terms of well-defined histopathological features) or macroscopic level (the viability of periprosthetic tissues).[6, 7] The published evidence supporting the

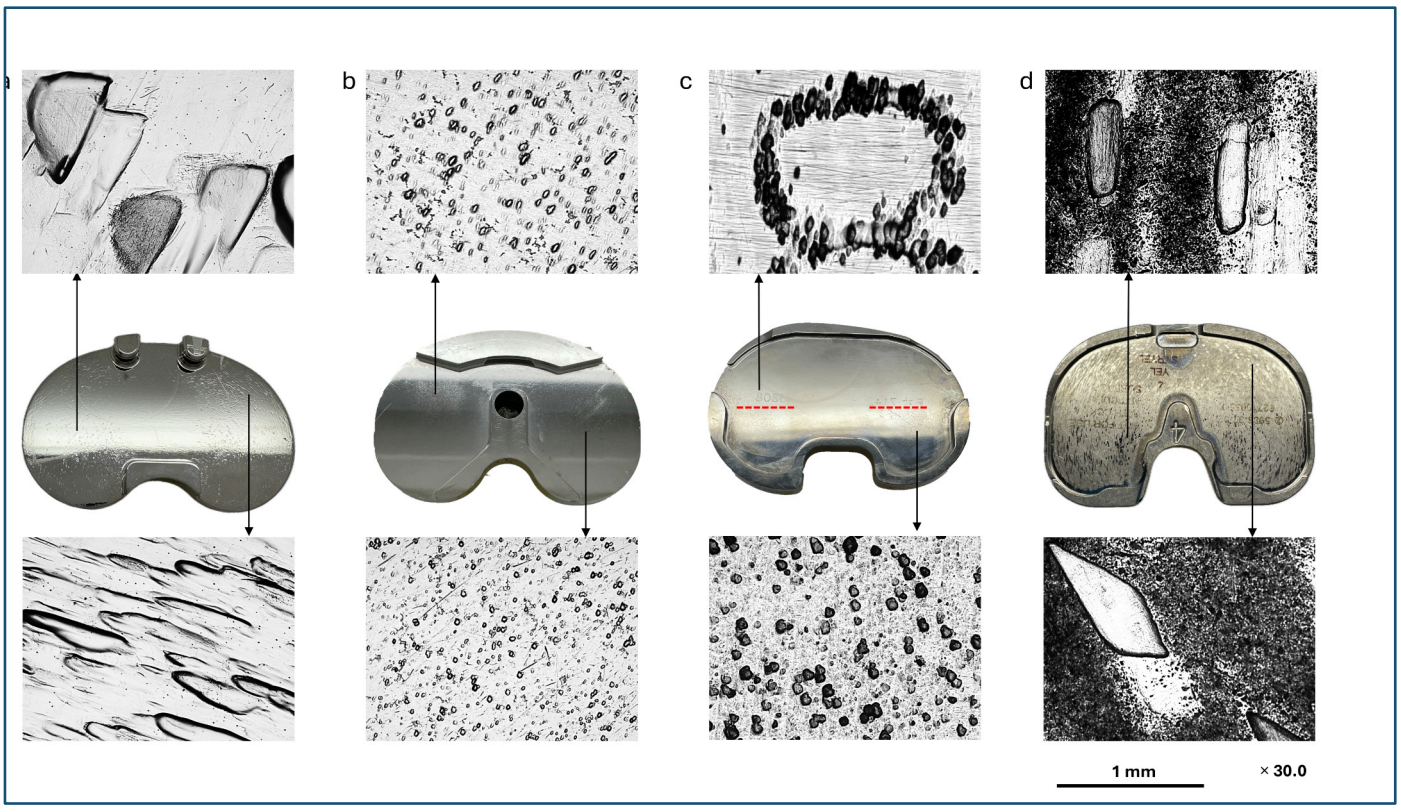

Fig 1: Light microscopic images of CoCr alloy (a and b) and Ti alloy (c and d) tibial trays showing pitting on the superior surface. Red dotted lines on Ti alloy tray c indicate imprinting of the lot number marking of the polyethylene insert on the superior surface of the tray. Pitting is present on over 50% of explanted trays we receive at ExplantLab.

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clinical relevance of nickel allergy is at best, even after decades of research, equivocal.[4;6-10] The continued use of the term nickel allergy, and the persisting use of skin patch and LTT tests to identify this ill-defined condition, has led many surgeons to doubt the clinical relevance - if not the very existence - of metal hypersensitivity.[11;12]

Diagnostics predated disease classification

It could be argued that LTTs and skin patch testing came to be viewed as the gold standard to diagnose metal allergy, before the disease had been well defined (Figure 1). If we look to specialties outside of orthopaedics, there are several hypersensitivity diseases which have been intensively studied over a number of years.[13] These diseases have well defined pathological features, established risk factors, and detailed pathogeneses. In these conditions, it is a well-recognised issue that, in general, skin patch testing and serological studies (including LTTs), identify exposure to an antigen, rather than detecting clinically relevant disease.[14] This is further discussed below.

Histopathological features of metal hypersensitivity were described after nickel allergy diagnostics

The failure of modern metal-on-metal hip arthroplasty was not a high point in the history of orthopedic surgery.[15] But one of the few positives that can be taken from the experience is the knowledge the orthopaedic community developed with regard to the understanding of immune responses to implants. Circa 2005, Willert and Davies provided a detailed description of the pathological responses seen in association with failed metal-on-metal hip prostheses.[16] These pathological features included prominent perivascular lymphocyte infiltration, formation of high endothelial venules, accumulation of sheets of macrophages and surface membrane necrosis.

The acronym ALVAL ("aseptic lymphocyte dominated vasculitis associated lesion") was coined. Clearly, ALVAL was a newly recognised condition.

As Davies wrote:

"At the present time, we do not know the prevalence or clinical implications of these histologic findings, but we suggest that they may represent a novel mode of failure."[17]

ALVAL is delayed type metal hypersensitivity

Following Willert et al's publications, clinicians and researchers now had a defined disease, with defined pathological features that could be quantified on tissue specimens. Because of this, and in addition to the large number of patients who presented to clinics around the world experiencing complications from metal related pathology, a substantial amount of knowledge was gained over a short period of time in the understanding of ALVAL.

It is important to note, however, that in their seminal 2008 paper on pseudotumour development following metal-on-metal hip resurfacing, the Oxford group speculated that these (at times, catastrophic) periprosthetic reactions could be due to nickel allergy. To reiterate the point: metal-on-metal failure was originally proposed to be due to nickel allergy.[18] It is also crucial to note that when the first reports of metal-on-metal hip failures began to emerge, blood metal ion testing was not routinely performed nor believed to be of benefit in patient management.

At around the same period in time, in our hospital we began to see an ever increasing number of patients who developed ALVAL responses to their ASR hips.[19] In an attempt to find answers, we established a retrieval laboratory to measure the volumetric material loss from the bearing and taper surfaces of explanted devices.[20] These values were compared to synovial, blood and serum metal ion concentrations and, most importantly, to the associated periprosthetic tissue responses. From the results, it

became clear that our patients were developing aggressive AVAL responses to abnormally functioning prostheses.[21]

The issue of nickel allergy was still at the forefront of our thoughts, however. We carried out a small study to investigate the possibility that LTT testing may show that these patients were sensitive to nickel.[21] We performed LTTs on blood samples obtained from a group of patients who had experienced failure of their ASRs secondary to ALVAL. We then compared these results to a control group who had elevated blood metal ion concentrations but were symptom free, with no abnormalities detected on cross sectional imaging. In the ALVAL group, only one of six patients tested positive for metal sensitivity on the LTT tests, whereas three of the five patients in the control group tested positive for sensitivity to a range of metals (all positive for nickel). The Oxford group, who had led the world in reporting their investigation of pseudotumours, carried out a similar study with larger numbers.[22] Their findings were consistent with ours.

Since Davies and Willert published their work[16;17], there have been over a thousand papers published on ALVAL, submitted from hospital and research centres all over the world. This global effort has allowed the following facts to be established:

1. ALVAL is a well-defined condition, in a histopathological sense.[17] The pathological features are consistent with a delayed type hypersensitivity response and, as would be expected with delayed type hypersensitivity, reimplantation with cobalt-chrome alloy is ill advised, with symptoms returning after temporary alleviation.[16;19]

2. ALVAL varies in intensity; multiple grading systems exist.[23-25] These grading systems largely agree with each other[26,,27], as they are generally in unison on scoring the same parameters; the primary one being the presence of lymphocyte perivascular cuffing.[16]

3. ALVAL has most frequently been identified in studies involving patients with metal-on-metal prostheses. However, a metal-on-metal bearing is not a prerequisite for the condition to develop[28-30], and ALVAL has been frequently identified in tissues excised during knee revision surgery.[31]

4.ALVAL is associated with abnormal fluid collections (which can build in pressure), and soft tissue and/or bone damage which can be extensive.[30]

5. The grade of ALVAL correlates with the thickness of synovial lining on MRI[32], the extent of surface membrane necrosis of the synovium[33] and the level of pain reported by the patient prior to revision.[34;35]

6. ALVAL is associated with elevations in blood, serum and synovial cobalt and chromium concentrations.[23;25;36]

Regarding the final point, for over a decade we continued to collect data to study the interaction between patient and implant factors and the development of ALVAL in several hundred patients. We found that while ALVAL was more common in devices generating excessive metal debris, beyond that, there appeared to be immunogenetic factors at play, with different patients displaying different tolerances before developing hypersensitivity.[37]

ALVAL shares a number of similarities with other hypersensitivity diseases in other medical specialties

There are a host of hypersensitivity diseases which can afflict the human body. They tend to share certain features, however. As Friedmann made clear: *"age, sex and genetic factors such as HLA haplotype can all influence whether and to what degree an individual reacts to a substance."*[38]

As just one example (there are many[13]), bird fancier's lung is a common form of delayed type hypersensitivity pneumonitis which results from

avian antigen exposure. It is related to the dose and duration of exposure[39;40], age and sex[41], but also depends on an individual's HLA genes.[42]

Genetic investigation

Given the existing knowledge regarding hypersensitivity diseases, in 2017, after a decade of data collection, we set about identifying patients with extreme phenotypes in an attempt to identify HLA genetic variants associated with ALVAL. Extreme phenotypes in this respect referred to those patients developing high grade ALVAL reactions following relatively low metal exposure, versus those who appeared resistant to developing ALVAL despite long-term exposure to large amounts of metal debris.

We quickly identified significant differences in the frequencies of specific HLA-DQ alleles, even with relatively small patient numbers. Not only that, but the peptide binding groove encoded by the primary HLA-DQ risk haplotype demonstrated an affinity for the N-terminal peptide fragment sequence of albumin, a recognised metal ion binding site.[43] These binding affinities, along with patient (age and sex) and implant factors (duration in vivo, presence of modular junction) were entered into a machine learning algorithm which was trained and tested using what was the largest dataset of patients in the published literature.[44] Extension of the genetic testing to include the whole genome did not identify genetic variants which improved the algorithm to any clinically relevant degree. The resulting commercial test **"Orthotype"** is now available for surgeons in the United Kingdom to use. The evidence validating Orthotype has been reviewed by the UK National Health Service and the test is provided by the NHS Blood and Transplant service.

https://hospital.blood.co.uk/diagnostic-services/histocompatibility-and-immunogenetics/service-developments/orthotype/

Orthotype

Orthotype is a test which can be used pre- or post-operatively. It involves a routine blood draw, with samples placed in EDTA tubes and transported at ambient temperature.

With Orthotype Pre-Op, the patient's HLA-DQ alleles are identified using next generation sequencing. The resulting haplotypes are then inputted into a machine learning algorithm, along with patient age and sex and device type, to provide the clinician with a relative risk over time (compared to the background population) of the patient developing ALVAL in response to a cobalt-chrome implant.

Orthotype Post-Op can be used to monitor or investigate patients who have already received a cobalt-chrome implant. With this test, blood metal ion levels concentrations are measured using the same samples, and these results are added into the algorithm to provide the clinician with a result: ARMD positive or negative. If positive, a graph is outputted which allows the clinician to view the risk of ALVAL developing over time. The sensitivity and specificity for detection of ARMD post-op is 89% [84-93] and 90% [87-92], with a weighted mean survival probability error of 1.8% for pre-op prediction of ALVAL at 1.8% and 3.1% for post-op ALVAL.[44]

Orthotype: strengths

Orthotype was developed and validated using gold standard histopathological examination of tissue excised at revision surgery. The validation process was performed stepwise, with the candidate's genetic variants identified first, then an algorithm developed and tested using prospectively collected data from three different countries. Histology results from 176 revision surgeries were included in the data set, along with clinical results from 430 patients followed up to a maximum of twenty years.[44] The same methodology was used in the field of infectious disease to successfully identify genetic variants

which confer protection from severe complications caused by COVID.[45;46]

Orthotype: limitations

The originally published validation study included only patients with metal-on-metal THRs or resurfacings. However, a national study is currently being carried out to provide additional prospective data with patients implanted with other joint prostheses. The test is performing in line with the originally stated sensitivity and specificity values.

Moving forward in the understanding, diagnosis and management of metal hypersensitivity

As discussed above, the phenomenon of "nickel allergy" has become inextricably linked with skin patch testing and LTTs. But the limitations of these tests as diagnostic tools are well recognized in other fields of medicine. For example, chronic beryllium disease is a pulmonary hypersensitivity disease resulting from exposure to the heavy metal, beryllium. In this HLA-mediated condition, exposure to beryllium leads to a cell-mediated immune response where T-cells become sensitised to beryllium resulting in progressive lung damage.[47] LTT screening of exposed workers commonly identifies individuals sensitised to the metal who have no evidence of lung disease. In other words, these "sensitised" subjects have a LTT beryllium specific response in peripheral blood, but no clinical or pathologic features of lung pathology.[48] A positive LTT in beryllium disease therefore indicates sensitisation, rather than the presence of pulmonary disease.[49] This effect is seen in other pulmonary hypersensitivity conditions, with positive skin patch and serological tests in up to 88% of exposed subjects who remain asymptomatic without evidence of disease.[14]

What is the implication of this? In orthopedics, we may have used measures of exposure or sensitisation to diagnose disease, rather than identifying disease and then developing diagnostic tests to identify disease. If this is indeed the case, it would explain why these tests have not been proven to accurately identify ALVAL or tissue related complications necessitating revision. The damaging knock-on effect has been to create scepticism that metal hypersensitivity even exists. Rather than doubting the accuracy or appropriateness of the tests, the doubt has been cast on the disease.[11]

ALVAL should be the foundation on which to assess the performance of diagnostic markers

How can we unify the research findings and improve the terminology? If we restrict ourselves to using evidence derived from a classical approach to medicine (signs, symptoms, biochemistry, imaging and histopathology), then it is clear that the evidence indicates that it is ALVAL that is the condition which constitutes a clinically relevant meaningful disease process; the condition which we should be aiming to identify and eliminate moving forward.

Why is ALVAL a controversial issue aside from metal-on-metal arthroplasty?

ALVAL is present in approximately 30% of tissue samples taken from patients undergoing revision of their knee arthroplasties[29;31;35] and the grade of ALVAL correlates to the levels of pain reported by patients prior to their revision procedures.[34;35] There is even evidence that ALVAL may masquerade as culture negative prosthetic joint infections, just as was the case with the first metal-on-metal ALVAL reactions encountered by unsuspecting surgeons.[31;50] So why is this condition still viewed with skepticism? Why is ALVAL apparently siloed in the world of failing metal-on-metal hips, and what are the obstacles preventing it gaining attention in other areas of arthroplasty?

The issue of diagnosis

ALVAL is diagnosed through histopathology. Being a

relatively novel condition, many non-specialist units may not be aware that ALVAL exists nor have the relevant expertise to identify it. In the UK, most knee surgeons do not send a periprosthetic tissue sample at revision for histological examination. The incidence and clinical significance of ALVAL therefore by definition cannot be determined (in the UK at least) within the bounds of current clinical practice.

A lack of awareness of evidence and persisting, inaccurate beliefs

There is no established culture in current knee arthroplasty practice to measure blood metal ion concentrations post-operatively, and metal hypersensitivity is regarded as a diagnosis of exclusion.[51] In these respects, there are striking parallels with the early management of patients with metal-on-metal hips. There remains a fixed belief that metal debris generation from a contemporary knee arthroplasty is clinically insignificant. However, a cursory examination of the literature on the subject identifies evidence to challenge these assumptions. Blood metal ions are frequently elevated to clinically relevant concentrations post-knee arthroplasty.[52-55] Skeptics may suggest that these elevations only occur with defective or failing devices. Yet evidence shows that even in the idealised environment of a knee simulator, approximately 12 % by weight of the wear products generated from a knee arthroplasty is metallic.[56] Furthermore, concerns have been expressed that the increased wear resistance of contemporary polyethylene changes may alter force transmission through the links of the arthroplasty chain, resulting in a change in the magnitude of wear debris generated at each interface.[57]

The unexplained phenomenon of nickel allergy in knees versus cobalt-chrome-associated ALVAL in hips

It is now clear that excessively wearing cobalt-chrome hip components precipitate high rates of ALVAL.[37;58] The standard cobalt-chrome alloy used in metal-on-metal hips (ASTM 75) is identical to that used in the vast majority of knee prostheses.[59] These cobalt-chrome alloys rarely contain more than 0.2% nickel by weight, compared to up to 65% of cobalt - amounting to a three hundred fold difference. To place nickel under scrutiny seems questionable. As another comparison, an Exeter hip contains fifty times the amount of nickel compared to a cobalt-chrome component. Global clinical experience has demonstrated which devices are more likely to provoke an ALVAL response. That is not to say that nickel associated ALVAL doesn't exist - far from it – but, just as with other diseases, histopathological analysis should form a cornerstone of the diagnostic process.[2]

Hypersensitivity to other biomaterials

To summarise, the available evidence indicates that ALVAL is the histopathological manifestation of delayed type metal hypersensitivity. Evidence also indicates that debris produced from cobalt-chrome alloy is the most relevant sensitising agent from a clinical perspective. Could it be cobalt, chromium, nickel or perhaps one of the other elemental constituents of cobalt-chrome alloy (such as molybdenum) that is the major culprit? Does it matter? The most relevant clinical question seems to centre on other orthopedic biomaterials, most notably titanium alloy. At our unit, and as part of the ongoing national Arthrogenex study, we are actively investigating titanium associated ALVAL. It certainly exists.

Reassuringly, it appears that the genetic risk factors associated with ALVAL secondary to cobalt- chrome exposure are not the same as those associated with titanium-induced ALVAL. Does this mean that future surgical practice may be based on biomaterial selection guided by an individual's DNA profile? Why not? This is already happening in other specialties to guide pharmacological treatment regimens.[60-63]

Corresponding Author:
David Langton MRCS PhD
Managing Director at
ExplantLab
The Biosphere
Draymans Way
Newcastle Helix
Newcastle Upon Tyne - UK

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