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Review article

Metal hypersensitivity in total knee arthroplasty

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ABSTRACT

Metals used in total knee arthroplasty cause hypersensitivity reactions in some patients. These reactions are known to be immune-mediated and are more likely to affect individuals with pre-existing metal sensitivity, but their mechanism is not fully known. It is difficult to predict pre-operatively whether a patient will be affected and there is no reliable investigation to guide implant choice. There appears to be little value in screening all patients for metal sensitivity before implantation as various studies have shown no significant difference in outcomes or failure rates post TKA in patients with history of metal sensitivity. However, the existing assessment tools are not specific enough to identify subtle problems with potential metal sensitivity association.

Symptoms of hypersensitivity reactions following total knee arthroplasty are often non-specific and difficult to differentiate from other acute presentations following total knee arthroplasty, for example infection. Metal hypersensitivity reactions are often a diagnosis of exclusion, and for this reason they are most likely under-diagnosed and under-reported. Management is controversial but periprosthetic hypersensitivity reactions will often ultimately require revision if no other cause is found. Metal debris are a concern in total hip arthroplasty and could represent another cause of metal-related pathology in total knee arthroplasty. Non-metallic materials are currently in development which may represent a preventative solution for metal hypersensitivity reactions in total knee arthroplasty, potentially also addressing additional concerns around the use of metallic implants such as the high density and thermal conductivity of the material in comparison with the replaced tissue.

1. Introduction

Total knee arthroplasty (TKA) is a widely utilised treatment for end-stage knee arthritis. Over 1 million TKA have been recorded in the England and Wales National Joint Registry (NJR) from 2003 and over 110,000 were recorded in the UK alone in 2017.[1] Rates of TKA are increasing, with an estimated increase of up to 600% in the USA over a 25 year period. The TKA is a financially efficient and generally clinically effective procedure. However, 10–25% patients are dissatisfied with their outcome, and less than 10% report no problems following TKA.[2]

With more patients requiring TKA because of expanding indications and increasing life expectancy, TKA revision surgery burden is expected to increase. Aseptic loosening is the most common cause of failure requiring revision. A less common but increasingly recognised cause of implant failure is that of metal-related pathology, estimated to account for 1.6% of all TKA revisions.[3]

The England and Wales NJR reports 18% of patients were revised for unexplained pain, a significant proportion.[1] It is likely that many of this subgroup suffer from metal-related pathology and that the 1.6% officially recorded is likely a gross underestimate. A number of different material combinations are available for TKA implants including metal alloys, ceramic, polyethylene, and polyetheretherketone (PEEK). The implant material in primary surgery

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Abbreviations

ACD	allergic contact dermatitis
ARMD	adverse reactions to metal debris
ALVAL:	aseptic lymphocyte-dominated vasculitis-associated lesions
PEEK	polyether ether ketone
MoM	metal-on-metal
MoP	metal-on-polyethylene

and in revision following unexplained pain was not recorded in the NJR report. The majority of TKA consist of a femoral component of cobalt-chromium alloy, which articulates with a polyethylene tibial component which usually has a metal backing.

Metal particles are released from metallic components by mechanical wear or corrosion. In some patients, metal sensitivity may cause implant-related hypersensitivity reactions, typically presenting as allergic contact dermatitis (ACD) and/or implant failure. Diagnosis is challenging and presentations often mimic chronic infection, with persistent painful synovitis, reduced range of motion and effusion.[4] Screening for metal hypersensitivity preoperatively and the relevance of a history of ACD in response to metal both remain controversial. Management of patients following TKA who present with sequelae of metal hypersensitivity has limited evidence basis, but may culminate in revision.[4]

Adverse reaction to metal debris (ARMD) is an umbrella term first described by Langton et al., in 2010. Its mechanism is not fully elucidated but is known to have an immune-mediated component dominated by lymphocytic activity, and to lead to characteristic histological changes which differ from those seen in osteolysis induced by polyethylene debris. Metal ions are released, and evidence suggests a component of systemic hypersensitivity. ARMD is particularly prevalent in patients with metal-on-metal implants.

This paper will focus mainly on the mechanism, management and screening for metal sensitivity. There will also be a discussion on the role of metal debris in TKA failure, and of possible strategies to avoid the impact of metal-related pathologies in TKA.

2. Hypersensitivity

2.1. Basic science

The classical definition of allergy is type 1 hypersensitivity. This is IgE-mediated, occurs over seconds to minutes and may result in anaphylaxis. Type I, II and III reactions do not usually occur with metal. Although termed “allergic contact dermatitis”, cutaneous reactions to metal seen in the general population are generally believed to be caused by type IV, delayed-type hypersensitivity reactions. These are mediated by T-cell lymphocytes.[5]

In cutaneous sensitisation, chemical allergens (haptens) access the stratum corneum and combine with proteins which bind to dendritic cells.[4] These cells drain from the skin via afferent lymphatics and present the hapten-protein complex to lymphocytes, initiating clonal expansion and sensitisation. Metallic allergens may sensitise via a different mechanism; metals in contact with biological systems corrode and produce ions.[5] As they differ from chemical allergens, these metal ions must form specific coordination complexes with proteins to allow immune recognition. The end result remains the same however, and an adaptive immune response sensitises to further exposures to the relevant metal.

In implant-related hypersensitivity reactions ions can be released chemically by corrosion, or by mechanical processes such as wear. Once the ion has combined with a protein it is not known which cell responsible for presenting the metal-protein complex. In addition to dendritic cells, other possible candidates for which cell is responsible for presenting the metal-protein complex include epithelial cells, macrophages, lymphocytes and parenchymal tissue cells.[5] Hypersensitivity reactions appear to be delayed cell-mediated responses, although debate remains about its precise mechanism.[4,5]

2.2. Incidence

The prevalence of metal sensitivity in the general population, as defined by positive results on test dermal patching, is 10–15%.[4] Patients with total joint arthroplasties (TJA) have a higher prevalence of metal sensitivity than the general population; a literature review found a prevalence of 25% in patients with well-functioning TJA implants and 60% in failed or poorly functioning implants.[5] Similar results have been found in TKA specifically. Granchi et al. studied 94 patients. They used dermal testing with haptens representative of cobalt and titanium-based alloys.[6] 15% of candidates for TKA without implants, 44% of those with stable implants and 57% with loose implant tested positive for sensitivity to one or more metal hapten. Positive patch testing was not significantly predictive of implant failure, and it is not known whether patients with metal sensitivity are more likely to have implant failure, or if implant failure sensitises patients. The authors suggested patients with previous symptoms of metal allergy were more likely to have TKA loosening, but their reported hazard ratio of 4 did not reach statistical significance.[6] While the specific revision burden caused by metal hypersensitivity is not known, the Australian Orthopaedic Association National Joint Registration recorded that 1.6% of all TKA revisions were caused by metal-related pathology. The implant materials and models of this subset were not individually reported.[3]

2.3. Clinical presentation & symptoms

Most of the ACD cases described in the literature following orthopaedic and other metallic implants were eczematous, while some were urticarial, bullous, or vasculitic. The majority resolved with removal of the implant and had positive patch tests.[7] As TKAs are implanted deep within the tissues away from the skin, metal hypersensitivity reactions may present differently. Dermatitis has also been reported in TKA.[8] Verma et al. studied 30 patients with localised dermatitis over the implant following TKA, the majority of which were eczematous in presentation. Interestingly only 7 of the 15 patients tested had positive patch testing results for metal.[8] The eruption was located on the lateral aspect of knee in all cases and so in those with negative patch tests neuropathy dermatitis secondary to intra-operative saphenous nerve lesion could be considered. Systemic dermatitis has also been known to occur following TKA, typically localising to body flexures.[7]

In addition to a full history and examination, blood tests including C-reactive protein, erythrocyte sedimentation rate and blood cultures must be performed. The presentation will often mimic chronic infection, however serum inflammatory markers are generally only mildly raised. Other more common causes of an acutely painful knee must also be considered, including aseptic loosening, hemarthrosis, dislocation and fracture.[4]

Metal hypersensitivity is a diagnosis of exclusion. Metal ion levels are raised in patients with well-fixed and well-functioning TKA, and so are little use in diagnosing metal hypersensitivity.[4,9] When investigations suggest metal hypersensitivity, allergy testing should be performed. Patch testing is generally first line. It is low cost and allows testing for a number of different metals.[10]

However, patch testing can be insufficiently sensitive or specific, and Granchi et al. found it was unable to differentiate between a stable and a failed implant.[11] It may reflect a purely cutaneous reaction, rather than an immunological response at the implant site.[12] Where available lymphocyte transformation testing (LTT) is often utilised to detect more systemic reactions. In LTT, patient lymphocytes and monocytes are challenged with metal salts, and their proliferation in response to these antigens quantified. LTT results correlate with poorly functioning implants and suspected metal hypersensitivity, but it is not possible to derive causality from a positive test result.[13] A recent study of 27 TKAs without evidence of infection or loosening revised for pain and suspected metal allergy found that "LTT results were insufficient for diagnosis of TKA failure due to an immune reaction".[14] Other authors suggest the combined use of patch testing and LTT to better inform management decisions, but again warn that neither are reliably sensitive or specific.[12,13]

Thyssen et al. propose diagnostic criteria for implant-related allergic contact dermatitis, including a time scale of weeks to months following implantation, positive patch testing for implant metal, localised eruption and recovery following revision.[10] For periprosthetic presentation, they suggest considering histology consistent with delay-type hypersensitivity, positive patch testing, positive *in vitro* testing, and recovery following revision. Suspicion of metal hypersensitivity as compared with aseptic loosening secondary to polyethylene wear is increased in patents with earlier symptoms following implantation (weeks to months vs years), previous history of metal allergy and presence of severe dermatitis or painful persistent synovitis.

In patients with painful TKA where no obvious cause is found, it is possible that their symptoms are related to metal sensitivity. No reliable test currently exists which is able to identify metal hypersensitivity reaction in such cases. Patients will typically present recurrent knee effusions and undergo a plethora of investigations without any meaningful outcome.

2.4. Dealing with hypersensitivity

For patients with persistent dermatitis with no evidence of periprosthetic disease, first line management should be topical steroids, and good results have been noted.[4,8] There have been limited reports of TKA revision for severe dermatitis refractory to steroid treatment, with complete post-operative resolution. For example a patient with widespread dermatitis following TKA (Depuy, PFC, CoCrMo lot 290,105/Ti6Al4V lot 1,016,010, Warsaw, Indiana, USA) had a highly positive patch test result with chromium only. All symptoms resolved following revision with a zirconium-niobium alloy prosthesis (Smith&Nephew, Oxinium, Zr-2.5Nb, Memphis, Tennessee, USA).[15]

For patients with TKA and hypersensitivity reaction affecting the implant, most patients will require revision surgery. Extensive synovectomy is required to reduce metal ion burden, and augmentation of bone stock may be necessary to ensure stability.[16] Suitable materials for revision implants include ceramics, oxidised zirconium, titanium or zirconium alloy, and cobalt chromium coated with zirconium nitride or titanium nitride.

Revision surgery must remain a last resort, and only when there is adequate confidence in the diagnosis. It must be emphasised that metal hypersensitivity as the cause of implant symptoms remains a diagnosis of exclusion. Other causes must be ruled out first, especially infection. Patient counselling for revision surgery for metal hypersensitivity in TKA must be appropriately guarded. They should be aware that there are no recognised guidelines, and evidence for revision surgery is limited.[4]

2.5. Predicting (screening) for hypersensitivity

Implant-related metal hypersensitivity may necessitate revision surgery, a costly undertaking with associated morbidity. Metal sensitivity prevalence increases following TKA and more patients have positive patch tests in failing implants.[17] This may reflect sensitisation following implant failure, rather than pre-existing sensitivity increasing probability of implant failure.

Most authors recommend against screening all patients prior to TKA, citing prohibitive costs and unnecessary use of more expensive implants for little benefit. They generally suggest patch-testing only in patients with a known history of previous significant metal hypersensitivity or prior implant failure due to metal hypersensitivity.[10,18] While the majority of failed implants have positive patch test results, it is likely that only a small subset of patients with positive patch test results will react to a TKA implant of that metal. In addition, Thyssen et al. found no difference in THA revision rates in a national registry for patients who had positive patch test results with implant metals as compared with those who did not.[19] The material and manufacturer of the implants used in the subset of patients who underwent revision surgery was not recorded. This still is an evolving field and our understanding will improve with time.

3. Pathology related to metallic wear particles

Adverse reaction to metal debris (ARMD) is used as a general term to encompass all adverse effects on periprosthetic tissues caused by TJA metal debris. The term was introduced to highlight local adverse reactions to metal-on-metal hips.

Aseptic loosening is the most common cause of TKA revision, representing 23% of early failures (less than two years post-operative), and 51% of late revisions (over two years post-operative),[20] This was previously believed to be caused by cement. However, despite improvements in cementing technique, aseptic loosening continued.[21] Polyethylene wear debris were suggested as an alternative cause by Amstutz et al. It was shown that wear particles activated periprosthetic macrophages, which in turn release osteoclast activating factor, oxide radials and hydrogen peroxide, and causes fibrosis, vascular proliferation and cell necrosis.[21] Polyethylene debris is now established as the main cause of aseptic loosening.

Metal-on-metal (MoM) hip bearings were developed due to improved wear characteristics and became very popular, but in the early 2000s it became apparent that metal debris was a serious issue.[22] and MoM hips have a ten year revision rate of 14–27%.[1] Willert et al. first described aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) in 19 MoM THA revisions. The majority of these revisions had demonstrated osteolysis or radiolucencies, recurrence of pain and the development of a large effusion. Periprosthetic histological findings were of a predominance of lymphocytes, macrophages, a large volume of fibrin exudate and necrosis.[23] Revision with MoM THA resulted in recurrence, while revision with metal-on-polyethylene (MoP) did not. The primary prostheses were cemented in two hips, of hybrid fixation in one and cementless in 16. Two of the cemented stems were made of iron-based alloy S30, the other of Ti6Al–7Nb alloy. All uncemented stems were made of Ti-6Albased alloys. 14 of the 16 cementless stems were revised without cemented, while all cemented stems were revised with cement. The implant type used in revision was not recorded. The longevity of MoP revisions likely reflects the reduction in source of metal debris in MoP hips compared with MoM hips. The Oxford group also published a case series on MoM hip resurfacing implants which present with pain at the groin, lateral hip or buttock.[24] They noted findings of locally destructive

non-infective masses which they termed “pseudotumours”. These were characterised by extensive necrosis and dense connective tissue. Some also contained cystic degeneration, and almost all contained metal wear particles. Histological findings were similar to those seen in ALVAL. The majority required revision surgery.

Most MoM wear particles are less than 100 nm. These are smaller than active polyethylene debris (100–1000 nm). The mechanism of immune activation is controversial, but as with polyethylene debris, local macrophages appear to phagocytose metal particles. However, in contrast to polyethylene debris the macrophages then present the resulting metal-protein complexes to circulating lymphocytes and initiate a cell-mediated hypersensitivity reaction dominated by lymphocyte activity in a process which seems to resemble type IV hypersensitivity. Positive patch testing is also more prevalent in failed MoM THAs compared with controls.[25]

Most published literature on ARMD focuses on MoM THA and the main concern with respect to metal debris in TKA tends to focus on metal debris produced intraoperatively. MoM hips generate metal particles at the junction between the femoral head and socket, that between the head and stem of the femoral component, and at junctions between modular components. Higher revision rates for ARMD in MoM hips reflect this. Revision to MoP articulation reduces but does not entirely eliminate sources of metal debris. Wear simulation studies demonstrated that 12% of wear debris by mass for a metal-on-polyethylene TKA were metal, suggesting metal debris could also contribute to metal-related adverse events in TKA.[26] Modular connections in contemporary TKAs may be a source of metal ions.

4. Alternative materials for TKA

One of the biggest challenges in orthopaedics is the development of wear resistant materials which reduce the generation of particles, while continuing to perform to a high standard. To this end, moderately cross-linked polyethylene tibial components and oxidised zirconium femoral components have demonstrated significant improvements.[27,28] Ceramic bearings also have excellent wear properties, are chemically inert and corrosion resistant. Mid- and long-term survival rates are comparable to commonly used alloy components; its brittleness and therefore potential for implant fractures limited its application previously but more recent generations have eliminated this.

Polyetherketone (PEEK) is a thermoplastic polymer. It is relatively biologically inert, strong and stiff. PEEK is also lightweight compared with metal alloys. Hallab et al. studied the effect of PEEK particles on macrophages. They demonstrated a reduced cytokine release response *in vitro* compared with ultra-high molecular weight polyethylene, suggesting PEEK is more biocompatible.[29] Anecdotally, patients with TKA complain of difficulty with extremes of temperature and are more aware of their knee in particularly hot or cold environments. It could be related to the thermal conductivity of metal used in implants, and a material with low thermal conductivity such as PEEK may prevent this. PEEK could represent an alternative material for use in TKA, but clinical data for its application in TKA is still relatively limited.

5. Conclusion

Implant-related hypersensitivity reactions are a cause of revision which is likely greatly underreported and could represent an unexploited opportunity to reduce revision rates for TKA. It is possible that these reactions may be a causative factor in the persistent dissatisfaction seen in some patients following TKA. In MoM hips, the local effect of a high load of metal debris is the cause of a greater failure rate. In MoP TKA, patient-dependent systemic hypersensitivity is the mechanism of failure. The diagnosis of hypersensitivity reactions is challenging and often not possible. Following routine investigations to rule out more common causes of implant failure, patch testing and LTT are the two most commonly utilised methods. Independently they have poor sensitivity and specificity in the identification of metal hypersensitivity as the cause of implant failure.[11–14] Together their accuracy is improved, but they remain a guide to the surgeon rather than explicit diagnostic tests.[4,12] They must be treated in the context of the clinical presentation. Screening for metal sensitivity preoperatively is neither practical nor reliable. The management of metal hypersensitivity reaction associated with TKA is controversial and there is little evidence available. Surgeons therefore have little guidance in deciding if revision surgery, with its associated morbidity, is the correct choice. Prevention is most likely the best approach to the problem. Prostheses without metal are one possibility, providing they are biomechanically strong, biologically inert and cost-effective. Current metal-based prostheses have significant inertia due to economy and the availability of longitudinal outcome data. While research into alternative materials continues it is unlikely to result in large scale adoption in the near future.

Author contributors

SWK performed the literature search and the wrote the manuscript draft. All other co-authors have contributed equally to editing and have seen the final manuscript and approved it.

Declaration of competing interest

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