Allergy in Total Knee Replacement. Does It Exist?

Review Article

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Abstract *Background:* There is little data on whether preexisting allergies to implant materials and bone cement have an impact on the outcome of TKA. *Questions/Purposes:* This review article analyzes the current literature to evaluate the prevalence and importance of metal and cement allergies for patients undergoing total knee arthroplasty. *Methods:* A review of the literature was performed using the following search criteria: “knee,” “arthroplasty,” and “allergy” as well as “knee,” “arthroplasty,” and “hypersensitivity.” *Results:* One hundred sixteen articles were identified on PubMed, Seventy articles could be excluded by reviewing the title and abstract leaving 46 articles to be included for this review. The majority of the studies cited patch testing as the gold standard for screening and diagnosis of hypersensitivity following TKA. There is consensus that patients with self-reported allergies against metals or bone cement and positive patch test should be treated with hypoallergenic materials or cementless TKA. Treatment options include the following: coated titanium or cobalt-chromium implants, ceramic, or

zirconium oxide implants. *Conclusion:* Allergies against implant materials and bone cement are rare. Patch testing is recommended for patients with self-reported allergies. The use of special implants is recommended for patients with a confirmed allergy.

Keywords allergy · total knee arthroplasty · oxinium · patch test

Introduction

The first reports of loosening after joint replacement caused by hypersensitivity or allergic reactions to metallic implants were published in the mid 70s and 80s [14, 19, 20, 67] and concerned hip arthroplasties with metal-on-metal bearings. More recently, there has been a trend towards studies examining allergies in metal on plastic total knee arthroplasties [14, 43].

The hypothesis that cutaneous and systemic hypersensitivity reactions develop in patients following total knee arthroplasty (TKA) is supported by studies showing a higher prevalence of positive patch tests after implantation of metallic TKA components [2, 6, 17, 22, 25, 51]. The higher sensitization to metal (in particularly nickel (Ni), chromium (Cr), and cobalt (Co)) might be caused by wear or corrosion. Although a positive patch test shows a strong correlation, no causal relationship has been established between dermal reactions and implants failure [62].

The “National Joint Replacement Registry of Australia” [3] notes “metal related pathology” in 1.8% and “undefined pain” in 9.2% of patients undergoing revision TKA. The overall revision rate was 3.45% after 10 years in 396.472 TKAs suggesting a revision rate of 0.06–0.32% secondary to metal or cement allergies. Still, these numbers are rather small and the role of allergies in total knee failures remains a controversial issue.

This review article analyzes the current literature to answer the following questions: (1) Can patients with an increased risk of implant allergy be recognized before surgery? (2) Is there a correlation between the presence of metal or bone

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cement hypersensitivity and implant failure? (3) Can the current literature be used to establish a treatment algorithm for patients with hypersensitivity to metal or bone cement undergoing TKA? (4) What treatment options are available for patients with an established metal allergy?

Methods

The search was limited to “PubMed” (www.pubmed.gov). The search criteria included the words “allergy,” “hypersensitivity,” “knee,” and “arthroplasty”. Two searches were performed: (a) “allergy,” “knee,” and “arthroplasty”; (b) “hypersensitivity,” “knee” and “arthroplasty”. One hundred sixteen articles were identified. Seventy articles were excluded after reviewing the title and abstract (some exclusion criteria: other joints than knee, allergic reaction to medication during surgery, infection, antibiotics, metallosis, and allergic reaction to suture material after surgery). Forty-six articles were included in the review: 17 case reports (Table 1), 4 reviews [5, 15, 42, 43], 16 retrospective articles [11, 17, 19, 26, 32, 33, 35, 41, 45, 46, 48, 51, 52, 54, 61, 63], 8 prospective articles [2, 8, 10, 22, 25, 40, 47, 69], and one “expert opinion” [39].

Results

(1) Patch tests were used to confirm a suspicion for an implant or bone cement allergy in 15 of the 17 case reports reviewed [1, 7, 9, 16, 18, 24, 27, 29, 34, 49, 55, 58, 59, 65, 66]. In only three case reports “lymphocyte transformation test” (LTT) was used [16, 49, 62]. Other diagnostic methods were not described in any of the 17 case reports. Thirty-nine patients were included in those 17 case reports. Eleven patients showed a positive skin test against nickel (Ni), 9 patients against cobalt (Co), 5 against chromium (Cr), 3 against benzoyl peroxide, 1 against gentamycin, 1 against copper and 1 against palladium. In 2 patients the patch test remained negative [58, 65]. LTT showed one hypersensitivity against Ni and Co [16], one against Cr [49], and one LTT remained negative [62].

Out of eight prospective studies, five included patch testing [2, 25, 40, 69]. One study used LTT [47], one study used a combination of patch test and LTT [22], two studies used neither of these tests [8, 10].

In nine of 16 retrospective studies, patch testing was used [17, 19, 33, 35, 45, 51, 52, 54, 61]. In one study, diagnostic procedures also included LTT, ELISA, and confocal microscopy [33].

All 4 review articles refer to patch testing, LTT, “Migration Inhibition Factor” (MIF), and evaluation of cytokines concentration with ELISA as possible diagnostic tests [4, 15, 42, 43]. Reviews outlined the importance of patient reported allergies and history (family history, exposure, occupation, and self-reported allergies) as a first diagnostic step.

(2) In all case reports, the main causes of “painful TKA” were excluded (malpositioning, infection, patellofemoral pain, etc.). In 17 case reports based on diagnosis by exclusion, revisions were performed in 9 instances [1, 9, 16, 18,

24, 49, 58, 62, 65] including 16 cases. In all 16 cases, clear improvements (pain, range of motion) were reported after revision and all systemic symptoms including contact dermatitis, hair loss, etc. disappeared. In all cases, an exclusion of infection was made using intraoperative tissue samples and only 5 patients out of 16 showed periprosthetic tissue changes (mononuclear infiltrate composed of lymphocytes, plasma cells, and macrophages), which were consistent with metal sensitivity [1, 9, 58].

No prospective study analyzed periprosthetic tissue samples to confirm the diagnosis of allergy after TKA. A conversion from preoperative positive patch test or LTT test (37/259; 14.3%) to postoperative positive patch or LTT test (40/172; 23.3%) was assumed as a sign of hypersensitivity to metal components or bone cement.

In 17 retrospective studies, two series reported on revisions for implant allergies [35, 61]. Thomas et al. [61] analyzed periprosthetic tissue in TKA revisions for suspected metal allergy. Four out of 25 patients showed type I changes according to the classification by Krenn et al. [36] (might be compatible to hypersensitive reaction).

(3) Mitchelson et al. [43] and Carulli et al. [15] reported different algorithms in their review articles. Innocenti et al. [33] developed a diagnostic algorithm.

(4) Three prospective studies [8, 10, 40] and two retrospective studies [32, 48] presented alternative materials and treatment options or compared metallic components to hypoallergenic implants. Bergschmidt et al. [8] compared ceramic femoral components ($n = 35$) with CoCr and CoCrMb (cobalt-chromium-molybdenum) femoral components ($n = 35$). Lutzner et al. [40] analyzed 60 uncoated Co-Cr-Mb-Ni TKAs and 60 coated (7-layer coating system with a final zirconium nitride (ZrN) layer) TKAs. Pre- and postoperatively patch tests were performed. Pellengahr et al. [48] reported about 35 titanium (Ti-6Al-4 V) TKAs in patch test positive patients in comparison to 45 CrCoNi-alloy TKAs. All three studies showed no significant differences in outcomes (ROM, Knee Society Score, HSS score, metal ion concentration, and WOMAC, SF-36).

Hofer et al. [32] showed a minimum 5-year follow-up of an oxidized zirconium femoral component in 109 TKAs. The authors reported similar survival rates compared to standard TKAs. Bergschmidt et al. [10] reported about 2-year follow-up results with ceramic femoral components in TKA in a prospective multi-center study ($n = 110$).

Discussion

This review of the current literature was performed with the aim of developing a rational approach to patients that present with self-reported allergies prior to surgery or that require a work-up for undefined pain and swelling after TKA.

The “National Joint Replacement Registry of Australia” [3] notes “metal related pathology” in 1.8% and “undefined pain” in 9.2% as reasons for revision in TKA, which suggests a revision rate of 0.06–0.32% secondary to metal or cement allergies after 10 years. While it is likely that allergies to metal or cement can trigger clinical symptoms and

Table 1 Summary of case reports

Author	Number of implants	Diagnostics		Implant	Revision	Histopathology
		Patch test	LTT			
Anand 2009 [1]	1	Ni, Co	–	CoCr (Zimmer)	Titanium (Biomet)	Mononuclear infiltrate (lymphocytes, plasma cells, and macrophages)
Beecker 2009 [7]	2	Ni, Co	–	CoCr	–	–
Bergschmidt 2012 [9]	1	Ni, palladium	–	CoCr	Ceramic, titanium	Lymphoplasma cellular fibrinous tissue, type IV allergic reaction
Dietrich 2009 [16]	4	Ni, Co	Ni, Co	CoCrMb	Titanium	–
Edwards 2007 [18]	1	Benzoyl peroxide	–	–	Cementless Oxinium®	–
Gao 2011 [24]	1	Cr	–	CoCrMb	–	–
Haeblerle 2009 [27]	1	Gentamicin	–	–	–	–
Handa 2003 [29]	1	Co, copper	–	Copper, Cr	–	–
Kaplan 2002 [34]	1	Bone cement (preoperatively)	–	cementless	–	–
Schuh 2006 [55]	1	Benzoyl peroxide, Ni	–	–	–	–
Thakur 2013 [58]	5	1. No test 2. Co 3. Co 4. No test 5. Negative	–	1.–5. CoCr	1.–5. Oxinium®	Periprosthetic lymphohistiocytic infiltrates in 3/5 patients
Thienpont 2013 [59]	1	CoCr	–	CoCr	–	–
Post 2013 [49]	1	Co, Cr, Ni	Cr	CoCr	Oxinium®	–
van Opstal [65]	1	Negative	–	TiAlVa	Zirconium alloy tibial baseplate	–
Verna 2006 [66]	15	Ni (4), Cr (2), Co (1)	–	CoCr	–	–
Thomsen 2011 [62]	1	–	Negative	CoCr	Multilayer coated	–

might ultimately lead to revision, allergies have not been associated with implant loosening [23]. Although a positive patch test shows a strong correlation, no causal relationship has been established between dermal reactions and implants failure [62]. Thus, it is not surprising that periprosthetic tissue changes consistent with metal sensitivity were demonstrated in only 31.25% (5/16) of these patients [1, 9, 58].

Clinical Presentation and Symptoms

The initial clinical symptoms may include pain at rest, joint effusions, and decreased range of motion [9, 49, 65]. Skin changes like dermatitis, rash, or hyperthermia are more specific for an allergy but are less common initial symptoms [27, 29, 55]. Decreasing range of motion is a quite common initial sign. The time-range of first symptoms is variable: Bergschmidt et al. [9] report first symptoms (effusion, decreased ROM, and pain) after 4 weeks, Edwards et al. [18] after 6 weeks (generalized knee pain, effusion, and skin rash), and Anand et al. [1] report swelling as a first symptom after 8 weeks. On the other hand, Gao et al. [24] indicate the first symptoms (rash and dermatitis only, no pain, and no decreased ROM) after 6 months. Thakur et al. [58] report persisting pain, swelling, and stiffness as late as 2 years after surgery (in a cohort of 5 patients). Systemic symptoms can also occur; Post et al. [49] describe extensive hair loss and generalized dermatitis.

Diagnostic Tests

Patient History

Self-reported allergies are an important first step in the diagnosis and evaluation of implant allergies. Bloemke et al. [11] showed a prevalence of self-reported cutaneous metal allergies or hypersensitivity in 14% of patients undergoing TKA. A significant gender difference occurred (22% (19/86) female and 2% (1/53) male patients). Two studies [26, 41] showed poor outcomes of TKA in patients with self-reported allergies. It is well known that patients' mental health is associated with poor outcomes after TKA. Patients reporting allergies are more likely to suffer from anxiety and depression, and these are associated with poor outcomes after TKA [24]. Many self-reported allergies are not confirmed by patch tests [24], and even if an allergy is confirmed a clear association between presence of an allergy and clinical symptoms cannot always be made. Schuh et al. evaluated 300 patients with a TKA and identified 20 patients (6.7%) with an allergy to metal or cement. Only one of these patients had clinical symptoms [54].

Since there is no clear association between self-reported allergies, or skin reactions and a positive patch test (skin) or periprosthetic hypersensitivity reaction (deep tissue) [37, 53, 60, 61] patients should be carefully educated on pros and cons as well as necessity of hypoallergic implants.

Patch Test

Patch testing is the gold standard for the evaluation of type IV hypersensitivity reactions [53]. Allergic reactions to

cement and metal in orthopedic implants display distinct characteristics of delayed-type hypersensitivity reactions [43]. Patch tests are in vivo tests, are widely available and easy to apply and provide results within days [53]. However, since there is a difference in antigen-presenting cells in the skin and in periprosthetic deep tissue it is still not clear if patch testing is the best screening test for allergic reactions in orthopedic patients [53, 61]. Nevertheless, 28 of 31 studies reviewed relied on patch testing making it the gold standard for the evaluation of a possible hypersensitivity to metal or bone cement.

Lymphocyte Transformation Test

Lymphocyte transformation test (LTT) is an in-vitro test, which measures the proliferation of lymphocytes derived from peripheral blood in the presence and absence of a potential allergen [53]. The main disadvantages of LTT are its limited availability, the limited number of allergens that can be tested, and the rapid decay of T cells that requires immediate transportation of the blood samples [53]. The main advantages of LTT are its higher sensitivity compared to patch testing [28]. The LTT also provides quantifiable data and is very reproducible [43]. In a prospective study, Niki et al. [47] tested if LTT is an effective preoperative screening tool prior to TKA. The study was able to identify all patients that developed metal related eczema during follow-up, however, the specificity of the LTT was very low [28]. Because of its price and the logistic challenges with current LTT, the test is limited to the evaluation of patients with a symptomatic TKA and unclear results of patch testing and imaging [28].

Further Diagnostic Methods

Carulli et al. [15] described a blood examination to assess the concentration of specific cytokines as well as the confocal microscopy of metal exposed thymidine activated macrophages. Beecker et al. [7] reported about a subcutaneous implantation of Co and Ti implant samples to detect hypersensitivity reactions. Innocenti et al. [33] described an alternative ELISA method to determine hypersensitivity against metal implants. All described tests have limited available data on the diagnostic value of these tests are scarce.

Intraoperative Biopsies

Intraoperative biopsies and the histopathological work-up remain the gold standard to confirm implant related hypersensitivity. The histological diagnosis of a metal or cement allergy requires a multidisciplinary approach according to Krenn. Krenn et al. [36, 37] described four types of periprosthetic membranes; they stated that allergic reactions are summed in type I periprosthetic membranes with pronounced lymphocytic infiltration. Particular attention has been devoted to the lymphocytic infiltrate without correlation to the characterization of the macrophagic infiltrate or to the morphological and elemental characteristics of the wear particles [37]. Three different lymphocytic infiltration patterns have been described [68]: (1) diffuse pattern with no aggregates; predominantly lymphocytes, sporadic plasma cells; (2) perivascular aggregates of predominantly T cells; and (3) perivascular aggregates containing T and B cells

with formation of germinal centers, associated with the presence of high endothelial cell venules. However, the clinical and prognostic importance of these lymphocytic infiltration patterns has not been clarified and the relationship to hypersensitivity reactions remains unclear [68]. Fibrous membrane formation even in the absence of a loose implant is common [44]. Thomas et al. [61] showed a fibrotic (type IV membrane according to Krenn) in 81% of the patch test positive patients. While some surgeons utilize arthroscopic biopsy to confirm a suspected metal allergy before revision surgery, usually the results of the histology are used to confirm the diagnosis after revision surgery.

Hypoallergenic Materials in TKA

If hypersensitivity against metal implants or bone cement is confirmed, hypoallergenic materials should be used for TKA. However, two studies [13, 59] report on patients with a confirmed metal allergy (patch test) who had no reactions and symptoms after several years with an orthopedic implant made of these materials. The treatment options include ceramic femoral components that do not contain any metal [10] or implant coatings. Ceramics (Al_2O_3 or ZrO_2) are biological inactive materials that have been used for over 30 years in total hip arthroplasties and have not shown to trigger hypersensitivity reactions. Bergschmidt et al. [8–10] showed in three studies the value of ceramic femoral components ($n = 108$) compared to CoCr components and presented a case report of a patient with suspected metal hypersensitivity requiring revision surgery using a ceramic femoral component. Ceramic femoral components are not readily available in the USA and are used mainly in Europe.

Fig. 1. Algorithm for diagnostic and treatment for patients in need of TKA. (LTT lymphocyte transformation test).

An alternative to a ceramic femoral component is the readily available zirconium oxide (Oxinium®, Smith&Nephew) femoral components in combination with a titanium base plate. Oxinium® femoral components contain less than 0.0035% nickel and display excellent tribologic properties including wear resistance, hardness, and wettability [56]. Hofer et al. [32] followed up 109 patients with Oxinium® femoral components and showed equal clinical outcomes to conventional CoCr components.

Fig. 2. Algorithm after TKA with metal implant and clinical symptoms. The decision in favor of revision should only be made after the overall clinical presentation, patch test, and comorbidities are taken into consideration.

Innocenti et al. [33] used Oxinium® components in 25 patients with suspected hypersensitivity. No hypersensitivity reaction or complications occurred. Oxinium hip and knee implants also have an excellent track record in the Australian registry [3].

The final treatment options are custom titanium niobium nitride (TiNbN) or titanium nitride (TiN) coatings [4]. The titanium or cobalt-chromium surface of a femoral component can be coated using nitrogen [12, 21], oxygen diffusion hardening [57], diamond-like-carbon surfacing [21], or physical-vapor-deposition with titan(niobium)nitride (Ti(Nb)N) [31]. Lutzner et al. [40] compared 60 coated to 60 uncoated CoCr implants. No increased plasma metal ion concentration was shown in either group. Nevertheless, there are reports of third body wear due to delamination of the TiN coating [30, 38, 50, 64] in hip arthroplasties. This can result in third body polyethylene wear [64]. There were no reports of adverse effects related to TiN coating of CoCrMo knee implants.

Algorithms

A number of papers have reported algorithms to screen for hypersensitivity against metals or bone cement in patients undergoing TKA [4, 22, 33, 63]. Most algorithms highlight the importance of the patient's history of metal hypersensitivity/allergic reaction. If the patient's self-reported history is positive, patch testing is usually recommended to confirm the allergy prior to surgery. If the medical history is negative, a further work-up is not recommended and there is no evidence that surgeons need to actively screen for allergies prior to TKA.

Metal hypersensitivity should be assumed in all patients with a positive patch test and alternative implants should be utilized. Further screening methods (LTT, ELISA, and confocal microscopy) are reserved for patients with a symptomatic TKA and a strong clinical suspicion for an allergy in the absence of a positive patch test. Figures 1 and 2 present possible algorithms for the evaluation of patients prior to TKA and for the symptomatic TKA, respectively. Attention should be given to the second point in algorithm two: Since allergies after TKA are very rare, it is essential to perform a thorough work-up to rule out other failure mechanisms (malalignment, loosening or inadequate sizing of the components, and deep implant infection).

Routine allergy testing is currently not recommended and patch testing is reserved for patients with a strong medical history of metal sensitivity. More sophisticated tests including LLT are reserved for patients with a negative patch test but a strong clinical suspicion for an implant allergy. Type I membranes on histologic analysis have been associated with metal hypersensitivity following TKA. Zirconium oxide implants are a readily available treatment option for patients with suspected metal allergy requiring primary or revision TKA. Alternatives include ceramic femoral components or custom coated implants.

Compliance with Ethical Standards

Conflict of Interest: Martin Faschingbauer, MD reports other from Deutsche Forschungsgemeinschaft, during the conduct of the study. Lisa Renner, MD has declared that she has no conflict of interest. Friedrich Boettner, MD reports personal fees from Smith & Nephew, during the conduct of the study; personal fees from Ortho Development, outside the work.

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