BioMed Research International

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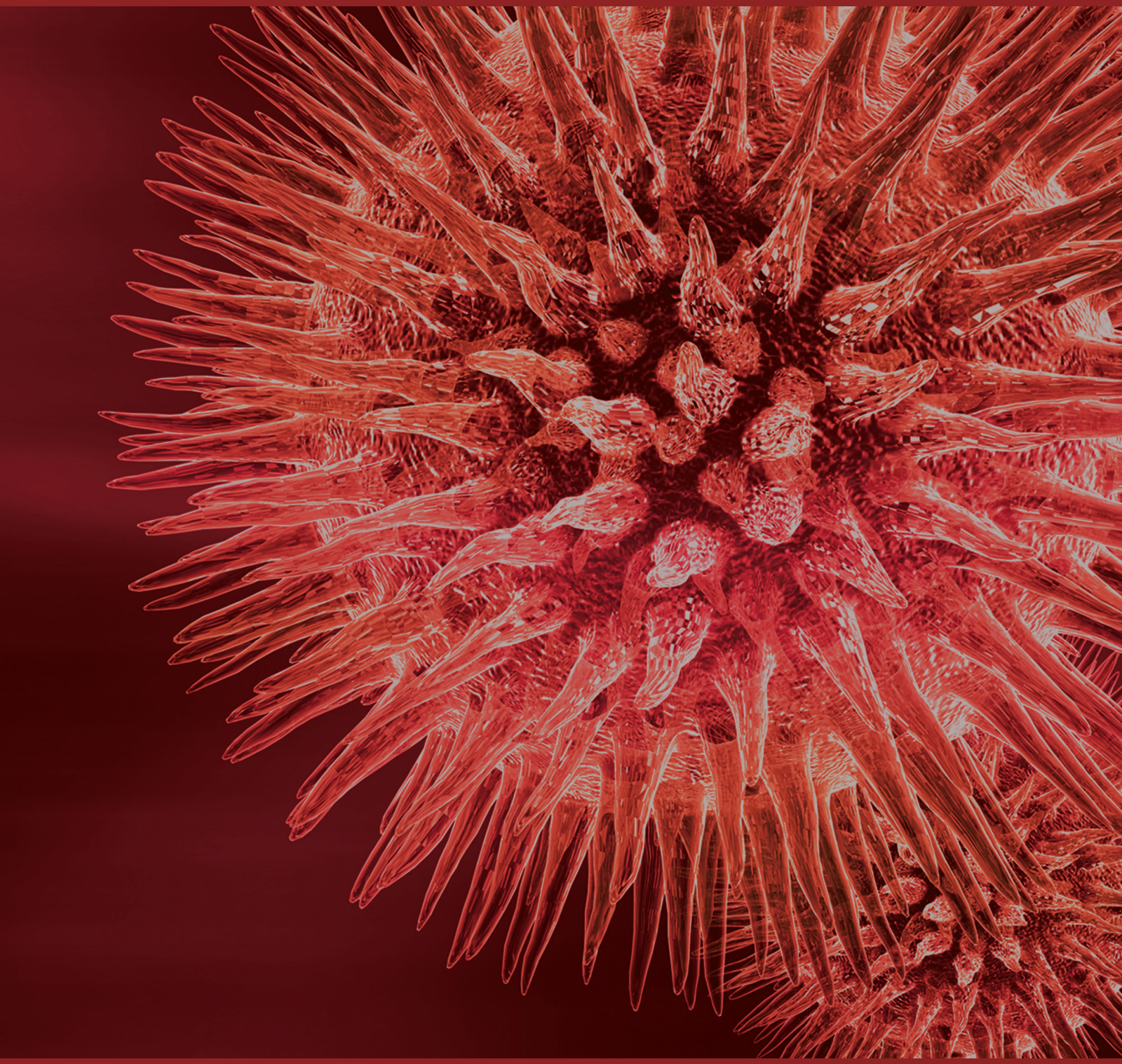
Guest Editors: Thomas M. Grupp, Sandra Utzschneider, and Markus A. Wimmer



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Editorial

Biotribology in Knee Arthroplasty

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During the last decade, new bearing materials, new methods in in vitro wear simulation, specific cell culture, and animal models to evaluate the response to particulate debris, and dedicated retrieval analysis programs to learn more about material degradation in vivo have been developed in the field of biotribology.

Improvements in knee arthroplasty design, materials, sterilisation techniques, oxidation resistance, and articulating surface treatments have led to superior performance of total knee prostheses by reducing the prevalence of disastrous wear, delamination, and structural fatigue and are expected to show substantial benefits in decreasing wear and osteolysis in the future.

As total knee arthroplasty today is being increasingly performed on younger, heavier, and more active patients, it appears desirable to reduce wear and further improve bearing materials and implant designs in the next decade.

This special issue presents 9 articles with original research papers, a clinical study, and a review article showing different dimensions of biotribology in knee arthroplasty.

The review of A. J. Mitchelson et al. summarizes the available literature in regard to biomaterial hypersensitivity after total knee arthroplasty (TKA) giving supportive evidence and approach consideration for metal ion allergic patients. In this field of knee implant allergy and metal ion hypersensitivity, the research paper of P. Thomas et al. describes a new approach to identify suspected allergy to TKA by combining allergy diagnostics with histopathology and periprosthetic cytokine assessment.

The paper of J. Friesenbichler et al. evaluates the serum ion concentrations of cobalt, chromium, and molybdenum of paediatric tumour patients after fixed hinge knee megaprosthesis in comparison to rotating hinge knee devices and metal-on-metal total hip arthroplasty.

J. Reinders et al. provide a new method of knee wear simulation in vitro based on two different constrained conditions, representing a ligamentous-stable TKA (sacrificed ACL) versus a ligamentous-unstable situation (insufficient anterior and posterior cruciates and medial collateral ligament). V. Ngai and M. A. Wimmer performed gait analysis on thirty TKA patients using the point cluster technique, characterizing a low and a high anterior-posterior motion category as variable inputs for knee wear simulation. A. C. Paulus et al. conducted unicompartmental knee wear testing under bone cement third-body contamination and examined the possible influence on particle size, morphology, and elevated particle numbers.

The study of S. M. Kurtz et al. supports the utility of using multidirectional pin-on-disc screening as a method evaluating wear properties of retrieved polyethylene implant components.

By A. Giurea et al., a clinical study on prospective early results of a modular rotating hinge knee design with carbon-fiber reinforced poly-ether-ether-ketone as a new bearing articulation in TKA was presented, demonstrating no premature material failure or unusual biologic response. Furthermore, within this paper a new classification of failure modes for revision knee arthroplasty was introduced.

Acknowledgments

Finally, the guest editors would like to thank all authors for contributing their excellent work to this special issue and all the reviewers for their thoughts and suggestions on the manuscripts.

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Sandra Utzschneider
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Review Article

Biomaterial Hypersensitivity: Is It Real? Supportive Evidence and Approach Considerations for Metal Allergic Patients following Total Knee Arthroplasty

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The prospect of biomaterial hypersensitivity developing in response to joint implant materials was first presented more than 30 years ago. Many studies have established probable causation between first-generation metal-on-metal hip implants and hypersensitivity reactions. In a limited patient population, implant failure may ultimately be related to metal hypersensitivity. The examination of hypersensitivity reactions in current-generation metal-on-metal knee implants is comparatively limited. The purpose of this study is to summarize all available literature regarding biomaterial hypersensitivity after total knee arthroplasty, elucidate overall trends about this topic in the current literature, and provide a foundation for clinical approach considerations when biomaterial hypersensitivity is suspected.

1. Introduction

Support for the theory of joint implant loosening caused by hypersensitivity reactions to metallic implant components was first presented in the mid-1970s [1, 2]. Studies were undertaken in response to clinical evidence of hypersensitivity reactions in patients after hip arthroplasty with metal-on-metal implants. Over the decades, this topic was examined in many publications. In a 2012 review of all available literature, Cousen and Gawkrodger established that first-generation metal-on-metal implants could cause sensitization of patients to the implant metals [3]. They also reported an association between metal sensitization and implant failure but did not establish a causal relationship [3]. A new generation of metal-on-metal implants is now available to surgeons. The widespread use of these new metal-on-metal implants, particularly in knee arthroplasty where their use is novel, raises questions regarding risks and benefits compared with more established implant options.

The theory that metal sensitivity and cutaneous allergic dermatitis develop in patients following implantation of metallic orthopaedic devices is supported by clinical and temporal evidence [4]. Reports also suggest that hypersensitivity to implant metals occurs in a considerable number of

patients, although the prevalence of this phenomenon is not known [4, 5]. In a prospective study, the incidence of sensitization to metals in orthopaedic implants, as determined by patch testing, increased by 6.5% following hip and knee arthroplasty [6]. Similarly, in a review of hip arthroplasty, the rate of sensitivity to nickel, cobalt, or chromium was 25% in patients with well-functioning implants; this is more than twice the rate found in the general population [7]. In patients with a failed or failing hip prosthesis, the rate of metal sensitivity rises dramatically to 60%, six times that of the general population [7]. One study examined rates of metal sensitization in patients who had undergone total knee arthroplasty (TKA) and found a sensitization rate of 20% in the control group with no implant, 48.1% in the group with the stable implant, and 59.6% in the group with an unstable implant group [8]. Mihalko et al. performed an analysis of available prospective and retrospective studies regarding hypersensitivity reactions after total joint arthroplasty; the findings of this analysis are provided in Table 1 [6, 9, 10] and Table 2 [1, 2, 11–18]. The available evidence indicates a correlation between metallic orthopaedic implants, the development of metal hypersensitivity, and implant loosening.

2. Results

2.1. Implant Composition and Wear. Orthopaedic implants can be made of a variety of metallic, plastic, and/or ceramic elements. The metal components of knee prostheses are most commonly stainless steel, followed by cobalt-chromium-molybdenum (CoCrMo) alloys, nickel, titanium, Vitallium (Austenal Company), beryllium, vanadium, and tantalum [4, 25].

In a knee with an implant, metallic surfaces are freely exposed to synovial fluid. Contact with biologic fluid results in metal corrosion [3, 6, 26–31]. Cadosch et al. reported evidence of growth and differentiation of human osteoclast precursor cells occurring directly on surgical stainless steel, titanium, and aluminum [30, 31]. The mature osteoclasts then directly corroded the metal surfaces and released ions into the joint space [30, 31]. Free metal-ion compounds may then bind to endogenous proteins and form metal-protein complexes [4, 25]. These metal-protein complexes may subsequently initiate an immune reaction. Caicedo et al. provided evidence that the macrophage inflammasome pathway is activated by implant debris [28]. CoCrMo alloy debris has been shown to induce macrophage activation, stimulate secretion of interleukin-1 beta (IL-1β), tumor necrosis factor α, IL-6, and IL-8, and upregulate nuclear factor-$\kappa\beta$ (NF-$\kappa\beta$) and downstream inflammatory cytokines [25]. Direct corrosion of metallic surfaces by osteoclasts similarly results in ion-induced secretion of proinflammatory cytokines [30, 31]. Although these inflammatory reactions are generally acute, implant debris in the periprosthetic region may in some instances result in a chronic inflammatory response [6].

2.2. Hypersensitivity Pathology. Exposure to metal ions can occur in a number of ways. Routine metal exposure in humans occurs through skin contact with jewelry, cell phones, clothing fasteners, and leather and through occupational exposure, dental filings, and medical implants [32]. Individuals are further exposed to trace metals through smoking and in cosmetics, food, and drinking water [33–35]. Nickel is the metal that most often leads to a hypersensitivity reaction; studies place the prevalence of nickel sensitivity in the general population between 8 and 25% [36–39].

Sensitization to metal is known to occur independently of the mechanism of exposure [4]. As previously mentioned, metal-ion exposure produces an adaptive immune response wherein macrophage activation leads to development of a delayed-type hypersensitivity reaction [4, 5, 7, 26, 40, 41]. In arthroplasty patients with a metal allergy, studies have shown elevated levels of interferon gamma and IL-6 [40, 41]. Similarly, in patients with nickel allergy, complicated joint implants were associated with substantially elevated levels of IL-17 when compared to uncomplicated implants [42]. These studies provide further evidence of delayed-type hypersensitivity reactions in response to implanted metal. Additionally, periprosthetic immune responses to metal have been shown to display characteristics of type I hypersensitivity reactions [40]. There is increasing support that metal hypersensitivity can be caused by orthopaedic arthroplasty components. Thyssen et al. presented a list of objective criteria which, when present in a patient, support a causative association between implant-released metal ions and metal hypersensitivity-induced allergic dermatitis, pain, and implant failure [43].

2.3. Aseptic Knee Implant Loosening. Implant wear debris is known to be an initiating event for aseptic implant loosening [44]. A significant number of failed knee implants display perivascular lymphocytic infiltration indicative of an adaptive immune response; however, the question remains if this finding truly suggests a causal relationship between metal hypersensitivity and implant failure [45]. Several studies have indicated potential pathomechanisms for aseptic implant loosening secondary to hypersensitivity. The common mechanism is the secretion of proinflammatory cytokines induced by metal ions; these lead to the formation of osteolytic lesions in the bone surrounding metallic implants [30]. The NALP3 inflammasome within macrophages has been shown to be a critical instigator and mediator of orthopaedic implant-induced osteolysis [46]. The osteolytic mechanism that responds to implant debris likely involves the receptor activator of NF-$\kappa\beta$ (RANK) and the receptor activator of NF-$\kappa\beta$ ligand (RANKL) pathway, as well as osteoprotegerin and IL-18 [47]. Titanium has been shown to directly increase the expression of RANKL, macrophage colony stimulating factor, and TNF-α [27]. Titanium ion-induced expression and secretion of CCL17 and CCL22, as well as upregulation of the CCR4 receptor, result in osteoclast precursor recruitment to the periprosthetic region, whereas the previously induced cytokines promote osteoclast differentiation and activation [27]. Chronic periprosthetic inflammation and the induction of macrophage-mediated aseptic osteolysis may ultimately result in implant loosening and failure [6].

Table 1: Hypersensitivity reactions after total joint arthroplasty reported in prospective studies.

Prospective study title	Publication	Author	Results
Sensitivity to implant materials in patients undergoing total hip-replacement	J Biomed Mater Res	Granchi et al. [19]	Patch test unable to differentiate stable versus unstable implants, equivalent implant lifespan in metal patch +; 10 yr survival for metal patch + 44% versus patch − 47%; poor survival for cement patch +
Allergy to components of total hip arthroplasty before and after surgery	Ital J Orthop Traumatol	Cancilleri et al. [20]	10/66 THA patch + (1/12 w/aseptic loosening patch +), 2/41 preop. patch +; hypersensitivity may play role in loosening, but likely small
Metal sensitivity in patients with metal-to-plastic total hip arthroplasties	Acta Orthop Scand	Carlsson et al. [11]	9/112 patch + preop., 12/112 patch + postop.; all complications except 1/246 explained by reasons other than hypersensitivity
Allergy in hip arthroplasty	Contact Dermatitis	Waterman and Schrik [21]	13/85 patch + preop. (13 metal), 25/85 patch + postop. (23 metal, 2 cement), 0/10 loose THA patch +; no evidence to suggest loosening because of hypersensitivity
The development of metal hypersensitivity in patients with metal-to-plastic hip arthroplasties	Contact Dermatitis	Nater et al. [22]	0/66 patch + preop., 4/66 patch + MOP conversion postop.; no clinical sequelae, no need to test
Metal sensitivity in patients with orthopedic implants: a prospective study	Contact Dermatitis	Frigerio et al. [6]	16/72 (22%) preop. + patch or LTT, (19/72 (29%) postop. (5 conversions of 72 total)); if preop. history insufficient, recommend for screening tests
Metal sensitivity before and after total hip arthroplasty	J Bone Joint Surg Am	Deutman et al. [23]	10/173 patch + preop., 4/66 converted patch + postop. MOP; no conclusion
Metal sensitivity in patients undergoing hip-replacement	J Bone Joint Surg Br	Rooker and Wilkinson [10]	6/69 patch + preop. MOP, only 1/54 patch + postop.; patch + may be effect not cause, no need to screen in MOP
The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants	Arch Dermatol	Mesinkovska et al. [9]	31 with history of hypersensitivity preop., 21 patch +, all did well with "allergen-free" implants; 41 suspected of hypersensitivity w/TJA, 10 patch +, 6/10 had resolution of symptoms with allergen free implant; recommend patch testing in those with history
Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty	Biomaterials	Niki et al. [24]	24/92 TKA were mLST+ preop., 5/24 developed eczema, Cr + in eczema patients but not in others; screening indicated
Prospective study summary			Preop. patch/LTT +: 56/618 (9.1%), postop.: 73/521 (14.1%) Conversion of patch/LTT preop. to postop.: 56/618 (9.1%) preop. versus 73/521 (14.0%) postop.

3. Patients

3.1. Published Case Studies. The majority of information regarding hypersensitivity reactions following TKA is derived from a limited number of case studies. The authors reviewed all available published reports of metallic knee implant-associated hypersensitivity reactions; details of the individual case studies are outlined in Table 3 and summarized in the following paragraph [12, 48–55].

In the 28 reported cases of metal hypersensitivity reactions after TKA, 23 of the patients were female [12, 48–55]. Seven patients had a history of metal hypersensitivity before the arthroplasty [52–54]. The orthopaedic implants associated with reactions were composed of various combinations of metals, including cobalt, chromium, molybdenum, copper, nickel, titanium, aluminum, and vanadium [12, 48–55]. Most patients presented with varying degrees of periprosthetic irritation, although one patient presented with systemic

Table 2: Hypersensitivity reactions after total joint arthroplasty in retrospective studies.

Retrospective study title	Publication	Author	Results
Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty	Dtsch Med Wochenschr	Eben et al. [15]	In cemented TJA: 22/66 symptomatic pts. patch +, asymptomatic patch + 3/26
Allergy to metals as a cause of orthopaedic implant failure	Int J Occup Med Environ Health	Kręcisz et al. [16]	14 poor implants, 8 patch + (7 ni, 6 cr), 3 underwent revision and improved
Early osteolysis following second-generation metal-on-metal hip-replacement	J Bone Joint Surg Am	Park et al. [17]	8/9 MoM w/osteolysis patch + to Co, 2/9 w/o osteolysis patch +; retrospective
Sensitivity to metal as a possible cause of sterile loosening after cobalt-chromium total hip-replacement arthroplasty	J Bone Joint Surg Am	Brown et al. [18]	0/20 loose MoM patch + (1977)
Metal sensitivity as a cause of bone necrosis and loosening of the hip prosthesis in total joint replacement	J Bone Joint Surg Br	Evans et al. [2]	9/14 w/loose joints patch +, 0/24 w/stable joints
Incidence of metal sensitivity in patients with total joint replacements	Br Med J	Elves et al. [1]	15/23 failed TJA patch +, 4/27 stable patch +, 8/13 w/derm rxn were patch +
Dermatitis on the knee following knee replacement: a minority of cases contact allergy to chromate, cobalt, or nickel but a causal association is unproven	Contact Dermatitis	Verma et al. [12]	7 of 15 patients w/cutaneous symptoms patch +
Metal sensitivity in patients with metal-to-plastic total hip arthroplasties	Acta Orthop Scand	Carlsson et al. [11]	13/134 MOP patch + postop.; unsure if hypersensitivity caused by THA, but, in pts. w/Hx of allergy, proceed w/caution
Retrospective evaluation of patch testing before or after metal device implantation	Arch Dermatol	Reed et al. [13]	5/22 with history of hypersensitivity preop. patch +, 0/22 referred for patch test postop. were patch +
Lymphocyte responses in patients with total hip arthroplasty	J Orthop Res	Hallab et al. [14]	More + LTT and cytokine release in THA, and esp. in loose THA
Retrospective study summary			Revised: 33/138 (23.9%) patch +, 44/303 (14.5%) patch + in stable TJA Failed/loose: 113/261 (43.3%) patch +, 32/146 (21.9%) patch + in TJA Total: 146/399 (36.6%) patch +, 76/449 (16.9%) patch − 10/16 (62.5%) revised TJAs LTT +

dermatitis. There was a report of decreased range of motion in three patients; in one of these patients, arthroscopy demonstrated a lymphoplasmacellular fibrinous tissue consistent with a delayed-type hypersensitivity reaction [48, 50, 55]. Skin patch testing was performed in all but 1 of the 28 patients, with 18 of the patients having positive results [12, 48, 49, 51–55]. Lymphocyte transformation testing (LTT) was performed in six patients, including the one patient who was not tested with a skin patch [50, 54]. Five patients had positive lymphocyte transformation tests. Aseptic implant failure was observed in two patients [53, 54]. Both patients experienced implant failure with the initial replacement and with the first revision procedure. After the second revision procedure using hypoallergenic implants, the dermatologic symptoms resolved and the implants remained stable. It is important to note that there have been two published case studies in which both patients had a history of metal hypersensitivity but did not develop any adverse hypersensitivity reactions following TKA even though the implants contained components to which the patients were allergic [13, 57].

3.2. Risk Factors. The risk of becoming sensitized to metal varies largely depending on an individual's exposure. Several risk factors for developing metal hypersensitivity have been identified, including age, gender, and occupation. With increasing age, there is a decreased risk of developing nickel hypersensitivity [36, 37, 39]. This may be attributed to decreased lifetime exposure of older individuals to metallic costume jewelry [36]. Exposure to costume jewelry (particularly earrings) may also account for the sex discrepancy that is observed in patients with metal hypersensitivity [36, 58]. In general, women are at an increased risk for developing hypersensitivity to several metals [8]. Epidemiologic studies place the rate of nickel sensitization in women between 17% and 32%, whereas the sensitization rate in men is significantly lower—between 3 and 10% [36, 37, 58]. The rate of cobalt sensitization is 11.2% in women and 8.4% in men [58]. The literature identifies only one metal to which men are more sensitized than women. The rate of chromium sensitization in men is 10.1% whereas in women it is 7.9% [58]. Interestingly, these differences correspond to metal exposures that

Table 3: Summary of case reports of metallic knee implant associated hypersensitivity reactions.

	Number of implants	Patient gender	History of metal allergy	Implant components	Presenting signs and symptoms	Patch test result	LTT result	Initial implant outcome	Treatment	Revision implant components
Beecker et al. [52]	2 (1 patient)	Female	Yes	Cobalt-chromium alloy	Erythema, edema, heat, eczema	Cobalt, nickel		Stable	Triamcinolone, diphenhydramine	
Bergschmidt et al. [48]	1	Female		Cobalt-chromium alloy	Arthralgia, heat, decreased ROM	Nickel sulfate, palladium chloride		Stable	Revision	Ceramic, titanium
Dietrich et al. [54]	4	Female	Yes	Cobalt-chromium-molybdenum alloy	Arthralgia, erythema, edema	Cobalt, nickel	Cobalt, nickel	Stable (3) Failure (1)	Revision	Titanium
Gao et al. [55]	1	Male	No	Cobalt-chromium-molybdenum alloy	Eczema, systemic dermatitis, decreased ROM	Chromium		Stable	Revision	Zirconium-niobium alloy
Handa et al. [49]	1	Male	No	Copper-chromium alloy	Eczema, exudate	Cobalt, copper		Stable		
Oiso et al. [51]	1	Male		Cobalt-chromium alloy	Erythema, edema, arthralgia, fever	Cobalt, chromium, nickel, manganese		Stable	Revision	Ceramic, titanium
Thomsen et al. [50]	1	Female			Arthralgia, eczema decreased ROM		Negative	Stable	Revision	Zirconium-nitride coating
van Opstal and Verheyden [53]	1	Female	Yes	Titanium-aluminum-vanadium	Arthralgia, eczema, edema	Negative		Failure	Revision	Zirconium alloy
Verma et al. [12]	15	Female (13) Male (2)	No	Cobalt-chromium alloy	Eczema	Nickel (4) Chromium (2) Cobalt (1)		Stable	Topical corticosteroid	

occur in traditionally sex-specific occupations. Chromium hypersensitivity is associated with concrete exposure in the construction industry, leatherwork and tanning, and occupations involved in cleaning [32, 36, 58]. Sensitization to cobalt is also associated with occupations involved in cleaning and leatherwork, as well as hairdressing and professions in the textile industry [58]. Nickel sensitization is associated with occupations in healthcare, agriculture, mechanics, and metalwork [58].

A history of metal allergy in patients may also be a significant risk factor that should be taken into consideration before TKA. Granchi et al. reported the implant failure rate that was four times greater in patients with a self-reported history of preoperative metal allergy compared with patients who did not have a metal allergy [8].

3.3. Presentation. As with all pathological processes, hypersensitivity reactions to metallic knee implants can present several ways. Metal hypersensitivity may result in localized or systemic allergic dermatitis, loss of joint function, implant failure, and patient dissatisfaction [32]. Hypersensitivity reactions after TKA are most commonly present in the first few postoperative months as pruritic, erythematous, eczematous, edematous, sometimes painful, and sometimes exudative lesions in the periprosthetic region [12, 48–55]. In patients with a TKA implant containing metal, the clinician should consider metal hypersensitivity when dermatologic allergic symptoms are reported. Furthermore, metal hypersensitivity should be considered in such patients when they present with arthralgia, when periprosthetic radiolucent lines appear, or when aseptic implant loosening is observed [59].

4. Screening

4.1. Patient History. The patient history plays an invaluable role in making a diagnosis in every field of medicine. When diagnosing metal hypersensitivity, patient-reported history of a metal allergy should not be ignored. In a study of 22 patients with a self-reported history of metal hypersensitivity, skin patch test results were positive in 19 patients [13]. A similar study found positive gold standard skin patch test results in 68% of the patients with a history of metal allergy [9]. It should be considered, however, that the patient history and gold standard skin patch test results do not necessarily correlate, particularly in patients with a history that is negative for metal hypersensitivity [60]. Frigerio et al. reported that patient history taking is appreciably less reliable than gold standard testing in determining metal sensitization; the sensitivity of patient history is 85.5% and the specificity is 83.5% [6].

4.2. Patch Testing. Cutaneous patch testing is the gold standard for in vivo evaluation of delayed hypersensitivity reactions [5]. As previously discussed, metal hypersensitivity to orthopaedic implants displays distinct characteristics of delayed-type hypersensitivity. Many physicians believe that the patch test method is an acceptable approach for evaluating hypersensitivity to orthopaedic joint implant components [8].

In the general population, there has been a significant increase in the number of positive patch test results over the past four decades; this increase is most likely attributable to a substantial rise in the number of metals tested [61]. Despite this increase in the general population, patients who have undergone TKA remain significantly more likely to have a positive patch test [8, 61]. The rate of positive patch test results to metals is even greater in patients with metal-on-metal implants and in those with a failed prosthesis [61]. This correlates with the finding that positive patch tests are associated with shorter implant lifespans [19].

There are several advantages to evaluating metal hypersensitivity with patch tests following total knee arthroplasty. In a published report of 21 patients with positive patch tests to metals, none experienced hypersensitivity reactions after TKA with hypoallergenic implants [9]. These findings can be viewed as support for the argument that preoperative patch testing potentially prevents significant morbidity [5]. Practical advantages of cutaneous patch testing include ease of performance, rapidity of results, the scope of evaluation, and widespread availability [19, 43]. As with all ideal testing methods, the risk to the patient in patch testing is generally quite low [5].

Without disputing the numerous advantages of patch testing, questions remain regarding the propriety of patch testing in evaluating implant-induced hypersensitivity reactions. Some investigators cite the differences in antigen-presenting cells in superficial and deep tissues as a cause for doubt; this doubt leads to questions regarding the validity of cutaneous test results as they relate to periprosthetic tissue [7, 8, 14, 25]. Other investigators have noted that, despite a strong correlation, no causal relationship has been definitively established between dermal reactions and implant failure [50]. Analyses have determined that patch testing results, although valuable in patients with suspected hypersensitivity, had no predictive value for complications when performed prior to arthroplasty [8, 61]. These arguments have contributed to the reluctance of orthopaedic surgeons to use cutaneous patch testing in routine orthopaedic practice [3, 25, 62].

Although primarily theoretical, a potential disadvantage of patch testing is that the process of in vivo patch testing could potentially induce sensitization in a previously non-sensitized patient [25]. If this occurred in a patient who had previously undergone arthroplasty, it could place the patient at risk of significant morbidity secondary to an iatrogenically induced hypersensitivity.

Patch testing remains the gold standard for evaluation of delayed-type hypersensitivity. Its preoperative use should strongly be considered in patients with a history of metal allergies and its postoperative use in patients presenting with either suspected metal hypersensitivity or implant failure in the absence of infection [5, 61].

4.3. Lymphocyte Transformation Testing. Lymphocytes transformation testing (LTT) can be used as an alternative method to determine metal sensitivity in a patient. This in vitro test measures the proliferation of lymphocytes from a patient's

peripheral blood in the presence and absence of a potential allergen [5]. It has been suggested for use when patch testing provides questionable results [5, 19].

LTT has several important advantages compared to cutaneous patch testing. In determining a patient's reactivity to metal, LTT offers greater sensitivity than patch testing [40]. Because of the nature of the LTT construct, highly quantifiable and reproducible measures of sensitivity are available; no such objective results exist for patch testing [43, 63]. Unlike patch testing, LTT cannot induce sensitization because it is performed in vitro [63]. The greatest risk to a patient with LTT is venipuncture. Most encouragingly, a prospective study using LTT prior to arthroplasty indicated that it may be effective as a preoperative screening tool for metal hypersensitivity [24].

LTT remains largely impractical for routine clinical use. The availability of laboratories equipped to perform this test is limited; such facilities are primarily restricted to university settings [5, 43]. Because few allergens are tested, LTT is much more restricted in breadth of evaluation compared to patch testing [5]. Although LTT is known to have a greater sensitivity compared to patch testing, the precise sensitivity and specificity of LTT have not yet been established [25, 40].

4.4. Other Screening Options. Beecker et al. reported on a case study of a patient with a known history of metal hypersensitivity and established positive patch test reactions to nickel and cobalt [52]. The patient underwent subcutaneous embedding of cobalt and titanium implants [52]. At 6 weeks, no reaction to the implanted metals was noted; however, after the patient underwent TKA of the left knee, periprosthetic allergic contact dermatitis developed [52]. One year later, the patient underwent total knee arthroplasty of the right knee [52]. Periprosthetic hypersensitivity reactions again developed [52]. No established guidelines exist regarding the depth or the duration of subcutaneous metal implantation as a screening test for hypersensitivity. This patient's outcome suggests the poor sensitivity of this method for at least the first 6 weeks of subcutaneous metal implantation. This approach is not recommended.

4.5. Timing. Standard screening of all patients for metal hypersensitivity prior to total knee arthroplasty is not appropriate [43]. In addition to generating unnecessary expense, a large portion of the general population tests positive for nickel allergy despite the absence of hypersensitivity symptoms [36–39]. Therefore, preoperative testing is only indicated in patients with a history of either metal allergy or previous aseptic orthopaedic implant failure [9, 43]. Some additional guidelines for preoperative patch testing exist. Schalock et al. recommend using a baseline series based on the patient's place of residence [5]. Various national and international dermatologic organizations have established appropriate baselines. A history of hypersensitivity to metals that are not included in the baseline series warrants expansion of the testing parameters [5].

Postoperative testing for metal sensitization is appropriate in a select group of patients. Such testing should be considered if a patient presents with recent onset periprosthetic allergic contact dermatitis or arthralgia and when radiolucent lines appear on radiographs or implant loosening is observed [5, 59]. Infectious etiologies of these symptoms should be ruled out first.

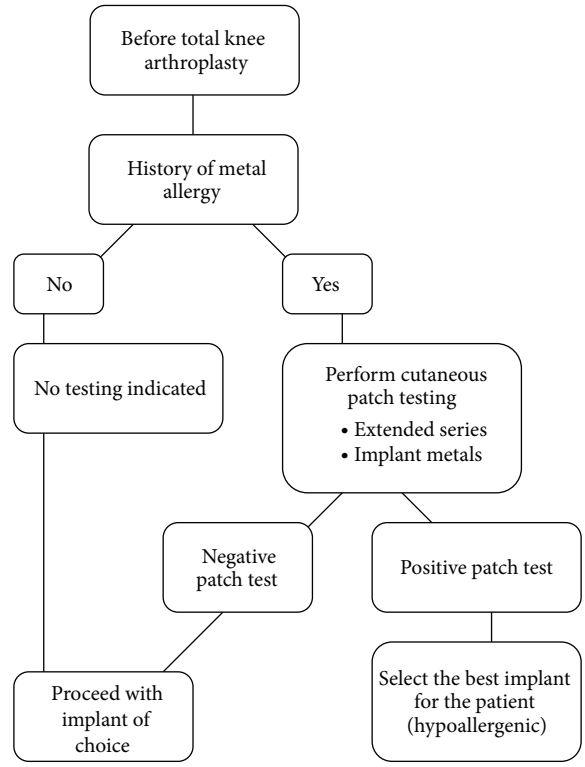

Figure 1

5. Prevention and Management

5.1. Case Study Follow-Up. In the case studies previously discussed, patients with metal hypersensitivity were managed with a variety of approaches. The details of individual case studies are outlined in Table 3. The dermatologic symptoms of 15 patients were resolved completely with the use of topical corticosteroid [12]. The bilateral intermittent cutaneous reactions of one patient were managed with topical treatment over an 8-year course with topical treatment [52]. Ten patients were treated with surgical revision utilizing hypoallergenic prostheses; the revision implants included four titanium-based implants, two zirconium-nickel coated implants, one zirconium-ceramic alloy implant, one titanium and ceramic implant, one cobalt and ceramic alloy coated implant, and one ceramic implant [48, 50, 51, 53–55]. One case study did not mention the treatment approach or patient outcome [49].

5.2. Approach Considerations. Several diagnostic algorithms have been suggested for orthopaedic patients with suspected metal hypersensitivity [5, 61]. Comprehensive diagnosis and treatment algorithm are presented in Figures 1 and 2, respectively. Postoperative intervention should follow positive patch test results only when patients are symptomatic or the implant demonstrates clear evidence of failure [5, 9]. Consideration

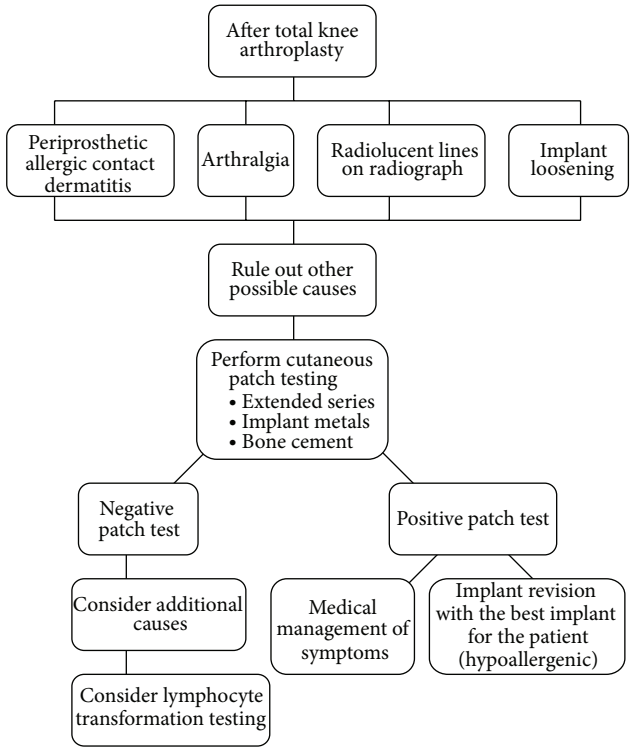

Figure 2

also should be given to nonmetal allergic reactions after TKA. Benzoyl peroxide found in bone cement may cause delayed hypersensitivity reactions [5, 64, 65].

There are many options when considering implants for patients who are sensitive to metal. The ideal prosthesis does not contain metals to which the patient has been sensitized [5]. Because titanium sensitivity is rare, it has been suggested that titanium implants be used in all TKA patients. These implants, however, are inappropriate for most patients because they are typically unnecessary and are substantially more expensive [43]. Patients who are sensitive to metal, even those with titanium-coated prostheses, experience greater functional limitations and decreased quality of life compared with their nonallergic counterparts with standard implants [56]. The most important consideration is whether aseptic loosening has occurred secondary to metal hypersensitivity [66].

6. Conclusion

Currently available evidence demonstrates both incidence and probable mechanisms for metal hypersensitivity reactions after total knee arthroplasty. This is an uncommon complication but must be recognized to ensure the health and satisfaction of patients. Some studies acknowledge the correlation but do not identify a causative relationship. However, based on the current evidence, the authors of this paper believe in a likely casual association between metallic knee implants and hypersensitivity reactions that can potentially lead to aseptic implant failure.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Rapid Prototyping for *In Vitro* Knee Rig Investigations of Prosthetized Knee Biomechanics: Comparison with Cobalt-Chromium Alloy Implant Material

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Retropatellar complications after total knee arthroplasty (TKA) such as anterior knee pain and subluxations might be related to altered patellofemoral biomechanics, in particular to trochlear design and femorotibial joint positioning. A method was developed to test femorotibial and patellofemoral joint modifications separately with 3D-rapid prototyped components for *in vitro* tests, but material differences may further influence results. This pilot study aims at validating the use of prostheses made of photopolymerized rapid prototype material (RPM) by measuring the sliding friction with a ring-on-disc setup as well as knee kinematics and retropatellar pressure on a knee rig. Cobalt-chromium alloy (standard prosthesis material, SPM) prostheses served as validation standard. Friction coefficients between these materials and polytetrafluoroethylene (PTFE) were additionally tested as this latter material is commonly used to protect pressure sensors in experiments. No statistical differences were found between friction coefficients of both materials to PTFE. UHMWPE shows higher friction coefficient at low axial loads for RPM, a difference that disappears at higher load. No measurable statistical differences were found in knee kinematics and retropatellar pressure distribution. This suggests that using polymer prototypes may be a valid alternative to original components for *in vitro* TKA studies and future investigations on knee biomechanics.

1. Introduction

Nearly one-fifth of the patients are unsatisfied after primary total knee arthroplasty (TKA) [1]. An extensive part of patients complain about pain in the anterior knee joint, which should be associated, amongst other things, with an increased retropatellar pressure [2–4]. Instabilities, subrespectively, luxation, and fractures of the patella after implantation are further complications and reasons for revision [5–9]. These given facts show precisely the requirement of research and development on this part of the knee joint.

It is common knowledge that knee biomechanics after total knee arthroplasty (TKA) are altered due to changes in pressure distribution as well as the kinematics pattern [3, 10, 11]. Workgroups showed that an external or internal rotation of the femur component changed the retropatellar pressure and kinematics [12–14]. However, these workgroups use commercial prostheses and therefore both the alignment of the trochlear groove and the flexion gap changed while rotating the femur component. The tendon stresses of the collateral and posterior cruciate ligament as well as the knee flexion axis were modified by using this method. Specially designed prototypes have been proposed to analyze the influence of different trochlea alignments as well as different trochlear shapes for total knee arthroplasty without influencing the femorotibial positioning of the prosthesis [15].

Additive technology, or rapid prototyping, is a current trend in the industry to produce prototypes in the early stage of development allowing evaluating the effects of design. These procedures are used in medicine amongst others for the reconstruction of jaw and face bones [16, 17], but also in the area of tissue engineering to produce scaffold for

the cell population [18]. Patient-specific cutting guides made by rapid prototyping are newly offered to the orthopedic field to specify the implantation of prostheses, in particular for knee surgery [19, 20]. The manufacturing of patient-specific knee prostheses made by rapid prototyping for scientific research is still in the early stage. Prototypes made of metal—for example, manufactured by laser sintering—are still expensive at this moment and require additional treatment, such as polishing to achieve surface roughness representative of the commercial prosthesis. Alternatively, methods such as 3D-printing or molding can be used to create polymer prototypes. In particular, 3D-printing is a quick and inexpensive method which allows high geometrical accuracy. However, the use of polymers rather than metallic alloys results in prototypes of reduced mechanical properties. It is unknown if such materials may be suitable for *in vitro* testing, in particular for *in vitro* knee kinematic studies which typically subject the knee joint to reduced body weights for a limited number of loading cycles.

This study therefore sought to determine if the use of rapid prototyped prostheses can serve as an alternative to the standard prostheses for *in vitro* studies for knee, in particular for the study of retropatellar biomechanics.

To test this issue, the sliding friction parameters of the standard bearing combination in TKA (ultrahigh molecular weight polyethylene versus cobalt-chromium alloy) were firstly measured and compared to the rapid prototype material. Additionally, PTFE was used as a counterpart against both femoral component materials in the friction test, because it is often used to protect the pressure sensitive foil against shear. The foil is sutured on the patella surface and has therefore contact with the femoral component [3, 11, 21].

Then, in a second step, rapid prototyped femoral components of a commercial prosthesis design were created and implanted in seven cadaver knee specimens. These were tested in a custom-made dynamic knee rig under standardized conditions while recording retropatellar pressure and knee kinematics, and these measurements were compared with the ones obtained for identical tests for standard components made of cobalt chromium in the same knee specimens.

2. Materials and Methods

2.1. Prostheses and Test Samples. Femoral components of a fixed bearing knee prosthesis (Columbus CR, Aesculap, Tuttlingen, Germany) manufactured from casted CoCr27Mo6 (standard prostheses material; SPM) and rapid prototype material (RPM; RGD 840 vero blue, Stratasys GmbH, Frankfurt) were obtained from the manufacturer (Figure 1). The material specifications of the RPM are shown in Table 1. Original CAD data were used to produce rapid prototypes for the femoral components in sizes 2 until 5 for each side (left/right knee) with a professional 3D-printer (Object Eden 350, Rehovot, Israel). These specimens were printed in thin layers (down to approximately 50 μm) of a liquid photopolymer resin (Table 1), which immediately polymerized under UV-light. Afterwards the rapid prototyped prostheses were polished submerged with fine grained sandpaper (up to grain size 1000). Finally, a roughness of $R_a = 0.44\,\mu$m was reached for the surrogates, while the prostheses made of SPM reached $R_a < 0.05\,\mu$m.

Figure 1: The Columbus CR prosthesis (Aesculap AG, Tuttlingen, Germany; top) and the test pieces (bottom) for the friction test made of the standard material (CoCr29Mo6) on the left and the rapid prototype material (RGD840) on the right side.

Table 1: Material properties of the photopolymer resin.

Parameter	RGD 840 vero blue
Ingredients	Several acrylate oligomers; acrylic monomer; isobornyl acrylate; photoinitiator
Modulus of elasticity	2000–3000 MPa
Tensile strength	50–60 MPa
Elongation to break	15–25%
Shore hardness	83–86 (Scale D)
Rockwell hardness	73–76 (Scale M)

Tibial insert was made of UHMWPE (GUR 1050).

For the ring-on-disc friction test ring-shaped samples were produced of SPM and RPM. The discs which were used as counterparts in the test setup were made of ultrahigh molecular weight polyethylene (UHMWPE) and polytetrafluoroethylene (PTFE; HighTechflon, Konstanz, Germany).

2.2. Ring-on-Disc Friction Test

2.2.1. Ring-on-Disc Rig. A tribological test setup according to ISO 6474 and Huber et al. was used to measure the friction coefficient (μ_R) [22]. The ring (friction area 160.2 mm^2; radius$_{external}$ = 10 mm; radius$_{internal}$ = 7 mm) rotated periodically with 1 Hz on the disc (diameter = 25 mm) with an amplitude of ±25°. Axial compression between ring and disc was adjusted with a manually controlled trapezoidal spindle. The compression was measured with a force transducer (HBM, Darmstadt, Germany), while the friction moment was detected with a beam using a half bridge strain gauge (HBM, Darmstadt Germany). This moment was converted into a force by using the geometrical parameters of the specimen (Figure 2). Both sensors were connected to a personal computer using an analog digital converter (compactDAQ with NI 9237 & NI 9236 modules; National Instruments, Austin,

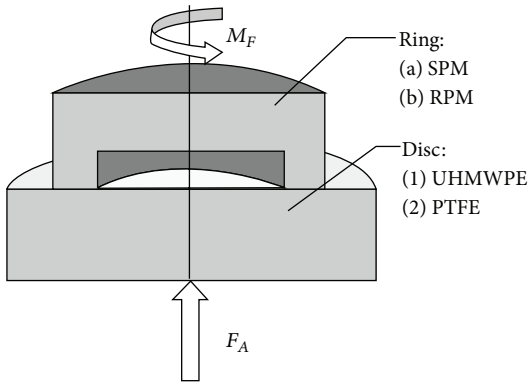

Figure 2: Schematic setting of the ring-on-disc rig with the demonstration of the axial compression force (F_A) and the friction torque (M_F) as well as the tested material combinations. The rotation of the ring occurs about the rotation axis, which is identic to the axial load transmission.

Table 2: Number of tested specimens subdivided in the four material combinations; UHMWPE and cobalt-chromium alloy are the common bearing material for knee arthroplasties; PTFE is not used *in vivo* but serves protection of the retropatellar pressure sensitive foil during *in vitro* examinations.

Femoral prosthesis material	CoCr27Mo6 (SPM)	RGD 840 vero blue (RPM)
UHMWPE (femorotibial counterpart)	$n = 6$	$n = 6$
PTFE (patellofemoral counterpart)	$n = 6$	$n = 6$

USA) and a self-written program code on LabVIEW (Version 2011, National Instruments, Austin, USA) to record sensors data continuously with a sample rate of 1000 samples per second.

2.2.2. Friction Test. Forty-eight hours before testing, all specimens were conditioned in a synovial replacement composed of newborn calf serum (S0125; Biochrom AG; Berlin, Germany) diluted with deionized water to reach a protein concentration of 30 g/L. Lubrication was secured using the same fluid during the test. The sliding friction coefficient (friction coefficient) of six specimens per material combination (Table 2) was measured in 250 N steps beginning from 500 N to 1500 N axial compression under ambient temperature. Friction force was measured five times at each axial load step. The friction coefficient was calculated by dividing the friction force by the axial force.

2.2.3. Statistics. An unpaired 2-way ANOVA (material pairing and axial load) with a Tukey post hoc test was used to compare each group (SPSS 21, IBM). Significance was approved with $P < 0.05$. Additionally the mean difference (MD) and the confidence intervals (CI) were presented.

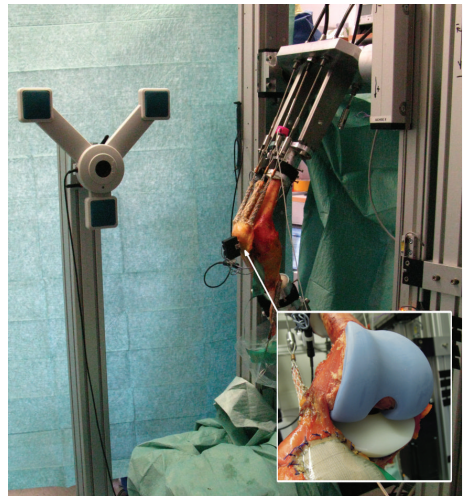

Figure 3: Knee rig with a mounted specimen with implanted TKA; knee kinematics were measured with an ultrasound markers on femur, tibia, and patella; by removing the anterior cables, pressure sensitive foil covered with Teflon tape behind the patella and prosthesis were visible (magnification-box).

2.3. Knee Rig Investigation

2.3.1. Knee Rig. The custom knee rig (Figure 3) simulates a loaded squat with a human specimen using two linear drives as presented in a previous publication [11]. The first actuator flexes and extends the knee with a constant velocity. Two angle sensors (8820 Burster, Gernsbach, Germany) in the upper "hip" and lower "ankle" joint are used to measure the flexion angle of the knee joint. The second stepper drive simulates the quadriceps muscle. The resulting force is measured with miniature force transducers (8417-6002 Burster, Gernsbach, Germany) near the tendons. Additionally hamstrings, vastus lateralis, and medialis muscle are simulated with 2 kg masses. A six degree of freedom force-moment-sensor measures the ground reaction (FN 7325-31 FGP Sensors, Cedex, France).

All sensors are amplified up to maximum 10 volts and digitalized with an 18-bit analog digital converter (PCI 6281 National Instruments, Texas, USA). The rig is controlled with a quad-core personal computer. Four parallel real-time program loops (LabVIEW, Austin, US) for each core are necessary to control the knee rig, while the first loop acquires the sensor data. The second loop is a parabolic PID-force-control loop to hold the ground reaction force constant with the loaded quadriceps muscle. The third loop controls the flexion and extension of the knee in a constant velocity. The last loop writes the sensor data into an ASCII-File.

For this study all specimens were tested with a ground reaction force of 50 N, a velocity of 3°/s, and a squat from 20° to 120° flexion and extension back to 20°.

Retropatellar pressure distribution (Tekscan, Boston, US) and femorotibial (ap-translation, femorotibial rotation) and patellofemoral (tilt, rotation, shift defined in [23]) kinematics were acquired during the squat with an ultrasound three-dimensional motion analysis system (CMS 20 Zebris, Isny, Germany) ensuring an accuracy of 0.1 mm and 0.1°.

2.3.2. Cadaver Preparation and TKA Implantation. Seven human knees (57.7 ± 13.0 years; 177.7 ± 6.3 cm; 82.4 ± 11.9 kg; 5 males, 2 females) were tested under weight-bearing conditions. The specimens were standardized in length with a femur cut 20 cm proximally and a tibia cut 15 cm distally from the epicondyle axis, respectively. The fibula head was fixed on the tibia using a cortical screw. Muscle and fat tissues were carefully removed from the tendons and bones. Finger traps were connected to the tendons and suture wires (Fibrewire, Arthrex, Karlsfeld, Germany) were used to fix the tendon into the metallic mesh of the traps. The diaphyses of the femur and tibia were embedded into pots with epoxy resin which were then mounted on the knee rig.

A pressure sensor (K4000; Tekscan; Boston, US), protected with an additional thin layer of PTFE-tape (Thickness: 125 μm, HighTechflon, Konstanz, Germany), was fixed at the articulating surface of the patella with sutures (Novosyn, B. Braun, Melsungen, Germany), with the osteophyte of the patella previously removed to ensure better contact. Before, the sensor was conditioned for 20 loading cycles and calibrated with a 2-point calibration line computed by the measurement software (I-Scan 6.1). The axial pressure for calibration and conditioning was applied with a material testing machine (Zwick Z010, Ulm, Germany).

Additionally a tripod of three ultrasound markers was attached to each bone and anatomic landmarks were identified on the specimen to define kinematic pattern in relation to the coordinate system of each bone.

An experienced surgeon (A. S.) implanted the prostheses as indicated by the manufacturer using a subvastus approach in the tibia first technique. The tibia was resected perpendicular to an intramedullary rod, while a slope of 3° was included in the inlay. A gauge instrument was used to balance flexion and extension gap. Then, an intramedullary rod was used to align the femoral component in a 4°–6° valgus rotation relative to the bone axis of the femur. The femural component was then rotated parallel to the anatomical transepicondylar axis, priorly defined using an inserted K-wire.

After implantation the specimens were tested in the knee rig by acquiring pressure and knee kinematics data without additional lubrication. Randomized change between the SPM and the RPM prostheses for each specimen allowed testing the implants consecutively. Between each test cycle the biological materials were prevented for dehydration by putting saline-soaked scarfs on the surface of the specimen.

2.3.3. Statistics. Results for the RPM were plotted against the SPM results at 5° intervals of flexion angle. A Deming-regression was performed for each specimen and each parameter to calculate the slope of the regression line. Equality criterion implies a linear regression whose slope is not significantly different to 1 using a one sample t-test.

3. Results

3.1. Coefficient of Sliding Friction of the Ring-on-Disc Test. Both material combination and axial load influence the sliding friction coefficient in the ring-on-disc rig ($P < 0.001$).

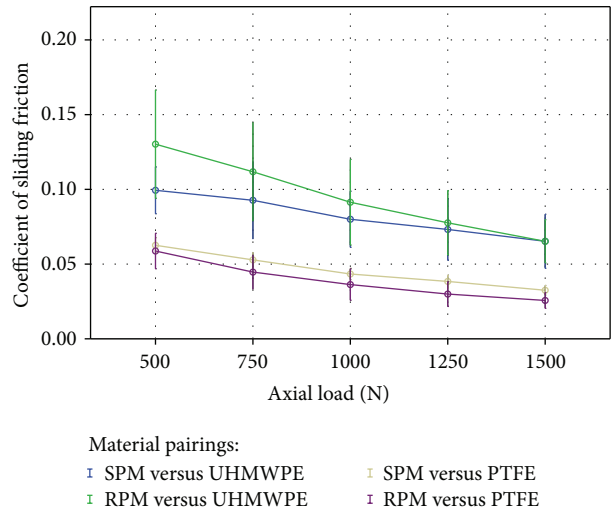

Figure 4: Dependence of the coefficient of sliding friction with rising axial load for the tested parameters; whiskers define the 95% confidence interval.

With increasing load, a decrease of the friction coefficient was measured in the four groups ($P < 0.001$). The friction test with the bearing partner UHMWPE provided significant higher friction coefficients than with PTFE ($P < 0.001$; Figure 4). There was no interaction between load and material combination measurable ($P = 0.52$).

The material combinations SPM and RPM against PTFE showed no differences (MD: 0.0068 (CI: −0.0047; 0.018)) in the friction coefficient ($P = 0.413$). In contrast, there was a significant difference (MD: −0.013 (CI: −0.025; −0.0016)) between the material combinations SPM, respectively, and RPM to UHMWPE ($P = 0.013$). Pairwise comparison revealed that the difference between SPM and RPM at 500 N (3.1 MPa) is significantly increased (MD: −0.031 (CI: −0.051; −0.011) $P = 0.002$). That difference tends to disappear with increasing axial loads ($F_A = 750$ N MD: −0.019 (CI: −0.039; 0.001) $P = 0.06$; $F_A = 1000$ N MD: −0.011 (CI: −0.031; 0.008) $P = 0.3$; $F_A = 1500$ N MD: $1.5 \cdot 10^{-5}$ (CI: −0.020; 0.020) $P = 1.0$; Table 3).

3.2. Knee Rig Study. For each measured specimen and each parameter, a linear regression was calculated by Deming-regression. Figure 5 represents a typical result obtained for quadriceps load measured for one specimen with both types of implant materials.

No significant differences were measured in the knee rig between the two tested materials (Table 4). A maximum quadriceps load of 647 ± 131 N with RPM and 620 ± 88 N with SPM was necessary to extend the cadaver knee and caused comparable results during the whole cycle ($P = 0.69$). Furthermore the maximum retropatellar peak pressure of 6.92 ± 2.01 MPa with RPM and 6.83 ± 1.79 MPa with SPM showed no significant differences ($P = 0.53$). Little deviations could be noticed at the maximum of the contact area (Figure 6). RPM showed a tendency to a higher contact area with 402 ± 63 mm^2 compared to the SPM with a maximum contact area

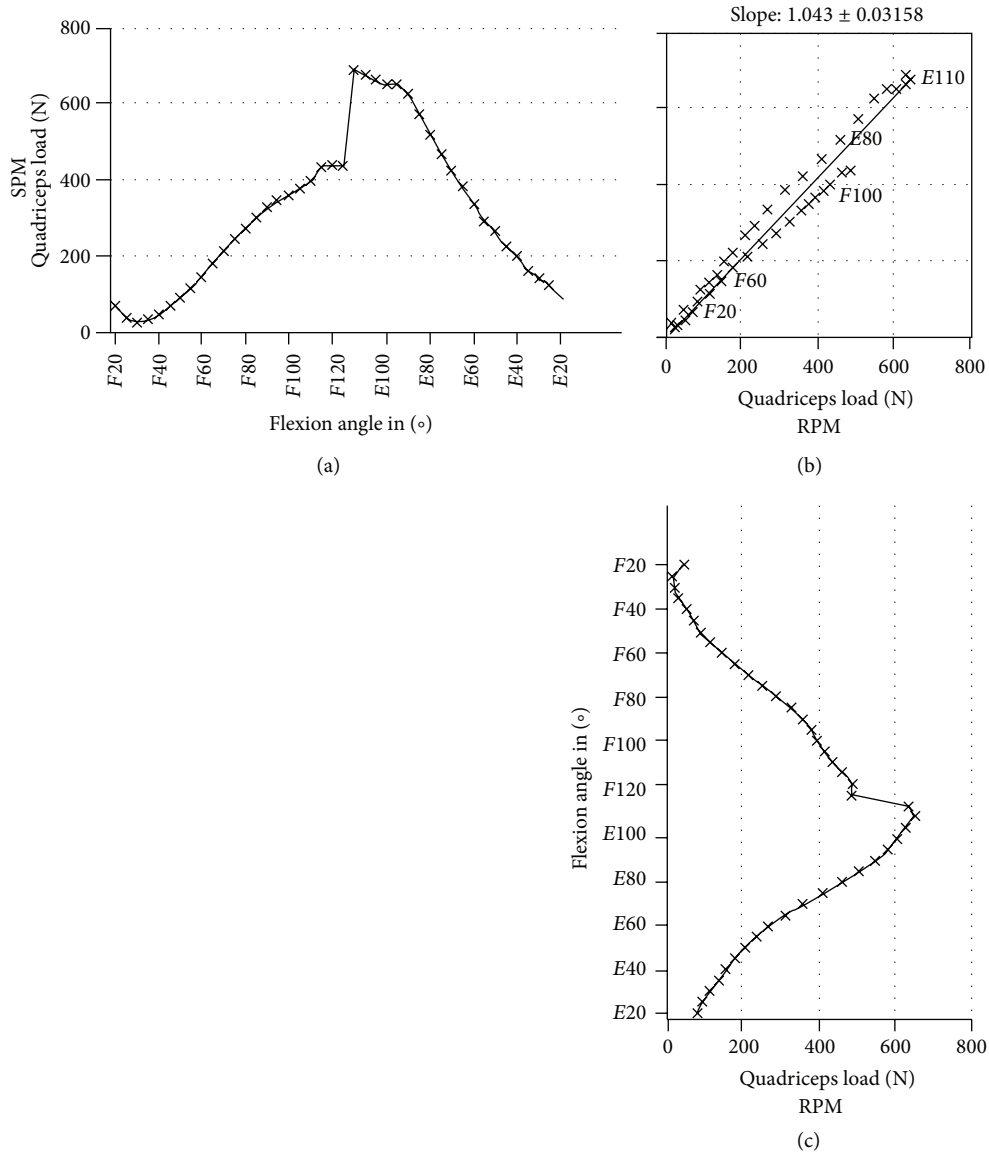

Figure 5: The left plot shows the quadriceps load in N against the flexion angle of the SPM and the plot at the bottom shows the flexion angle against the quadriceps load of the RPM. The diagram in the center is a projection of both plots and compares the RPM material (y-axis) and the SPM (x-axis). Angles are identified in the upper right corner plot with flexion (F), extension (E) angle. The Deming-regression line with slope and standard deviation of the slope (crosses) are shown.

of 380 ± 61 mm^2. However, the change in contact area was not significant ($P = 0.31$). Similar behaviors between the RPM and the SPM in terms of kinematics of the femorotibial joint were depicted. Equivalent results of the patellar tilt of 4.95° ± 1.93° with RPM and 4.87° ± 1.86° with SPM as well as the patellar rotation of 5.29° ± 3.72° with RPM and 5.13° ± 3.47° with SPM could be obtained. The measurement of the lateral shift of the patella provided an average value of 4.87 mm (SPM ±2.0 mm; RPM ±2.2 mm) for both materials.

4. Discussion

Prototype constructions used in cadaver studies provide a useful way to investigate the biomechanical interaction between the patellofemoral and tibiofemoral joints separately after TKA. For research purposes Walker et al. produced several types of polymer prostheses by stereolithography [24]. Any validation of these prototypes and the proof of a similar biomechanical behavior compared to original prosthesis were not included in these studies. However, so far little is known about differences that may occur between standard implant materials and rapid prototype polymers in biomechanical studies at the knee joint. Our study is the first to demonstrate that prostheses made from RPM behave comparably to original prostheses in the knee rig.

Our study goal was to evaluate the usability of polymer rapid prototypes compared to the standard cobalt-chromium alloy prostheses for patellofemoral joint research.

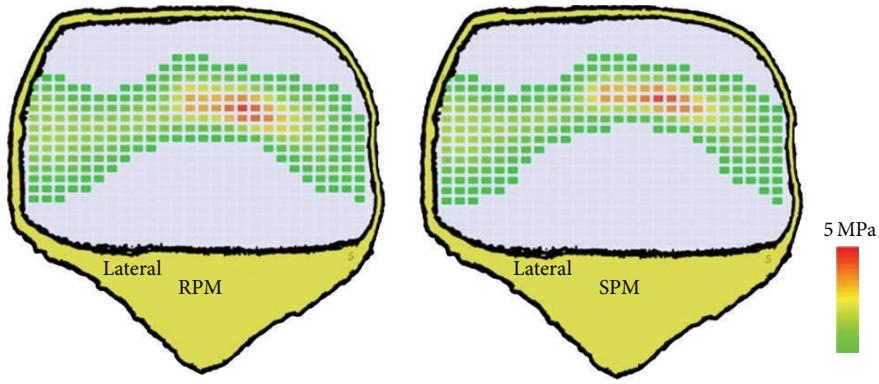

Figure 6: Retropatellar pressure distribution of both prosthesis materials (left: rapid prototype material; right: standard prosthesis material) at a flexion angle of 120° in one representative specimen.

Table 3: Descriptive statistics of the friction coefficients with standard deviation of the tested material combinations at different axial loads (axial pressure).

Axial load (pressure)	SPM versus UHMWPE	RPM versus UHMWPE	SPM versus PTFE	RPM versus PTFE
500 N (3.1 MPa)	0.099 ± 0.015	0.130 ± 0.035	0.063 ± 0.005	0.059 ± 0.011
750 N (4.7 MPa)	0.093 ± 0.025	0.111 ± 0.034	0.053 ± 0.005	0.044 ± 0.011
1000 N (6.2 MPa)	0.080 ± 0.018	0.091 ± 0.029	0.043 ± 0.004	0.036 ± 0.010
1250 N (7.8 MPa)	0.073 ± 0.020	0.078 ± 0.025	0.038 ± 0.004	0.030 ± 0.008
1500 N (9.4 MPa)	0.065 ± 0.017	0.065 ± 0.021	0.032 ± 0.003	0.026 ± 0.005

Table 4: Calculated slope by Deming-regression for the tests with SPM and RPM in the knee rig. Additionally the results of the *t*-test against the slope of 1, which represents an identical behavior between both materials.

Parameter	Slope with standard deviation	*P* value
Quadriceps force	1.014 ± 0.086	0.69
Retropatellar peak pressure	0.977 ± 0.091	0.53
Contact area	1.051 ± 0.012	0.30
ap-translation	1.086 ± 0.207	0.31
Femorotibial rotation	0.956 ± 0.138	0.43
Shift of the patella	1.081 ± 0.169	0.25
Tilt of the patella	0.960 ± 0.176	0.57
Rotation of the patella	1.057 ± 0.243	0.57

We expected first that the friction coefficients of both standard prosthesis material and rapid prototype material in different combinations of counterface material coupling were not different. Second, we expected that, for the weight-bearing loads typically involved in *in vitro* kinematic testing of the knee, the rapid prototyped materials may provide result of motion patterns and patella-contact forces, which are not significantly different from the standard clinical materials.

Our study results do not validate our first hypothesis. Whereas significant differences of the friction coefficient of the patellofemoral material combinations (PTFE) were not found, there were significant differences of SPM and RPM combinations with UHMWPE as counterface at a low axial load of 500 N ($P = 0.031$). With increased axial pressure, however, the friction coefficient of both materials against UHMWPE converged until no difference was measurable at 1500 N ($P = 1$). This difference might be a result of the higher surface roughness of the surrogates compared to original one.

Our second hypothesis was validated by tests in the knee rig. Indeed, comparable behaviors of SPM and RPM for the analyzed parameters were observed. Based on this, we believe that the tested RPM may be suitable for the *in vitro* testing of prostheses and the kinematical analyses in the knee rig, despite friction differences with standard prosthesis materials at low loads, when used in combination with UHMWPE.

A few limitations must be accounted in analyzing our results which may affect the validity of our conclusions to other study contexts. First, the measured coefficient of friction of material combinations depends on an amount of parameters: surface roughness, the used lubrication, the velocity, and the used axial load [25–29]. Small differences can also be obtained with the use of different friction rigs. In this study a rebuilt ring-on-disc simulator according to ISO 6474 was used, which simulated a radial sliding of a ring on a disc. On the other hand, studies such as the ones from Saikko were based on a pin-on-disc-test rig, while Wang et al. used a rig where the coefficient of friction was measured in a total hip prosthesis.

For each material combination a consistent reduction of the coefficient of friction was documented while increasing axial load. This obtained behavior was supported by Saikko and Wang et al. [30, 31]. Both of them determined an exponential decrease of the sliding friction coefficient of UHMWPE compared to cobalt-chrome alloy by increasing loads (Table 5).

Table 5: Load-dependent friction coefficient of UHMWPE against CoCr-alloy compared to references; the coefficients of friction were calculated from the determined exponential formulas of publications.

Pressure	Present study	Saikko [30]	Wang et al. [31]
3.1 MPa	0.099	0.158	0.083
4.7 MPa	0.093	0.119	0.063
6.2 MPa	0.080	0.099	0.052
7.8 MPa	0.073	0.084	0.044
9.4 MPa	0.065	0.074	0.039

To avoid shear forces in the sensitive pressure film, many workgroups covered the film with PTFE-tape [3, 11, 21]. Therefore the cartilage of the patella was replaced by a PTFE foil which has a friction coefficient ranging between 0.03 and 0.06 against SPM. Friction measurements on hip hemiprostheses showed similar friction coefficients between 0.02 and 0.11 for cartilage against surgical steel [32] and 0.02 up to 0.2 and 0.02 to 0.38 compared to cobalt-chrome alloy [33, 34]. However, such differences may not affect our conclusions in the current study design, as both prosthesis materials were subjected to similar testing conditions.

A second limitation comes from testing conditions in the knee rig. A small ground load was used in the knee rig, which may be a limitation for extrapolating our results to studies where higher loads would be simulated. However, Müller et al. and Victor et al. showed that reduced loads resulted in an amplitude change but do not alter the progression of the measured data [35, 36]. The simplified testing conditions and lower loading magnitudes therefore reduce the material requirements needed for the *in vitro* testing of knee prostheses. Biomechanical aspects such as wear, mechanical, and fatigue resistance as well as biocompatibility are minorly relevant for kinematic tests with human cadaver knees. However, differences in friction behavior can alter kinematics and contact behavior in the specimen. Therefore it is important that the results of the knee rig study affirm both, the same intra-articular pressure and knee kinematics by the use of rapid prototyped and standard prostheses material.

A third limitation is that both RPM and SPM materials were compared in only seven knee specimens. From statistical point of view, the number of specimens tested might not fully exclude a type II error. Thereby, the number of specimens is comparable to other studies [11, 14, 36–39].

The usage of a single knee prosthesis design with a rather flat-shaped trochlea can also be a forth limitation in our study. Therefore the generalized transfer of these results to other knee replacement systems is not possible. Moreover only the typical material of the described 3D-printer could be analyzed, so the transferability to other printable materials and surface roughness is restricted. Despite these limitations, we believe that our pilot study successfully demonstrated the validity of using rapid prototype implants made of polymers as surrogates in kinematic testing of the knee. There are many benefits to using prototyped knee prosthesis for *in vitro* studies. Firstly, a separately biomechanical examination of the femorotibial and patellofemoral joint is possible. Secondly, different prostheses can be implanted on the same bone cuts, which enable quick and accurate change of the component without additional bone resections. Thirdly, different prosthesis alignments are feasible with the use of the same bone cuts, by modification of the articulating surface geometry only. Fourthly, a test of different prototypes in the same specimen is possible without reoperation and therefore, due to the paired observations, fewer specimens may be necessary to reach the same statistical outcome.

5. Conclusion

This pilot study showed that knee prostheses produced from rapid prototype polymer can produce knee kinematics and retropatellar pressure distributions comparable to those obtained with original knee prostheses in the knee rig. Therefore it is possible to use this technique to get more comprehension of TKA biomechanics. Furthermore, consecutive biomechanical analyses of various knee prostheses designs could be analyzed in the same knee without any reoperation of the joint *in vitro*. Future studies will focus on modifying implant orientations for better understanding of the effects of malignment on patellofemoral joint mechanics and the relation to pain experienced by patients.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Research Article

Patients with Intolerance Reactions to Total Knee Replacement: Combined Assessment of Allergy Diagnostics, Periprosthetic Histology, and Peri-implant Cytokine Expression Pattern

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We performed a combined approach to identify suspected allergy to knee arthroplasty (TKR): patch test (PT), lymphocyte transformation test (LTT), histopathology (overall grading; T- and B-lymphocytes, macrophages, and neutrophils), and semiquantitative Real-time-PCR-based periprosthetic inflammatory mediator analysis (IFNγ, TNFα, IL1-β, IL-2, IL-6, IL-8, IL-10, IL17, and TGFβ). We analyzed 25 TKR patients with yet unexplained complications like pain, effusion, and reduced range of motion. They consisted of 20 patients with proven metal sensitization (11 with PT reactions; 9 with only LTT reactivity). Control specimens were from 5 complicated TKR patients without metal sensitization, 12 OA patients before arthroplasty, and 8 PT patients without arthroplasty. Lymphocytic infiltrates were seen and fibrotic (Type IV membrane) tissue response was most frequent in the metal sensitive patients, for example, in 81% of the PT positive patients. The latter also had marked periprosthetic IFNγ expression. 8/9 patients with revision surgery using Ti-coated/oxinium based implants reported symptom relief. Our findings demonstrate that combining allergy diagnostics with histopathology and periprosthetic cytokine assessment could allow us to design better diagnostic strategies.

1. Introduction

Hip and knee replacement are very successful surgical procedures to restore quality of life in osteoarthritis patients [1] and correspondingly implantation rates are steadily increasing [2]. However, in a substantial part of such patients implant failure leads to implant revision. A recent review lists a total knee replacement (TKR) revision rate of 9.5% in Germany and of 8.4% in the USA for the year 2011 [2]. Within the spectrum of conditions leading to TKR failure [3] adverse reactions may be found, but the role of allergy is still a controversial issue. Cutaneous metal allergy is frequent in the general population, for example, approximately 13% to nickel (Ni), 2% to cobalt (Co), and 1% to chromium (Cr) [4]. Either wear or corrosion leads to peri-implant and systemic metal (particularly Ni, Cr, or Co) exposure of arthroplasty patients [5], and correspondingly, prevalence of metal sensitivity in patients with failed implant is reported to be increased [6–8].

With regard to total hip replacement, aseptic loosening was mostly attributed to wear associated macrophage dominated foreign body response as underlying mechanism [9, 10]. Over the last decade, attention has turned to the role of hypersensitivity in peri-implant inflammation. In particular in metal-on-metal arthroplasty a subgroup of patients was described showing rather peri-implant lymphocytic inflammation as potential elicitor of implant failure [11–13]. Described histologic changes include diffuse, perivascular or lymph-follicle (lymphoid) like infiltration of lymphocytes and few macrophages, high endothelial venules, and in part tissue necrosis [13–15]. Metal allergy as a contributing factor was suggested by the observed linkage between peri-implant lymphocytic inflammation, patch test reactivity to metals, and enhanced lymphocyte transformation test (LTT) response to metals in a series of such patients [16]. There is however still controversial discussion, as to which extent metal allergy contributes to the "umbrella term" adverse reactions in hip arthroplasty [17, 18]. In fact, metal allergic patients may well tolerate the respective metals containing implant [8, 19]. With regard to TKR there also exist reports on cutaneous metal allergy found in association with complications [20, 21], but it is not yet further investigated whether such metal allergy is responsible for the biological reaction. As we are seeing patients with suspected implant intolerance reactions in a special outpatient ambulatory, we wondered whether in a series of patients with complicated TKR a potential metal sensitivity could be linked to a particular peri-implant histological picture and cytokine expression pattern. To address potential clinical relevance of the findings we further contacted the patients to see if they have had some benefit from revision surgery with particular attention to the potential use of "hypoallergenic" materials upon revision surgery.

Thus, the aim of the investigation was to better prove allergic etiology in complicated TKR by combining different diagnostic steps and by assessing the clinical relevance of the findings in a followup.

2. Materials and Methods

2.1. Patients and Controls. A total of *45 patients* took part in the study. The study was approved by the ethics committee. The following patient groups were analyzed.

25 knee arthroplasty patients (16 m, 9 f, 37–75 years) with CoCrMo based TKR and complications like loosening, recurrent effusions, and pain were presented by their treating orthopaedic surgeons to our ambulatory for allergy diagnostics, since preceding diagnostics gave no indication of problem elicitors like malpositioning/malalignment, fracture, or infection. According to the allergy diagnostics results, these patients were further assigned to three groups. *Group I*: 11 patients (patch test positive and LTT positive), *Group II*: 9 patients (patch test negative and LTT positive), and Group III: 5 patients (patch test negative and LTT negative).

The study included *12 patients* (1 m, 52–89 years; "*OA-control group*") without implant, but degenerative joint disease/osteoarthritis (OA) prior to knee arthroplasty.

The study included *8 patients* (2 m, 53–75 years; "*PT-control group*") without implant, but having undergone patch test (PT) for suspected allergic skin diseases. 6/8 had Ni-PT reactivity, 2/8 had no Ni-PT reactivity.

In the 25 TKR patients, potential metal sensitivity was assessed by PT and LTT; furthermore, periprosthetic tissue samples were obtained for histology, molecular analysis, and microbiology. In addition a WOMAC score was obtained at the ambulatory visit to have feedback on the patients' perception of daily life activity and of pain. In the 12 OA patients ("*OA-control group*"), at primary TKR tissue samples were obtained for histology, molecular analysis, and microbiology. In the 8 "PT-*control group*" patients, biopsies were obtained from the 6 Ni-PT reactive and the 2 Ni-non reactive PT areas for histology and molecular analysis. The characteristics of the 45 patients are summarized in Table 1.

2.2. Patch Test (PT). In the 25 TKR patients an European standard series of 30 contact allergens including a Co, a Cr, and a Ni preparation (Hermal, Reinbek, Germany) supplemented by a metal allergen series (Brial Allergen GmbH, Greven, Germany) as well as a bone cement component series in case of cemented arthroplasty was tested on the patients' back. Test preparations were applied in Finn chambers for 2 days and reactions were evaluated on the day of removal and at 3 days after application. In the patients with bone cement series testing, an additional reading was performed after 1 week. Grading of the skin reactions was as recommended by the German Contact Dermatitis Research Group.

2.3. Lymphocyte Transformation Test (LTT). Peripheral blood mononuclear cells (PBMC) were obtained from the heparinized blood of the TKR patients by density centrifugation on Ficoll-Hypaque (Phadia, Freiburg, Germany). Cells (1×10^6/mL) were cultured in RPMI1640 medium (Biochrom, Berlin, Germany) supplemented by autologous serum, glutamine, antibiotic-antimycotic-solution, and nonessential amino acids. All cultures were performed in quadruplicate in 96-well plates (Nunc, Roskilde, Denmark). Stimuli were the pan T-cell mitogen phytohemagglutinin (PHA) 2.4 μg/mL, tetanus toxoid (TT) 5 μg/mL, $NiSO_4$, $CrCl_3$, and $CoCl_2$ (7 concentrations each from 1×10^{-4} M to 1×10^{-6} M) and culture medium alone as control. After 5 days, cells were pulsed with ^{3}H thymidine overnight and proliferation was assessed by incorporated radioactivity. The stimulation index (SI) was calculated by the ratio of mean counts per minute (cpm) of stimulated to unstimulated cultures. SI > 3 was considered as positive.

2.4. Analysis of Peri-Implant Tissue. In the 25 TKR patients, tissue specimens were obtained from the newly formed articular capsule at the time of revision. At least 2 probes were sent for microbiological evaluation to the Endoklinik Hamburg. The other two probes were processed for histology and one probe for molecular analysis. In the 12 OA-patients tissue specimens were obtained at the moment of primary arthroplasty implantation for histology and molecular analysis as above. The 8 "*PT-control group*" patients underwent

Table 1: Patients characteristics.

	Sex		Age (years)	Tissue from	Implant survival (month)
Group I (revision surgery, patch test+, LTT+)	7 m	4 f	ø59.0 (37–75)	Knee	ø25.7 (6–30)
Group II (revision surgery, patch test−, LTT+)	7 m	2 f	ø64.2 (53–71)	Knee	ø28.0 (12–60)
Group III (revision surgery, patch test−, LTT−)	2 m	3 f	Ø69.8 (59–75	Knee	Ø23.4 (7–42)
OA-control Group (gonarthrosis before arthroplasty)	1 m	11 f	69.2 (52–89)	Knee	—
PT-control Group					
(patch test+ biopsies)	1 m	5 f	64.25	Back	—
(patch test− biopsies)	1 m	1 w	(53–75)	Back	—

punch biopsy of their Ni-PT areas on the back after test reading on D3. One probe each was obtained for histology and molecular analysis.

2.5. Histological Examination. The formalin-fixed tissues were processed and stained with haematoxylin-eosin. Immunohistology was performed with antibodies to T-cell (αCD3), B-cell (αCD20), macrophage (αCD68 resp KP1), and neutrophil (αCD15) antigens. The sections were microscopically examined and the proportionate distribution of the tissue components including macrophages, diffuse or perivascular accumulation of T- or B-lymphocytes, and plasma cells as well as the overall reaction pattern of the tissue specimen were semiquantitatively assessed. The grading score was according to Krenn et al. [24] and in the case of the TKR-patient derived samples the consensus classification [24] was used. This consensus classification does subdivide the peri-implant tissue reaction patterns into a particle dominated foreign body like response (Type I), a granulocyte dominated infectious type (Type II), the mixture of Types I and II (combined Type, Type III), and a paucicellular and rather fibrotic reaction (Type IV, indifferent type).

2.6. Molecular Analysis. The following probes were obtained in RNA-conserving liquid for subsequent analysis: from each of the 25 TKR patients and 12 OA-control patients peri-implant and subcutaneous tissue (reference) probe; from the patch test control group 6 Ni-PT-positive probes and 2 probes from Ni-non-reactive test site (reference).

Total RNA was isolated from the tissue specimen by phenol/chloroform extraction and reverse transcribed into cDNA by the use of AMV reverse transcriptase. The expression of the following cytokines was analysed by semiquantitative RT-PCR in the LightCycler: IFNγ, TNFα, IL1-β, IL-2, IL-6, IL-8, IL-10, IL17, and TGFβ. The expression value was determined in comparison to the house-keeping gene EF1-α [25] by the $\Delta\Delta$Ct-method by Schmittgen and Livak [22].

2.7. Comparison of Pre- and Postoperative WOMAC Score. A modified score system has been used in accordance with the publication of Roos et al. [23]. As from the Groups I and II patients preoperative WOMAC knee score was available, we further contacted patients after revision surgery to also get (at not less than 6 months after surgery) their postoperative WOMAC score information. Particular focus was put on patients with revision by use of "hypoallergenic" material.

3. Results and Discussion

Metal implant allergy still remains a diagnosis of exclusion, with a delay in diagnosis due to missing disease specific criteria and need of combining different diagnostic steps. Thus various complication elicitors are questioned first in TKR failure and metal implant allergy is diagnosed by a combination of PT, LTT, and histopathology [26, 27]. The study presented here aims to support improvement of diagnostic tools.

3.1. Allergy Diagnostics. Within the 20 patients with metal sensitivity, 11 (Group I) showed PT reactions to metals (in part multiple reactions): 10 to Ni, 6 to Co, 2 to Cr, and one of these 11 patients also showed PT reactions to bone cement components (to gentamicin and benzoyl peroxide). In 6/11 additional LTT data were available and showed 5x Ni reactivity and 1 nonreactive LTT. In the remaining 9 patients (Group II) with negative PT to implant components but positive LTT we found 9x LTT reactivity to Ni, 1x to Co. These data are summarized in Tables 2–4. In several studies increased metal sensitivity has been found in patients with arthroplasty [6, 7]. At a larger scale, when comparing 100 symptom-free to 200 complicated arthroplasty patients, such increased incidence of metal allergy—in particular to Ni—could be reproduced [21]. Most data on in vivo metal release conditions are derived from hip arthroplasty patients. However local Co and Cr release is seen also in TKR and respective systemic exposure of the patients is reported [28].

Table 2: Patch test/LTT results and histology grading, group I.

Patient number	Age, sex	Patch test reaction	LTT-reaction	CD3-infiltrate		KP1	CD20	CD15	Rating (Type I–IV according to [24])
				Qualitative	Quantitative				
10	37, m	Ni, Co, Cr	n.d.	Micronodal perivascular	+	++	−	−	Type 4
8	51, f	Ni,	Ni,	Micronodal perivascular	++	+	−	−	Type 4
15	59, f	Ni	n.d.	Micronodal perivascular	++	++	+	−	Type 4
9	74, m	Ni, Co	n.d.	Micronodal perivascular	+++	++	−	−	Type 4
3	51, m	Co	n.d.	Diffuse	−	+	−	−	Type 4
18	58, f	Ni,	Ni	Diffuse	−	−	−	−	Type 1 (Necrosis)
7	75, m	Ni	Ni	Diffuse	+	++	−	−	Type 4
1	63, m	Ni, Co, Ge, Be	Ni	Diffuse	+	++	+	+	Type 4
16	57, m	Ni, Co	Ni	Diffuse	+	+	−	−	Type 4
17	68, m	Ni, Co, Cr,	n.d.	Diffuse	+	+	−	−	Type 4
19	56, f	Ni,	neg	Diffuse	+	++	−	−	Type 1

Findings in 11 patients with CoCrMo based knee arthroplasty with complications and positive patch test reaction. Ni = nickel, Co = cobalt, Cr = chromium, Ge = gentamicin, B = benzoyl peroxide; n.d. = not done; LTT = lymphocyte transformation test.

Table 3: Patch test/LTT results and histology grading, Group II.

Patient number	Age, sex	Patch test reaction	LTT-reaction	CD3-infiltrate		KP1	CD20	CD15	Rating (Type I–IV according to [24])
				Qualitative	Quantitative				
11	61, m	neg	Ni	Diffuse	−	+	−	−	Type 4
12	65, f	neg	Ni	Diffuse	−	++	−	−	Type 1
14	66, m	neg	Ni, Co	Diffuse	−	++	−	−	Type 4
2	71, m	neg	Ni	Diffuse	+	++	+	−	Type 1
4	66, m	neg	Ni	Diffuse	+	+	−	−	Type 4
5	64, m	neg	Ni	Diffuse	+	+	−	−	Type 4
6	53 m	neg	Ni	Diffuse	+	++	−	−	Type 4
13	69, m	neg	Ni	Diffuse	+	−	−	−	Type 4
20	63, f	neg	Ni	Diffuse	+	++	−	+	Type 1

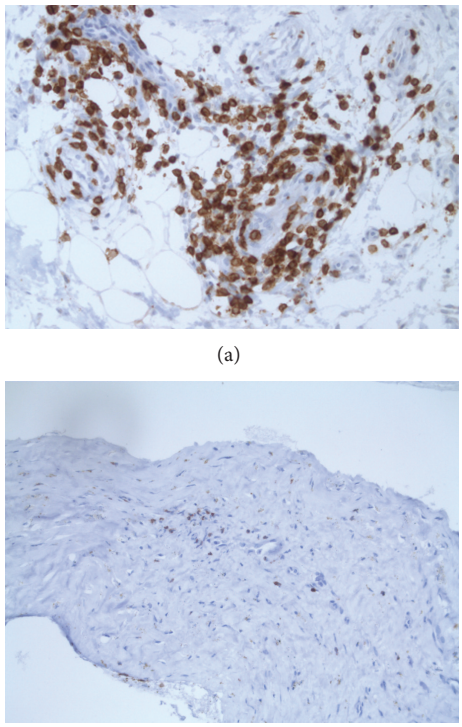
Findings in 9 patients with CoCrMo based knee arthroplasty with complications, negative patch test but positive lymphocyte transformation test (LTT); abbreviations see Table 2.

Table 4: Patch test/LTT results and histology grading, group III.

Patient number	Age, sex	Patch test reaction	LTT-reaction	CD3-infiltrate		KP1	CD20	CD15	Rating (Type I–IV according to [24])
				Qualitative	Quantitative				
IAR 6	59, f	neg	Neg	−	−	−	−	−	n.a.*
IAR 18	73, f	neg	Neg	−	−	−	−	−	Type 4
IAR 23	74, f	neg	Neg	−	−	−	−	−	Type 4
IAR 26	68, m	neg	Neg	−	−	−	−	+	Type 2
IAR 5	75, m	neg	Neg	Focal	+++	+++	+++	+++	Type 2

* n.a.: not applicable because of fibrinoid necrosis.
Findings in 5 patients with CoCrMo based knee arthroplasty with complications, negative patch test, and negative LTT; for abbreviations see Table 2.

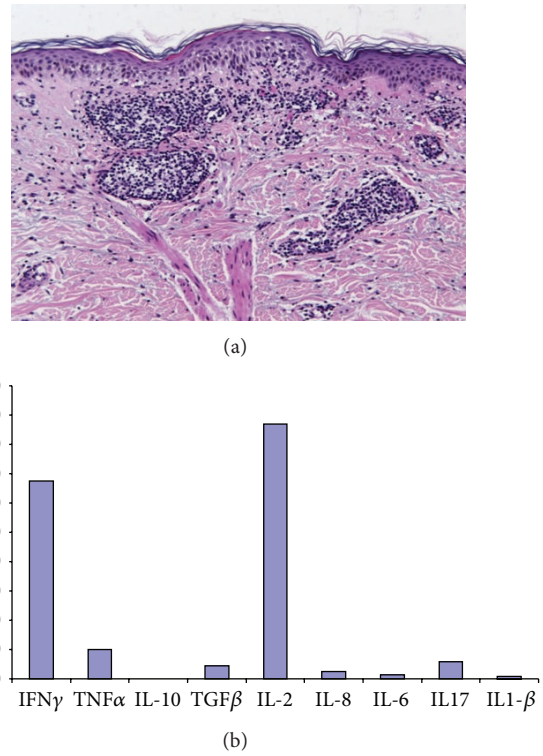
Furthermore, also substantial Ni release might be observed in CoCrMo-arthroplasty patients [29]. The predominance of Ni allergy in our patient groups might thus not only reflect relative predominance of Ni allergy in the general population. On the other hand, even symptom-free patients with well performing knee arthroplasty may have cutaneous metal allergy to implant alloy metals [8, 19]. Thus, as Granchi et al. stated in 2012 [30] that presence of metal sensitivity may not mean implant failure mechanism at the single patient level.



(a)

(b)

Figure 1: (a) Example of perivascular lymphocytic infiltrate; αCD3 stain. (b) Example of scattered periprosthetic lymphocytes; αCD3 stain.



(a)

(b)

Figure 2: (a) Histology of patch test (PT) reaction to Ni showing perivascular T-lymphocytic infiltrates, scattered eosinophils, and epidermal "spongiotic" changes. (b) Relative inflammatory mediator expression in biopsy of positive PT reaction to Ni. Analysis based on semiquantitative real-time RT-PCR.

3.2. Histological Examination. We next wondered if the periprosthetic tissue analysis would help to discriminate hyperergic tissue response. For this purpose, four conditions were chosen for comparative analysis of tissue specimen. For example, periprosthetic tissue samples were obtained from (1) the 20 TKR patients with complications and metal sensitivity (Groups I and II); (2) the 5 TKR patients with complications but no metal sensitivity (Group III); (3) 12 patients with degenerative knee joint disease/osteoarthritis (OA-control group) at primary arthroplasty; and (4) the cutaneous biopsies that were performed at PT sites in 8 PT patients (PT-control group) of whom 6 had positive, eczematous PT reaction to Ni and 2 had no PT reaction to Ni. The rating of periprosthetic/(neo) capsule tissue response was done according to the standardized consensus classification initially published by Morawietz et al. in 2006 [31] and revised by Krenn et al. [24]. In addition focus was put on the presence of T-lymphocytes, B-lymphocytes, neutrophils, and macrophages—and furthermore probes of Groups I, II, and III patients were also sent to microbiology evaluation. Several unexpected findings were made: 9/11 patients in Group I and 6/9 patients in Group II had a collagen fibre rich, connective tissue resembling periprosthetic tissue reaction (Type IV/indeterminate type). And only 5 of the 20 metal sensitive patients had the overall picture of the "wear particle induced type" with macrophage dominated response. This is in contrast to the general observation of mostly wear particle/foreign body response like tissue pattern in failed arthroplasty and to the only 15% Type IV (fibrotic) response reactivity in the 370 samples analysed by Morawietz et al. [31]. There were no signs of infections in these 20 samples of our Groups I and II patients. Despite being a predominant "arthrofibrosis"-like, paucicellular reactivity, presence of lymphocytes was noted in perivascular or scattered distribution (Figures 1(a) and 1(b)). In contrast, out of the 5 patients without metal sensitivity two showed infection and lymphocytic inflammation was only seen in one of these patients. In OA-patients, again, lymphohistiocytic infiltrates were noted together with absence of neutrophils. These findings are summarized in Tables 2, 3, and 4. Figures 1(a) and 1(b) are representative histology findings of patients in Groups I and II. Biopsies from Ni-induced allergic patch test reactions were characterized by perivascular and sometimes diffuse lymphohistiocytic infiltrates together with contact allergy-typical epidermal changes as shown in a representative sample (Figure 2(a)). Witzleb et al. speculated that perivascular or diffuse presence of (T-)lymphocytes in periprosthetic tissue could be interpreted as hyperergic response [15]. However, von Domarus and coworkers [32] described T lymphocyte infiltration as a common finding in tissue samples of retrieved aseptically loosened metal-on-polyethylene arthroplasties. Thus, they conclude that neither necrobiosis nor infiltration of T-lymphocytes should be considered to be specific for metal hypersensitivity reaction.

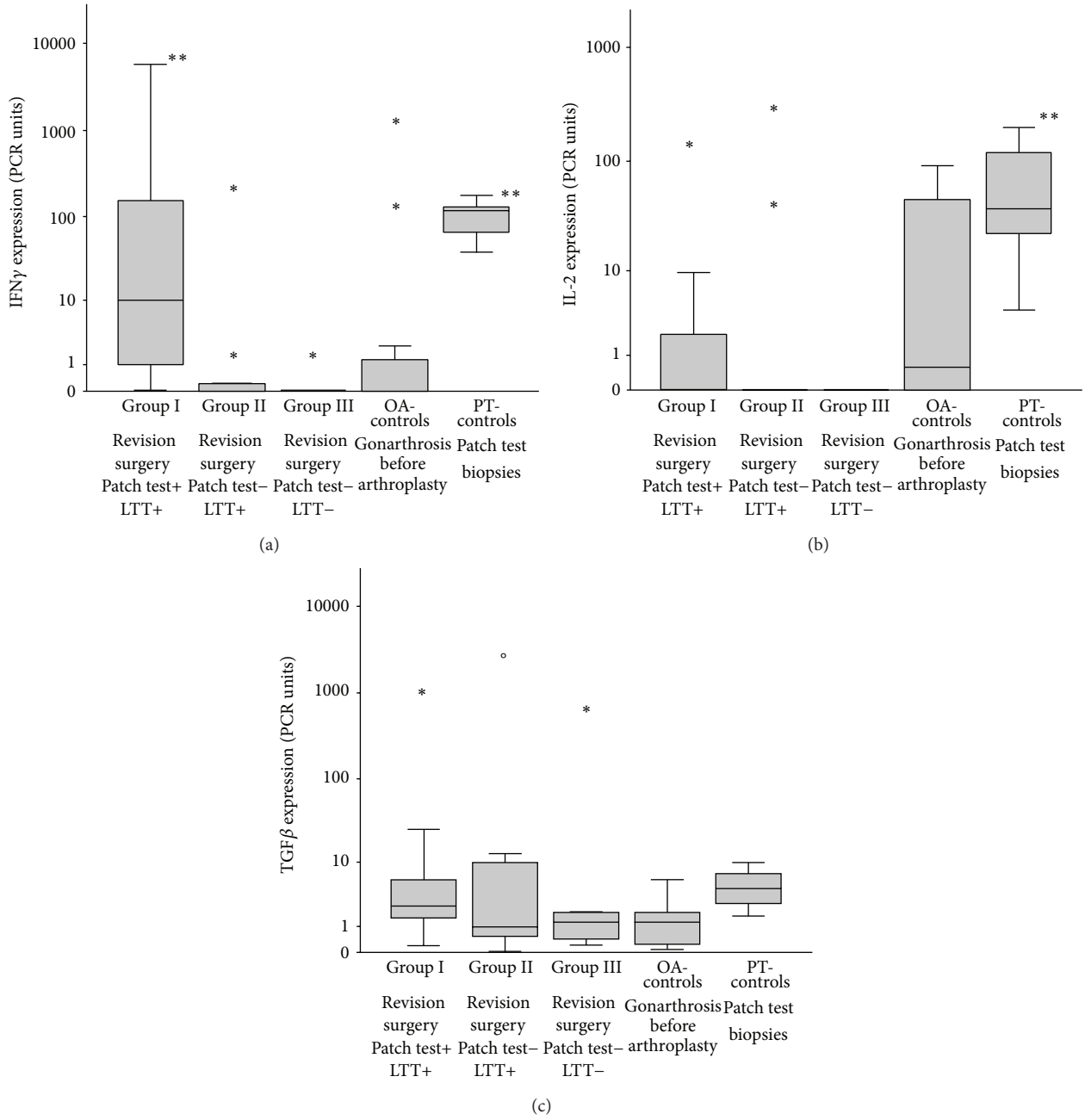


Figure 3: (a) Cytokine expression of IFNγ in the tissues of the 5 different patient groups; cytokine expression was analysed in comparison to the house-keeping gene EF-1α and to the patients control tissue by the $\Delta\Delta$Ct-method [22]; $^{**} = P < 0.005$ (Wilcoxon-Mann-Whitney-test done by SPSS statistical software). (b) Cytokine expression of IL-2 in the tissues of the 5 different patient groups; cytokine expression was analysed in comparison to the house-keeping gene EF-1α and to the patients control tissue by the $\Delta\Delta$Ct-method [22]; $^{**} = P < 0.005$ (Wilcoxon-Mann-Whitney-test done by SPSS statistical software). (c) Cytokine expression of TGFβ in the tissues of the 5 different patient groups; cytokine expression was analysed in comparison to the house-keeping gene EF-1α and to the patients control tissue by the $\Delta\Delta$Ct-method [22] (Wilcoxon-Mann-Whitney-test done by SPSS statistical software).

3.3. Cytokine Expression Profile. In view of the partly inconclusive publications [27, 32–34] we next wondered whether assessment of inflammatory mediator expression could improve characterization of the tissue response pattern. In Figure 2(b) the cytokine RNA expression pattern of an acute ongoing specific cutaneous delayed type hypersensitivity reaction to Ni is shown. Major findings are the marked upregulation of IFNγ as typical marker of the Th1-response stimulating the cellular immune response and of IL-2 indicating T-cell activation and proliferation [35]. When assessing the groups of metal TKR patients with/without metal sensitivity and OA-control group, such upregulation of IFNγ was also particularly visible in Group I patients, for example, TKR with complications and patch test reactivity

to metals. Out of the other mediators assessed, in the TKR patients IL-2 expression was more prominent in Group I and in OA-patient Group - and TGF-ß expression slightly more in Groups I and II. This is the case also for IL-6 (in Groups I and II) and one patient in Group II (patient with periprosthetic infection). These other mediators are not shown as there was only some individual increase of TNFα in OA-patients but no major difference between the different groups. Increased TH1 lineage commitment is reflected by increased IFNγ expression. Here we found marked IFNγ upregulation not only typically in the Ni-induced PT reactions, but in particular also in the Group I TKR patients, suggesting its role in periprosthetic disease progression. Interestingly, Jämsen and coworkers recently reported that they found scattered CD3+ T cells in the interface tissue of aseptically loosened hip arthroplasty with predominant macrophage related wear particle response. However, neither by quantitative PCR nor by immunohistochemistry they could show significant TH1 (namely, IFNγ) or TH2 (IL-4) mediator expression [36]. Since apart from IL-6 [37] in particular TGF-ß might play a central role in the onset and persistence of periprosthetic, articular fibrosis [38], we here analysed its respective expression in the different tissue samples. We observed an increase of TGF-ß expression in the metal sensitive TKR patients with however interindividual variations. Figures 3(a)–3(c) summarize these findings.

3.4. Comparison of Pre- and Postoperative WOMAC Score. 19 of the 20 TKR patients responded to our request and completed a postoperative WOMAC scoring. 9 patients reported that at revision a "hypoallergenic" TKR had been implanted (8x Ti-based surface coating, 1x oxinium based implant). 8/9 patients did profit from this approach, as shown in Figure 4. So far there are only case reports or small patient series regarding the potential benefit from the use of "hypoallergenic" TKR [39, 40]. These results however stress the need of follow-up studies at a larger scale.

There are however limitations in the study: the facts that periprosthetic tissue samples may reflect only the actual stage of a dynamic process and that OA patients may not be as well a "control" as interface tissue probes from patients with well-functioning implants and the limited sample number in this investigations. Thus further studies are needed to validate the multimodular diagnostic approach in metal implant allergy.

4. Conclusions

This study demonstrates for the first time the potential of utilizing combined analytic steps to provide an approach to develop diagnostic characteristics of metal implant allergy. Allergy diagnostics (PT and LTT) and periprosthetic histology point to immunological response to implant alloy metals and the pattern of inflammatory mediator expression adds to functional differentiation.

Unexpected findings were the predominant "fibrotic" type IV interface response in the metal sensitized TKR patients and the marked IFNγ expression in the PT-positive TKR patients.

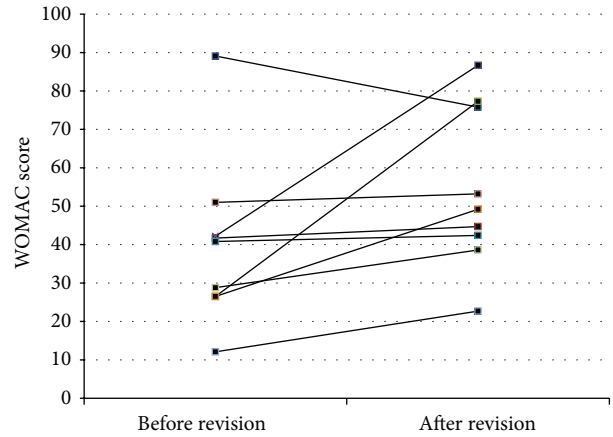


Figure 4: WOMAC score before and after revision surgery in 9 patients who received "hypoallergenic" material (8x titanium, 1x oxinium). The score-system has been used in accordance with the publication of Roos et al. [23].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

PMMA Third-Body Wear after Unicondylar Knee Arthroplasty Decuples the UHMWPE Wear Particle Generation *In Vitro*

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Introduction. Overlooked polymethylmethacrylate after unicondylar knee arthroplasty can be a potential problem, since this might influence the generated wear particle size and morphology. The aim of this study was the analysis of polyethylene wear in a knee wear simulator for changes in size, morphology, and particle number after the addition of third-bodies. *Material and Methods*. Fixed bearing unicondylar knee prostheses (UKA) were tested in a knee simulator for 5.0 million cycles. Following bone particles were added for 1.5 million cycles, followed by 1.5 million cycles with PMMA particles. A particle analysis by scanning electron microscopy of the lubricant after the cycles was performed. Size and morphology of the generated wear were characterized. Further, the number of particles per 1 million cycles was calculated for each group. *Results*. The particles of all groups were similar in size and shape. The number of particles in the PMMA group showed 10-fold higher values than in the bone and control group (PMMA: 10.251×10^{12}; bone: 1.145×10^{12}; control: 1.804×10^{12}). *Conclusion*. The addition of bone or PMMA particles in terms of a third-body wear results in no change of particle size and morphology. PMMA third-bodies generated tenfold elevated particle numbers. This could favor an early aseptic loosening.

1. Introduction

Unicondylar knee arthroplasties (UKA) in the meanwhile show excellent results in the treatment of a medial compartment osteoarthritis, which is certainly due to the sparing of soft tissues that results in better tibiofemoral and patellofemoral kinematics [1] and an increased range of motion compared to total knee arthroplasty (TKA) [2]. While the 10-year-survival rates of UKAs have been shown to be equivalent to those of modern TKA [3], clinical evidence has demonstrated a higher revision rate of UKA compared to TKA [4]. It is commonly accepted that accumulating wear debris after total joint arthroplasty finally leads to an aseptic loosening of the prosthesis, although the exact mechanism of this inflammatory process is not understood in detail yet [5, 6]. But in several studies it could be demonstrated that number, size, and shape of the wear particles influence the extent of the inflammatory biological reaction resulting in periprosthetic osteolysis [7–9]. Submicron particles, especially, increase the biological reaction [8]. It can be assumed that even minor changes in the wear rate have distinctive effects on the amount of accumulating wear particles. This correlation between the gravimetric wear rate of tibial inserts in knee simulator tests and the particle number analysis could be shown in a previous study, as minor changes in the particle size or wear rate showed considerable effects on the particle number [10]. Third-body wear after UKA, especially, might influence the wear generation and the particle morphology and thus lead to an early failure of the prosthesis. Bone and cement fragments (polymethylmethacrylate, PMMA) that occur during the implantation of the prosthesis can easily be missed in the posterior regions of the femorotibial joint gap relating to the minimally invasive approaches [11].

The aim of this study was to analyze the influence of third-bodies (bone- and PMMA-particles) on number, size, and shape of wear debris generated in an UKA joint simulator.

First it was hypothesized that an occurrence of third-body debris can lead to elevated particle numbers. The second hypothesis was that bone as well as PMMA debris alters size and shape of the generated particles.

2. Materials and Methods

The simulator experiments have been described in a previously published study [12]. Sections 2.1–2.3 summarize the simulator tests.

2.1. Prostheses. For this investigation, fixed bearing unicompartmental knee prostheses (Univation-F, Aesculap, Tuttlingen, Germany) were used with a metal on polyethylene articulation.

The intermediate-sized femoral and tibial (F3/T4) components were made from CoCr29Mo6 alloy and the gliding inserts were composed of UHMWPE (GUR 1020, γ-irradiated, 30 ± 2 kGy). The inserts were fixed at the tibial baseplate component by a snap-fit-mechanism. The medial side of the meniscal bearing had a concave shape and the lateral side was planar. Before testing, the bearings were accelerated aged, according to the standard as described in the "ASTM F2003 - 02(2008)" to simulate the oxidation process of UHMWPE in air [14].

2.2. Simulator Specifications. Before wear testing the gliding surfaces were preconditioned in the test solution until no increase of weight was measurable. The test fluid simulated synovial liquid with a protein content of 30 g/L. The applied lubricant was changed every six days (25% (v/v) newborn calf serum (Biochrom, Germany) with 0.1% (m/v) sodium azide solution in sterile water with EDTA (AppliChem, Germany) for pH stability and Amphotericin B (Biochrom, Germany) as a fungicidal). The lubricant was changed every 0.5 million cycles. The specimens were tested on a servohydraulic knee wear simulator (EndoLab, Germany) with four test stations; the test specifications followed the ISO [15].

2.3. Wear Particle Generation. The simulator was stopped at 8.0 million cycles; the overall test period was divided into three parts. The first part was a standard test with 5.0 million cycles as prescribed by the ISO [15]. In the following two periods, the test solution was contaminated with third-body wear debris in a concentration of 5.0 g/L. The particles were produced by a micro-bone-mill (Aesculap GB060R, Tuttlingen, Germany). Between 5.0 and 6.5 million cycles cortical porcine bone particles were added to the test lubricant. From 6.5 to 8.0 million cycles, cement particles with zirconium dioxide as radiolucent (Palacos R, Heraeus Medical, Germany) were mixed within the simulator lubricant. The test phase after adding the different particles was therefore during the steady state phase of the inserts [12]. The morphologic parameters of the debris can be found in Table 1. Mean diameter (MD), equivalent circle diameter (ECD), form factor (FF), aspect ratio (AR), and roundness (R) of the third-body wear debris were recorded [16].

Table 1: Size and shape of third-body particulate debris.

Parameter	Porcine bone particles	PMMA particles
Mean diameter (μm)	671.6 ± 186.4	644.2 ± 262.6
ECD (μm)	519.0 ± 142.9	548.4 ± 237.3
FF	0.41 ± 0.12	0.57 ± 0.12
AR	1.74 ± 0.62	1.74 ± 0.70
Roundness	0.50 ± 0.14	0.42 ± 0.14

2.4. Particle Isolation. Within every 500000 cycles the simulator was stopped; the serum was removed and digested in the following using the "acid digestion" method [17]. The digested lubricant was then centrifuged at 5000 g for 30 minutes to remove the third-body wear debris (the used bone particles consist of milled cortical bone, which has a density of ≈1.5 g/cm^3 [18]; the PMMA particles had a mean density of ≈1.18 g/cm^3; the UHMWPE particles had a density of <0.96 g/cm^3). The specimen was taken out with a pipette (Gilson, Pipetman, made in France, GD29041) three times 1 mL, while the pipette tip was dunked for about 1 cm in the centre of the Falcon tube. 10 mL of each serum sample supernatant was added to 50 mL of hydrochloric acid (37% v/v; Merck, Darmstadt, Germany) and mixed with a magnetic stir bar at 60°C for approximately one hour. Then, 3 mL of this digestion solution was added to 150 mL of methanol (Merck, Darmstadt, Germany) and filtered through a 0.02 μm polycarbonate membrane (Anodisc 47, Whatman plc, Maidstone, Kent, United Kingdom). The filter membrane was then dried for 6 hours and sputter-coated with gold.

2.5. Particle Analysis. The particles recovered on the filter membranes were imaged by scanning electron microscopy (SEM, Zeiss EVO, Carl Zeiss Microscopy GmbH, Jena, Germany). The particles were analyzed at a magnification of 5000–10000 diameters. 20 random, nonoverlapping fields of view were analyzed per sample. Images of each field of view were captured, and the particles were measured using a digital image analysis program [10] (Leica QWin, Image processing and analysis application, Leica Microsystems, Wetzlar, Germany).

The boundary of each particle was defined on the basis of a gray-scale level threshold.

In accordance with the ISO, mean diameter (MD), equivalent circle diameter (ECD), form factor (FF), aspect ratio (AR), and roundness (R) were recorded [16]. According to Sieving et al. [13] the percentage of particles with an AR in the range from 1 to 2.39 and ≥2.4 was calculated. Furthermore, the particle number was calculated using the following formula as reported before ($N_{(p)}$ is absolute particle number; $n_{(p)}$ is examined particles; $G_{(v)}$ is volumetric wear rate; $d_{(m)}$ is equivalent circle diameter) [10]:

$$N_{(p)} = \frac{n_{(p)} \times G_{(v)}}{\sum_{k=1}^{n} \left(\left(\pi \times d_{(m)}^3 \right) / 6 \right)}. \quad (1)$$

The mentioned wear rate was recently found and described by Schroeder et al. in a recently published manuscript [12].

Table 2: Median size and morphology parameters of all analyzed particles.

	Area (μm^2)	Roundness	AR	ECD (μm)	FF	Mean diameter (μm)
Bone particles	0.013* (0.003–8.978)	0.674* (0.084–1.176)	1.337* (1.000–5.931)	0.129* (0.062–3.381)	0.680* (0.067–0.903)	0.144* (0.057–5.383)
PMMA particles	0.011* (0.003–8.401)	0.516* (0.067–1.176)	1.509* (1.000–11.862)	0.118* (0.062–3.271)	0.606* (0.035–0.887)	0.130* (0.057–5.742)
Control	0.012* (0.003–6.690)	0.578* (0.062–1.176)	1.509* (1.000–9.897)	0.124* (0.062–2.919)	0.629* (0.033–0.902)	0.130* (0.057–4.995)

* $P < 0.05$; in brackets: min.–max.

Table 3: Percentage of particles in the distribution described by Sieving et al. [13].

	Aspect ratio	
	1–2.39 (%)	≥2.4 (%)
Bone particles	93.65	6.35
PMMA particles	86.58	13.42
Control	90.16	9.84

The numbers were calculated from the mean volumetric wear rate values.

2.6. Statistical Analysis. Statistical analysis was performed to analyze the significance of variance between the three groups using the Kruskal-Wallis one-way analysis of variance by ranks, as the data showed a nonparametric distribution. The differences were considered significant at P values < 0.05.

3. Results

3.1. Wear Particle Size and Morphology. Overall the particles of all groups showed similar size distributions of polyethylene wear, with a rounded median ECD of 0.13 μm (min: 0.06 μm; max: 3.38 μm) for the bone group, 0.12 μm (min: 0.06 μm; max: 3.27 μm) for the PMMA group, and 0.12 μm (min: 0.06 μm; max: 2.92 μm) for the control group. All differences were statistically significant ($P < 0.05$).

Furthermore, the majority of all analyzed particles were approximately round in shape, smooth, granular, and irregular and had similar AR values (median): 1.34 (min: 1.00; max: 5.93) for the bone particle group, 1.51 (min: 1.00; max: 11.86) for the PMMA particle group, and 1.51 (min: 1.00; max: 9.90) for the control group. All size and shape parameters can be found in Table 2 (statistically significant results, $P < 0.05$). The particle size distribution is demonstrated in Figures 1 and 2 using box plots.

99.77% of the particles in the bone group were <1.0 μm, 99.61% in the PMMA group and 99.71% in the control group were in the submicron size range.

In the bone particle group 6.35%, in the PMMA group 13.42%, and in the control group 9.84% of the particles had an AR ≥ 2.4 (Table 3). Figure 3 shows example SEM images of the wear particles and gives the impression of mainly round and granular particles. Furthermore, a particle size distribution for each size interval is given in Figure 4.

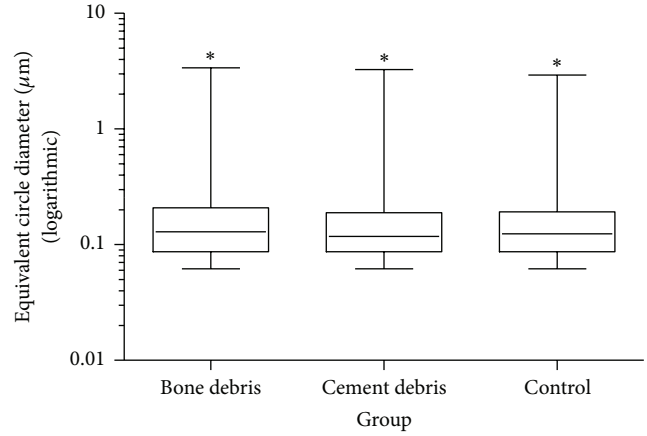

Figure 1: Size distribution measured by the ECD of all groups in a logarithmic box plot. The results of all groups differ significantly (* $P < 0.05$).

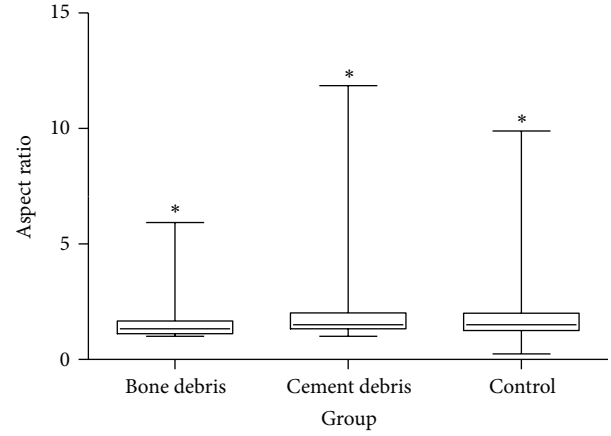

Figure 2: The morphology of the particles given by the aspect ratio. The cement debris group tends towards more fibrillar particles. The results of all groups differ significantly (* $P < 0.05$).

3.2. Number of Particles. We found differing particle numbers for each group. First, a difference between the running in and the steady state phase was found. In the running in phase 5.126×10^{12} particles were calculated per 1 million cycles. In the steady state phase the particle number decreased to $1.804 \times 10\ 10^{12}$. Interestingly, the addition of bone particles

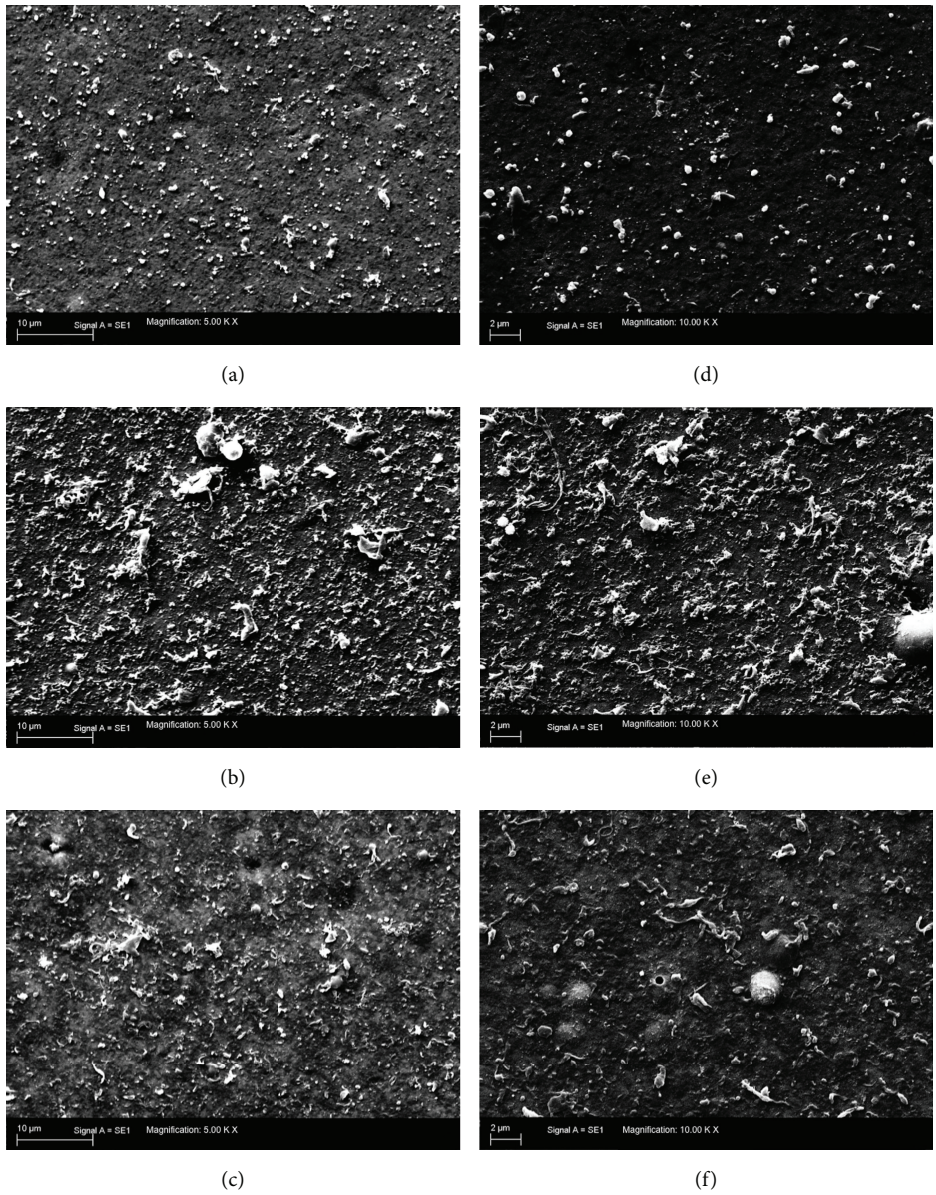

Figure 3: SEM sample images of all tested groups. (a) and (d) show the debris of the bone debris group; (b) and (e) demonstrate the enormous number of particles in the cement group; (c) and (f) serve as examples for the control group. (a), (b) and (c) are 5000x magnified; (d), (e) and (f) are 10000x magnified.

did not lead to an increase of the particle number (1.146×10^{12}), whereas the added PMMA particles in the PMMA particle group decupled the polyethylene wear particle number (10.252×10^{12}; Figure 5). The huge number of accumulating particles can already be suggested in Figures 3(b) and 3(e).

4. Discussion

This study demonstrated that free cement debris can significantly increase the generation of wear particles in unicondylar arthroplasty. The first hypothesis could only partly be accepted, as only the addition of PMMA third-body wear debris lead to higher particle numbers, whereas cortical bone particles did not affect the particle generation. The second hypothesis had to be rejected; the particle morphology was not altered by third-body wear debris clearly, although statistical tests showed highly significant differences.

Clinical evidence as well as retrieval studies had disclosed the issue concerning third-bodies after UKA [11, 19]. Schroeder et al. had proven in a simulator-based study that the wear rate is definitely influenced by cement third-body wear debris [12]. But so far, there are no studies known by the authors concerning the influence of third-body wear in UKA on the generated particle morphology and number. It is basically known that particle size, morphology, and number affect the biologic response resulting in an osteolysis that finally leads to an aseptic loosening and consequently to

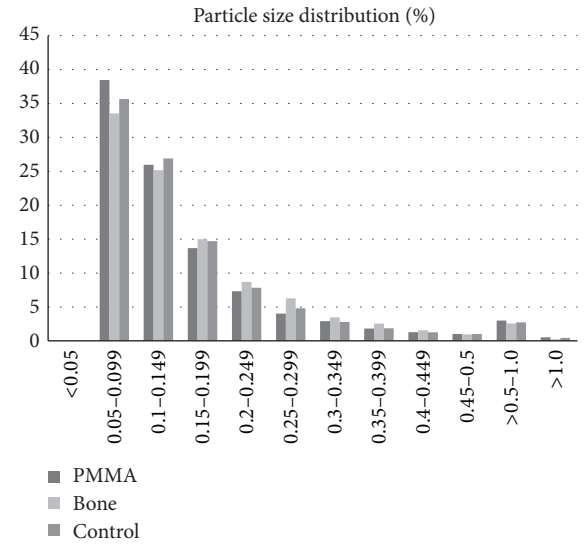

Figure 4: Particle size distribution measured by the ECD for each size interval.

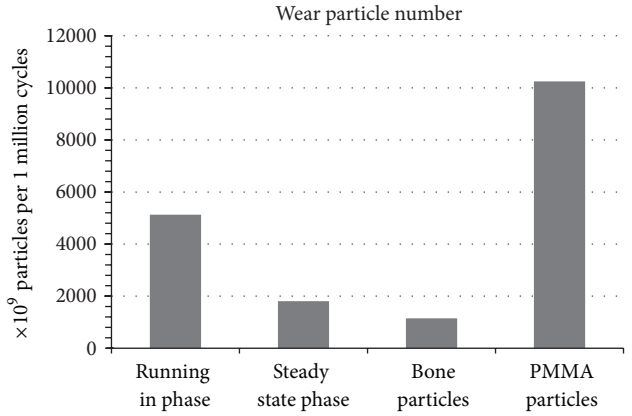

Figure 5: The change of the polyethylene wear particle number in the progress of the simulator tests, respectively after the addition of the third-body wear.

failure of the prosthesis [7, 8]. Therefore, our objective was to analyze the generated wear particles of a fixed bearing UKA under the influence of third-body debris like cortical bone and cement in terms of particle size, morphology, and number.

Schroeder et al. previously described the simulator testing [12] that defined a high contamination of third-body wear particles of 5.0 g/L, as former studies have shown a negligible effect of third-bodies in a concentration of 3.0 g/L and below [20]. The used concentration is approximately 25 times higher for cement and 20 times higher for bone debris compared to findings in TKA during surgery [21].

In this investigation, for the particle analysis using the acid digestion method [17] and the following SEM analysis, the removal of the added third-bodies was necessary. Thus, the particle lubricant after acid digestion underwent an additional ultracentrifugation step to remove the third-bodies in order to ensure a SEM analysis that just focuses on the generated wear debris. This step is mentioned neither by the ISO nor by the ASTM [16, 22]. This step was successful as no particles in the size range of the third-body debris could be found. On the other hand the loss of particles, especially of the bigger particles, cannot be excluded against the background that over 99% of the particles were sized submicron.

In this test setup a 0.02 μm pore polycarbonate filter membrane was used. An unknown amount of particles below this size might have been lost before the SEM analysis. Currently, it is known that the pore size of the filter could influence the results of the particle analysis. Scott et al. demonstrated that filtration through 0.05 μm is necessary to isolate a greater number of submicron wear particles [23]. With the 0.02 μm pore size filter which was used the majority of the particles should have been isolated.

In general, joint simulators allow preclinical evaluation of wear of artificial joints in a controlled environment [24]. The results of knee simulator studies, in terms of wear volume and size of the debris produced, have been shown to be similar to those found in early retrieved knee prostheses [25–27].

Overall, the particle size distribution in the present study is comparable to those of former particle analyses of bicondylar knee prostheses. As already mentioned, the most particles were found to be submicron, which correlates with the SEM based findings of a knee simulator based study that compared cross-linked and conventional polyethylene inserts for bicondylar knee systems [10]. In this study the mean diameter of the analyzed particles was between 0.37 μm and 0.48 μm and therefore submicron [10]. In the present study the particles are even smaller with 0.13-0.14 μm (given as median) as demonstrated in Table 2. Furthermore, a recent retrieval study by Minoda et al. verified a mean ECD of wear particles from well-functioning total knee prostheses of various material types and designs in a size range from 0.64 μm to 0.81 μm [28]. In this study a filter with a 0.1 μm pore size was used, which might explain the slightly larger values of the particle size distribution.

Interestingly three research groups investigated the impact of methodology concerning a standardized particle analysis in a round robin test [29]. They found that several not exactly defined differences in the complex methodology of wear particle analysis significantly influence the results, for instance, the use of different pore size filter membranes or the use of different SEMs [29]. Therefore, the relatively wide interobserver variability is roughly explainable.

The particles found in the present study were mostly round in shape, smooth, granular, and irregular. According to the sizing of Sieving et al. [13] only the PMMA particle group showed a higher percentage of particles with an AR $\geq$ 2.4 (13.42%) [13]. This is an important fact, as it is known that fibrillar particles with an AR $\geq$ 2.4 show increased inflammatory reactions compared to round and granular particles [13, 30]. This has to be assessed with regard to the particle size distribution: Green et al. reported that even small differences in the size range (mean size 0.24 μm versus 0.45 μm and 1.71 μm) lead to different reactions of macrophages *in vitro* [7]. The particles with a mean size of 0.24 μm were the most reactive [7]. As the most particles of

all groups in the present study are even smaller it has to be assumed that they are in a biologically reactive size range. The PMMA group, especially, tends towards a higher percentage of fibrillar particles, which are supposed to be biologically more reactive.

Respectively, there are no relevant though statistically significant differences between the groups. The statistical significance is rather due to the extremely high group sizes. This problem occurred in a former study as well [10]; the statistical rating has to be used only carefully.

The most imposing difference between the tested groups in the present study was yet the absolute number of particles per million cycles. The particles were calculated using a previously developed formula [10]. The calculation of the particles is essentially based on two factors: first, the measured gravimetric/volumetric wear rate of the polyethylene inserts and, second, the hypothesized volume of the wear particles. In the calculation of the volume the three-dimensional shape of the particle is assumed to be spherical. Therefore, the ECD of the particles is used as diameter for the calculation. This is an approximately simplified model of the particle shape, as the real volume cannot be assessed using SEM. As the most particles have an AR < 2.39, this assumption seems to be justified [10]. However, the addition of PMMA third-bodies lead to tenfold particle generation compared to the steady state phase and the bone particle group. It is important to note that the number of particles in a given total volume increases as the particle size decreases. This might explain the rather high particle numbers compared to the findings by Utzschneider et al. [10]. They had found particle numbers in the range of $5–20 \times 10^9$ [10].

The findings in the present study have to be associated with the complex cellular pathogenesis in the development of periprosthetic osteolysis in response to wear debris [5, 6]. Thus, it has to be assumed that PMMA third-bodies via the generation of multiple particles, especially, negatively influence the biologic reaction and finally lead to an increased inflammatory reaction that ends in an aseptic loosening of the prosthesis. Other factors, including particle surface texture and surface chemistry, could influence the cellular response as well. Further investigation in adequate *in vivo* models is mandatory to clarify the biological activity of the wear debris isolated in this study.

As limitations in the present study the wear simulation tests have to be named. They were performed in a single series of 8.0 million cycles divided in four test groups, rather than different series testing each step. But the advantage in this setup is the identical positioning of the prosthesis throughout the 8.0 million cycles allowing identical test conditions for all groups. Another limitation is the point of time of the addition of the third-bodies. First, they were added after reaching the steady state phase which allows using that phase as a control concerning wear rate and particle generation. This certainly can not totally be transferred to the clinical situation, as the third-bodies are most likely placed already during the implantation of the prosthesis. The order of the third-body particles might influence the results as well. As the wear rate did not change after adding the third-body bone particles compared to the steady state phase, negligible changes of the wear pattern were assumed [12].

The particle analysis was performed using a grayscale detection method. This allows objective particle measurements. On the other hand, small grayscale differences cannot be captured by the software, which might lead to values that do not reflect the absolutely correct size and shape of the particles. Additionally, the geometrical structure of the particles can only be assumed, as SEM analysis does not allow a three-dimensional measurement of the particles.

5. Conclusion

The results of the present study demonstrate the evident effect of PMMA third-body wear particles on the particle generation after UKA in a knee simulator based study. The PMMA particles increase the generation of numerous particles and slightly alter the particle morphology towards fibrillar particles. This might lead to an elevated inflammatory response after UKA *in vivo* and, therefore, even lead to an early failure of the unicondylar knee prosthesis.

In this regard the careful removal of PMMA debris and a thorough lavage after UKA implantation is mandatory. In order to detect missed PMMA pieces, postoperative X-ray diagnosis should be used to verify hidden third-bodies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Variability of TKR Knee Kinematics and Relationship with Gait Kinetics: Implications for Total Knee Wear

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Several factors, including compressive load and knee kinematics, have been shown to influence wear. External knee moments (a surrogate for load) have recently been correlated with the medial and lateral wear scar areas of an unconstrained, PCL retaining knee design. Therefore, the purpose of this study was to determine whether differences in kinetics during level walking are accompanied by specific differences in relative knee kinematics. Thirty TKR patients were gait tested using the point cluster technique to obtain 3D motions of the knee. External knee moments were calculated from ground reaction forces recorded with a multicomponent force plate. The subjects were separated into two distinct anteroposterior (AP) motion categories: a low motion group and a high motion group. Similarly, the low and high motion groups for internal-external (IE) rotation were also identified. For the IE motion, there was no significant difference between the transverse internal rotation moments between the two IE motion groups. However for the AP motion groups, a higher external peak flexion moment was found for the group displaying less AP motion. These observations suggest that subjects with higher joint moments execute smaller ranges of AP motion and thus are likely to incur less wear.

1. Introduction

Advances in implant design and material research for the articulating components have made total knee replacement (TKR) surgery a common solution to relieve pain and disability from degenerated joints. However, the clinical lifespan of the prostheses is limited due to wear of the ultrahigh molecular weight polyethylene (UHMWPE) tibial liner and subsequent loosening of the prosthesis [1–3]. Thus, many patients outlive their implant and are required to undergo costly and disruptive revision surgery.

Implant tribology is a system effect, which is a function of the articulating surface material and geometrical characteristics, surrounding environment and applied load and motion. Specifically, wear of the UHMWPE tibial liner is affected by implant design, articulating material properties and relative knee load and motion [4, 5]. With level gait considered as the most frequent functional activity [6], the issue of varying gait styles entailing numerous combinations of kinetics and kinematics at the knee arises. McEwen et al. [4] showed that reduced displacements and rotations during TKR wear testing caused a significant decrease in the wear rate. Previously, it has been shown that wear scars are linked to patient specific kinematics [7]. Since both knee motion and moments have been shown to individually influence wear, the question of whether a specific relationship between gait kinematics and kinetics exists that could help shed light on the biotribological phenomenon in the in vivo situation. This relationship could identify particular gait patterns and the subsequent influence on TKR wear, leading to important implications in future design and preclinical wear evaluation. Since knee kinetics may govern the resulting knee kinematics, the purpose of this study was to explore possible relationships between the two gait-related parameters in order to recognize particular gait patterns. Given that the variability of secondary motions within the subject population was far greater than the variability observed in the primary flexion-extension (FE) profiles [8], it was hypothesized that relative differences in secondary knee motions were significantly related to external moments.

2. Patients and Methodology

Thirty TKR patients were invited to undergo gait analysis and obtain knee joint motions during level walking at self-selected speeds. Details characterizing the primary and secondary knee motion patterns during an entire cycle of level walking were previously published [9]. The current study used the same patient population. Briefly, the 30 TKR patients (15M/15F, 67 ± 9.3 yrs (50–84 yrs), average implant in situ time of 6.0 ± 4.6 yrs (1.3–16 yrs), and average BMI of 28.9 ± 5.0 kg/m^2 (21.7–38.9 kg/m^2)), consented for this Institutional Review Board approved study. All patients had a successful primary TKR using a posterior cruciate ligament (PCL) retaining design (10 subjects were implanted with a Miller-Galante II (MGII, Zimmer Inc.) and 20 subjects were implanted with a NexGen Cruciate-Retaining (NGCR, Zimmer Inc.)). All operations and follow-up studies were performed at a major medical center with five surgeons involved. Knee joint motions were obtained during level walking at self-selected speeds through gait analysis using the point cluster technique [10]. The flexion-extension (FE) rotational motion, anterior-posterior (AP) translational motion, and internal-external (IE) rotational motion of the tibia were described from a fixed femoral system, where the femoral coordinate system was fixed at the midpoint of the transepicondylar line of the distal femur (TEP axis, which is close to the instantaneous axis of motion). Details of the methodology can be found in Ngai and Wimmer, 2009 [9]. External knee moments were also collected during these gait tests. A multicomponent force plate (Bertec, Columbus, USA) was used to record foot-ground reaction forces (GRF) together with lower extremity kinematics. Motion and force data were time-synchronized at 120 Hz. Using a rigid link model of the foot, shank, and thigh [11], inverse dynamics was used to calculate 3D external moments and intersegmental forces about the knee using the 3D GRF data and segment kinematics as input. A computer program was used to process data (CFTC, Chicago, USA). The FE pattern, AP knee motion, and IE rotation were not found to be statistically different between the MGII and NGCR patient groups [9]. Thus, all subjects were combined into one subject group. Based on the obtained data, 1 MGII subject's AP data set was excluded due to processing difficulties.

The subjects were then classified into two distinct AP motion group classes. Similarly, the entire subject group was also classified into two IE motion group classes. The rationale for establishing groups rather than investigating individual data was based on the indication that significant correlations were hidden due to the large variability in ranges of motion between subjects. Therefore, categorizing and averaging data in motion groups would help to smooth data and identify the influencing factors with respect to the principal measures, that is, the secondary knee motions. Such an approach for analysis has been used previously [12]. By ranking all subjects from the lowest to highest motion and splitting them into two equally sized subgroups, a low motion group (LMG) and a high motion group (HMG) of 15 subjects each was created for both AP and IE motions, resulting in 4 groups total. The range of tibial AP translation from midstance to terminal stance and the range of IE rotation from terminal stance into swing were calculated for each subject. The individual AP ranges were averaged per LMG and HMG motion groups. Similarly, the individual IE ranges were averaged per LMG and HMG motion group. Within the AP and IE categories, group to group statistical comparisons of kinetic and kinematic gait variables were conducted using Mann-Whitney U and chi-square analyses (SPSS, Chicago, USA). To address the hypothesis that relative differences in secondary knee motions were significantly related to external moments, it was of particular interest to evaluate the relationship between AP motion and the sagittal plane moments and the IE motion with the transverse plane moments, though all relationships were investigated.

3. Results

As expected, the AP ranges calculated were different between the two established groups both in magnitude and timing during the gait cycle (GC; Figure 1(a)). Similarly, the IE ranges averaged per group were also recognizably different (Figure 1(b)). While the AP group differences occurred during stance phase, the IE group differences occurred during swing phase.

Both AP motion groups showed similar AP translation to each other from heel-strike to midstance (0%–30% GC) with posterior tibial travel exceeding 10 mm (Figure 1(a)). This heel-strike movement was followed by anteriorly directed tibial translation which was remarkably different between the two established groups. During the second half of stance (starting at 43% gait for LMG and 61% gait for HMG), both subject groups switched to again translate posteriorly into swing and completed swing phase in anterior tibial translation. The IE motion groups were also similar in pattern to each other with minimal rotation throughout heelstrike to terminal stance (0%–50% GC) (Figure 1(b)). Both groups then exhibited external tibial rotation during preswing starting at 50% GC, with a significant difference in the range of rotation during initial swing (62%–75% GC). It is important to note that the displayed motion patterns do not directly translate into contact point movement, since the radii of the femoral condyles vary throughout flexion from distal to posterior and from medial to lateral side. However, the definition of the coordinate system in this study makes the data directly comparable to knee simulator input data defined in ISO standard 14243-3 [13].

All moment plots had a similar patterning between groups; however, there were differences in peak of the external flexion moment when the subjects were categorized according to their AP motion (Table 1). The LMG displayed a higher external peak flexion moment than the HMG. This observation was further substantiated by differences in other important gait variables: the LMG displayed a larger knee flexion range from heel-strike to midstance and a larger toe-out angle (described as the degrees of external rotation of the foot from the sagittal plane) than compared with the HMG (Table 1). Since a borderline significance existed between the toe-out angles of the two motion groups, it

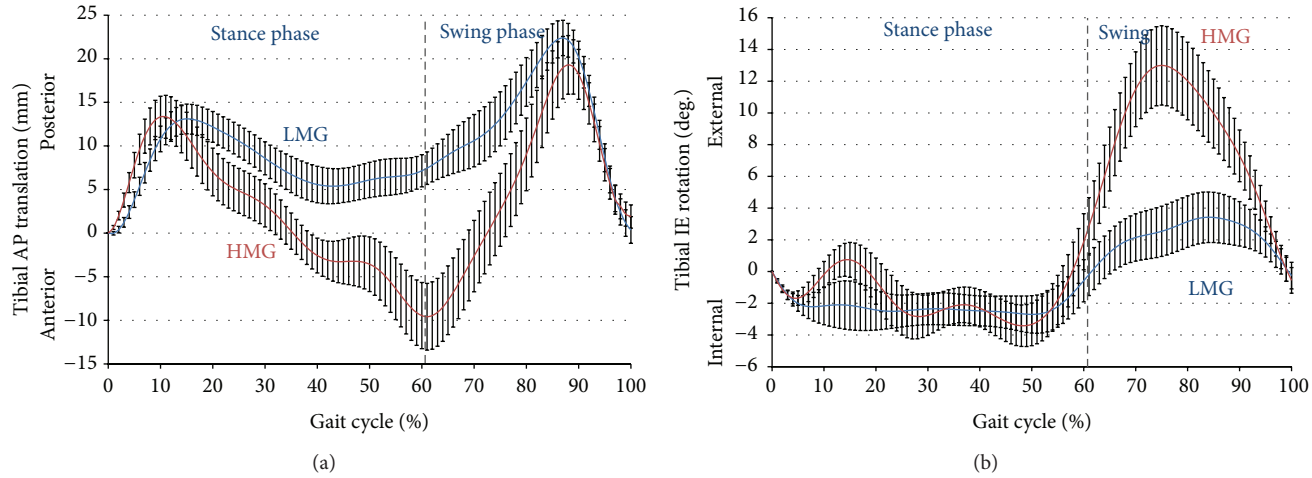

Figure 1: AP wave form (a) and IE wave form (b) of the low and high motion groups during gait. A full gait cycle from heel-strike to heel-strike is shown for the low motion group (LMG; blue) and the high motion group (HMG; red). Stance phase and swing phase are separated by a dashed line. Data are shown as mean ± standard error of the mean (SEM).

Table 1: Demographic and kinetic variables of low (LMG) and high (HMG) motion groups. One subject's data from the AP HMG had to be excluded due to processing difficulties.

	AP motion groups			IE motion groups		
	LMG	HMG	*P*	LMG	HMG	*P*
Design (MGII/NexGen)	5/10	4/10	0.683	5/10	5/10	1.0
Age (years)	67.6 ± 2.14	66.5 ± 2.72	0.780	68.7 ± 2.41	65.5 ± 2.42	0.461
BMI (kg/m^2)	27.5 ± 1.34	30.2 ± 1.19	0.290	27.8 ± 1.33	30.0 ± 1.24	0.267
Implant in situ time (years)	5.6 ± 1.2	6.5 ± 1.2	0.949	6.02 ± 1.20	60.3 ± 1.20	0.775
Gender (M/F)	11 M/4 F	4 M/11 F	**0.027**	8 M/7 F	7 M/8 F	1.0
Total IE range from stance to swing (deg.)	16.33 ± 1.62	15.97 ± 1.93	0.561	NA	NA	NA
Total AP range from mid to terminal stance (mm)	NA	NA	NA	20.61 ± 2.60	22.52 ± 4.75	0.505
HS to MS knee flexion range (deg.)	18.38 ± 0.59	14.86 ± 1.02	**0.023**	16.81 ± 0.98	16.43 ± 0.92	0.744
Minimum knee flexion at heel-strike (deg.)	−0.350 ± 0.94	0.490 ± 1.33	0.621	1.69 ± 1.02	−1.58 ± 1.12	0.148
Toe-out angle (deg.)	21.4 ± 2.28	16.94 ± 2.04	0.057*	15.59 ± 1.59	22.79 ± 2.39	**0.021**
Peak flexion moment (%Bw. × Ht.)	2.36 ± 0.21	1.80 ± 0.20	**0.037**	NA	NA	NA
Max internal rotation moment (%Bw. × Ht.)	NA	NA	NA	0.857 ± 0.058	0.734 ± 0.092	0.233
Speed (m/s)	1.25 ± 0.053	1.20 ± 0.054	0.505	1.24 ± 0.03	1.20 ± 0.069	0.624
Stride length (m)	0.780 ± 0.021	0.773 ± 0.019	0.715	0.790 ± 0.012	0.762 ± 0.025	0.305
Cadence	109.60 ± 2.72	109.26 ± 2.50	0.880	110.36 ± 2.31	108.5 ± 2.89	0.412

Data are mean ± SEM, **bold** indicates $P < 0.05$, and * indicates borderline significance.

was expected that the range of IE rotation from terminal stance to swing would also be significantly different. However, this speculation was not supported (Table 1). There were no statistically significant differences in implant design, in situ time, age, weight, or BMI between the two motion groupings; however, a gender difference was detected (Table 1). Both groups walked similarly regarding time distance parameters. Mean stride length and cadence were almost identical and there was no difference in walking speed.

There was no significant difference between the transverse internal rotation moment or the range of AP translation between the two groups. Only one gait variable was significantly different between the LMG and HMG: the LMG displayed a smaller toe-out angle (Table 1). As with the AP

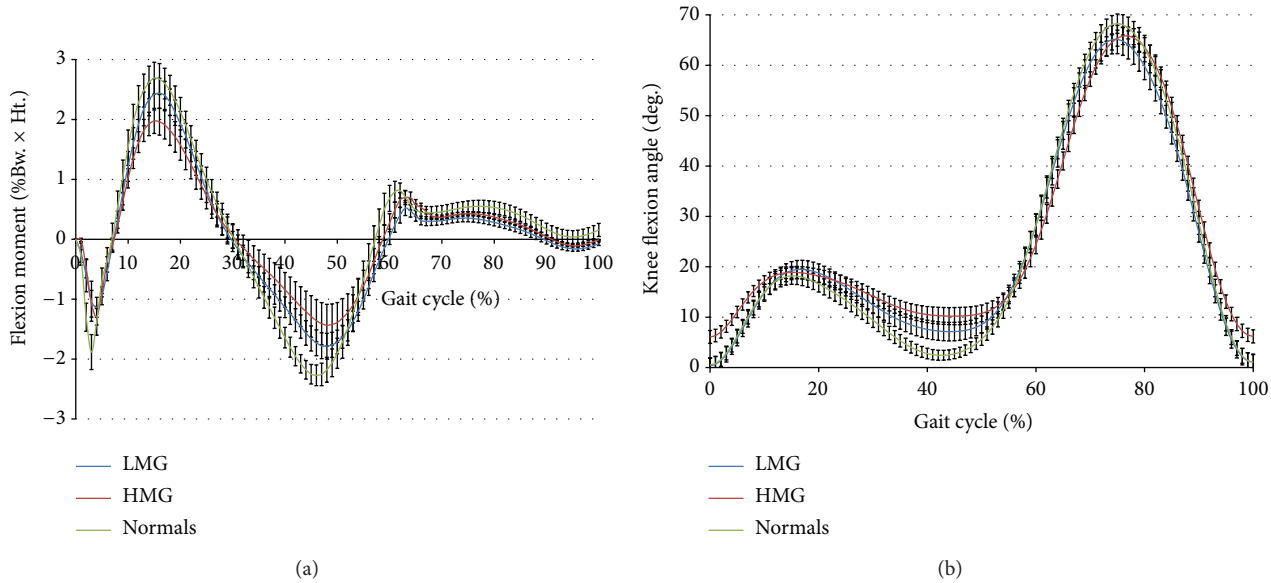

Figure 2: (a) Knee flexion moment and (b) knee flexion rotation of the low and high AP motion groups compared with normal controls. Data are shown as mean ± SEM.

groups, there were no significant differences in prosthesis design, in situ time, age, weight, BMI, stride length, walking speed, or cadence. There was also no difference detected in gender separation between the two groups.

4. Discussion

Both joint kinematics and joint kinetics are important input parameters for knee wear testing. The International Organization for Standardization (ISO) provides two different standards for knee wear testing. ISO 14243-3 describes input based on joint kinematics, while ISO 14343-1 describes forces as input. To explore possible kinematic and kinetic relationships and to identify gait patterns within this population, subjects were categorized into low motion and high motion groups for the secondary motions (AP and IE), resulting in 2 groups per motion. Possible correlations with external knee moments and other kinematic and kinetic gait variables were investigated. Though IE rotation kinematics did not have significant relationships with kinetics, differences in AP knee kinematics were accompanied by differences in gait kinetics, thus partly supporting our hypothesis. For the AP motion groups, the LMG displayed a higher peak knee flexion moment—often considered a surrogate marker for quadriceps use, while differences of all other kinetic variables were insignificant. Additionally, the HMG consisted primarily of females, possibly relating to higher joint laxity than observed in males [14]. Interestingly, the large differences in AP movement between groups did not exhibit significantly different total IE range of rotation, though a borderline significance in toe-out angle was found (Table 1).

It is well established that TKR patients walk with a variety of gait patterns, many of them abnormal [15]. A reduced external peak flexion moment has been related to a diminished net quadriceps use [16]. However, the net moment of the extensor muscles can be generated with and without cocontraction. In other words, a lower external flexion moment can mean reduced agonist (extensor) activity, or increased antagonist (flexor) activity, or both. As shown in this study, a reduction in the net quadriceps moment is accompanied by higher translational motion in the sagittal plane. The magnitude of the peak flexion moment in the AP LMG was similar to that observed for a group of previously tested normal subjects, displaying approximately 2.12% Bw. ∗ Ht. (Figure 2(a)). This more normal behaviour is also mirrored in the knee flexion range from heel-strike to midstance (Figure 2(b)), with an active quadriceps to better support and extend a flexed knee. It is conceivable that the higher external flexion moment is reflective of higher muscle activity of both quadriceps and hamstrings, thereby providing increased stability to the ACL deficient knee due to increased cocontraction. The thus generated higher contact force and related friction at the tibial plateau may reduce resultant secondary joint motions. Quadriceps muscle strength is an important determinant of physical function after TKR [17] and has been related to intrinsic anteroposterior stability in TKR [18]. Fascinatingly, implant longevity has been positively associated with the peaks of the sagittal plane moments, implying that higher flexion moments relate to longer in situ time [19]. This observation may appear counterintuitive, since higher loads are expected to cause more polyethylene damage. However, smaller ranges of secondary motion could incur less implant wear despite the higher external flexion moment and increased flexion-extension rotation of the femoral condyles. Johnson et al. [20] have shown that small variations in AP translation and IE rotation motion can have a large effect on polyethylene wear

in TKR. Wear testing with various input waveforms will be necessary to identify the actual effects of gait variability on wear.

In this study, the tibia rotated externally with increasing knee flexion angle during the swing phase of gait. At first sight this may seem contradictory to literature. Freeman and colleagues, for example, reported internal rotation of the tibia with increasing flexion angle in cadaver knees [21] as well as in unloaded and loaded living knees using MRI [22]. This makes sense since the knee is rolling on a larger curvature laterally than medially and thus moves a greater distance on the lateral plateau during femoral rollback with knee flexion [23]. However, as Blankevoort [24] noticed, this motion pattern is highly susceptible to load changes and not necessarily dependent on passive joint structures. More recently, Andriacchi and coworkers reviewing the importance of functional analysis in evaluating knee kinematics concluded that relative knee motion is dependent on activity rather than on knee flexion angle. In their studies, the tibia rotated internally during squatting but externally during stair climbing with increasing flexion angle [25].

The study has several limitations, which are briefly discussed in the following paragraph. There were no X-rays available and the influence of prosthetic alignment, especially tibial slope, on the motion parameters could not be evaluated. Also, the results of this study are possibly influenced by the limitations of skin-marker gait testing, which can only estimate the positions of the underlying osseous structures [26]. Since the rotation axis of the knee is not fixed and though the point cluster method has been developed and validated to reduce artefacts produced by skin movement, overestimations of movement are possible, particularly during high flexion (i.e., swing phase).

The differences in the AP motion groups occurred during stance phase. Kinetic data during stance are more reliable than those during swing since they are calculated from force plate readings. Kinetics during swing phase are based purely on modeling limb acceleration and thus may be more artefact prone. Since the differences in the IE motion groups occurred during swing, inaccuracies in kinetic calculations in this phase may have resulted in a type II error and potential relationships may have been obscured.

5. Conclusions

In summary, this study demonstrated that TKR gait is highly variable and ideally a broad spectrum of gait styles should be tested before a prosthetic device is released to the market. The identified relationship between anterior-posterior translation during stance phase and the peak external flexion moment may help to constrain the necessary input and aid in the identification of the most relevant and/or representative input data for both wear testing standards. Furthermore, the identified relationships may help in the interpretation of observed wear scars on retrievals. However, future wear tests are necessary to identify the actual relationship of gait variability and wear. In addition, due to the variety of gait styles, in silico wear models that support experimental testing may be warranted. This study and the forthcoming wear tests provide grounds to open up discussion for any necessary changes to the current knee wear testing standards.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Can Pin-on-Disk Testing Be Used to Assess the Wear Performance of Retrieved UHMWPE Components for Total Joint Arthroplasty?

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The objective of this study was to assess the suitability of using multidirectional pin-on-disk (POD) testing to characterize wear behavior of retrieved ultrahigh molecular weight polyethylene (UHMWPE). The POD wear behavior of 25 UHMWPE components, retrieved after 10 years *in vivo*, was compared with 25 that were shelf aged for 10–15 years in their original packaging. Components were gamma sterilized (25–40 kGy) in an air or reduced oxygen (inert) package. 9 mm diameter pins were fabricated from each component and evaluated against CoCr disks using a super-CTPOD with 100 stations under physiologically relevant, multidirectional loading conditions. Bovine serum (20 g/L protein concentration) was used as lubricant. Volumetric wear rates were found to vary based on the aging environment, as well as sterilization environment. Volumetric wear rates were the lowest for the pins in the gamma inert, shelf aged cohort. These results support the utility of using modern, multidirectional POD testing with a physiologic lubricant as a novel method for evaluating wear properties of retrieved UHMWPE components. The data also supported the hypothesis that wear rates of gamma-inert liners were lower than gamma-air liners for both retrieved and shelf aging conditions. However, this difference was not statistically significant for the retrieved condition.

1. Introduction

Total joint replacements, which represent the current standard of care for end-stage, degenerative hip and knee disease, typically incorporate a metal or ceramic component articulating against a counterface of ultra-high molecular weight polyethylene (UHMWPE) [1]. The tribological behavior of UHMWPE biomaterials is known to be influenced by their extent of crosslinking, which improves wear resistance [2–5], or by oxidation, which decreases it [6–9]. There is great interest in evaluating changes to the wear behavior of UHMWPE formulations after implantation in the body [8, 10–16].

Pin-on-disk (POD) testers are currently employed as a screening tool for orthopaedic biomaterials, because they can economically identify promising bearing couples before expensive joint simulations are warranted [17]. Although earlier POD testers were not capable of reproducing clinically relevant wear mechanisms, multidirectional POD testers are able to rank the tribological properties of different formulations of clinically relevant ultra-high molecular weight polyethylene (UHMWPE) *in vitro* [17]. Through efficient design, POD testers with up to 100 individual specimen stations are now available [18], which can evaluate a potentially statistically relevant sample size for biotribological simulations.

POD simulation has been successful in evaluating the as-manufactured and *in vitro* aged UHMWPE [17]. However, little is known about the response of *in vivo* aged UHMWPE in POD testers. Oxidation of gamma sterilized UHMWPE occurs after exposure of oxygen in air as well as after implantation in the body [8, 10–16], either of which would

theoretically increase wear rate of the material. However, clinical studies of human patients demonstrate the opposite trend; namely, the wear rate of UHMWPE components tends to *decrease* with implantation time [19]. Thus, the extent to which *in vivo* conditions will affect the tribological properties of UHMWPE remains poorly understood. The objective of this study was to assess the suitability of using POD testing to characterize the biotribological behavior of retrieved UHMWPE components for total joint replacement. We also compared the oxidative effects of irradiation in air and in inert gas on the wear resistance of UHMWPE and evaluated the magnitude of these effects on shelf-aged and retrieved implants. We hypothesized that irradiation in inert gas would result in lower wear rates compared to irradiation in air. Our second hypothesis was that retrieved implants would be more wear resistant than shelf-aged implants.

2. Materials and Methods

Retrieved ($n = 25$) hip liners that were consolidated from GUR 1050 resin and gamma irradiated with a dose of 25–40 kGy were identified from our center's institutional collection of over 2,000 retrieved devices based on their sterilization method (air versus inert) and implantation time (>10 years). Shelf-aged implants ($n = 25$), which were aged 10–15 years, served as never implanted controls. In each group, 13 implants were irradiated in air and 12 implants were irradiated in inert gas (Figure 1). We selected these four cohorts of UHMWPE materials to analyze because of their extensive track record in the literature [8, 20].

Two cylindrical specimens were produced from each liner using a 9 mm diameter core punch. Of the two cores obtained from the retrieved liners, one core was obtained from the superior half and the second core was obtained from the inferior half ($n = 2$ pins per retrieved liner, 50 pins total). The cores were machined on a lathe to ensure flat surfaces. Thus, the measurements pertain to the wear resistance of material near the surface. For the shelf-aged liners, 1 mm of the surface of one core was removed using a lathe to expose the highly oxidized region whereas the second core was lathed similar to the retrieved cores ($n = 2$ pins per shelf-aged liner, 50 pins total). Specimens were soaked in distilled water for five days before testing.

Multidirectional POD wear testing in a physiologically relevant lubricant was conducted on a Super-CTPOD with 100 stations (Phoenix Tribology, England) (Figure 2) [18]. The counterface disks were wrought CoCr alloy with an average roughness of 1 ± 0 nm as measured by white light interferometry using a NewView 5000 Model 5032 equipped with advanced texture analysis software, MetroPro 7.7.0 (Zygo, Middlefield, CT). The lubricant used was alpha calf serum with a protein concentration of 20 g/L (Wear Testing Fluid, HyClone, UT). Each pin had its own chamber filled with approximately 15 mL lubricant, which was maintained at $37 \pm 1^{\circ}$C. An elliptical wear pattern (major axis 10 mm and minor axis 5 mm) was employed to produce multidirectional wear. The average sliding speed was 24 mm/s. Static loading was applied to generate 2.0 MPa of nominal contact stress.

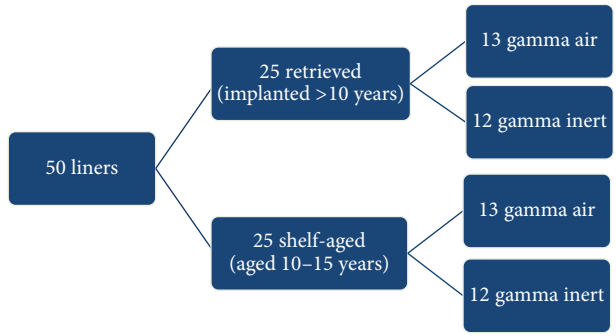

Figure 1: Schematic of the four cohorts for the retrieved and shelf-aged UHMWPE components.

The testing was carried out to 2.5 million cycles at 1.0 Hz. Gravimetric measurements were carried out at 0, 0.25, 0.50, 1.00, 1.50, 2.00, and 2.50 million cycles using a calibrated digital scale (accuracy = 0.01 mg). At each testing interval, articulating surfaces of pins were photodocumented. The lubricant was replaced after each interval analysis. Five gamma air and five gamma inert pins were employed as load soak control to compensate for the absorption of fluid by pins. To convert mass loss to volumetric loss, 0.931 g/cm^3 was used as bulk density of GUR 1050 UHMWPE [1]. Wear rates were calculated using a linear regression of volumetric losses.

The distribution of wear rates was tested for normality using the Shapiro-Wilk Test and found to be not normal. Thus, nonparametric statistical testing was used throughout this study. Differences between groups were evaluated with Kruskal-Wallis one-way analysis of variance followed by post hoc Dunn test. Statistical significance was assumed for $P < 0.05$.

3. Results

Total volumetric loss and volumetric wear rates for pins grouped by sterilization environment, aging environment, surface/subsurface measurements, and superior/inferior measurements are shown in Figures 3 and 4. Volumetric wear rates were found to vary based on the aging environment (i.e., shelf-aged or retrieved, *in vivo*; $P < 0.0001$), as well as sterilization environment (i.e., gamma air or gamma inert; $P < 0.0001$). However, we were unable to detect statistically significant differences in wear rates between surface/subsurface measurements or superior/inferior measurements when controlling for sterilization environment and aging conditions ($P > 0.05$). Therefore, pins were then pooled together based only on aging environment and sterilization environment, and volumetric wear rates were recalculated (Figure 5).

Volumetric wear rates (WR) were highest for the pins in the shelf-aged gamma air cohort (WR = 39.4 ± 13.7 mm^3/MC; Figure 5; $P < 0.0001$). The retrieved gamma air pins had the next highest wear rates (WR = 7.2 ± 7.0 mm^3/MC). Although the gamma inert retrievals had lower wear rates (WR = 7.0 ± 6.9 mm^3/MC), this difference between gamma inert shelf-aged pins and gamma inert retrievals was not statistically

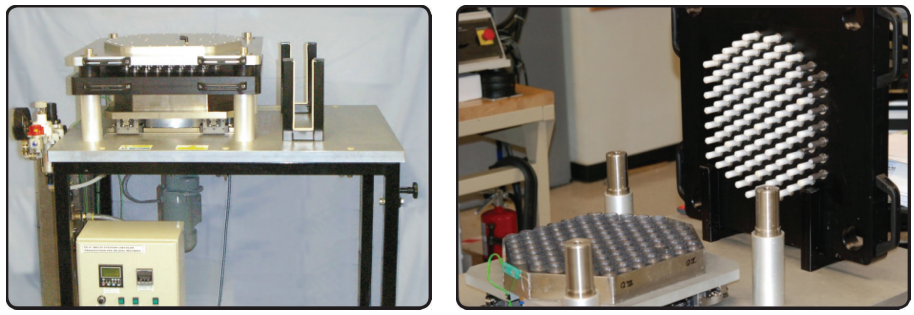

Figure 2: Photographs of the 100-station pin-on-disk tester (load soak station not shown).

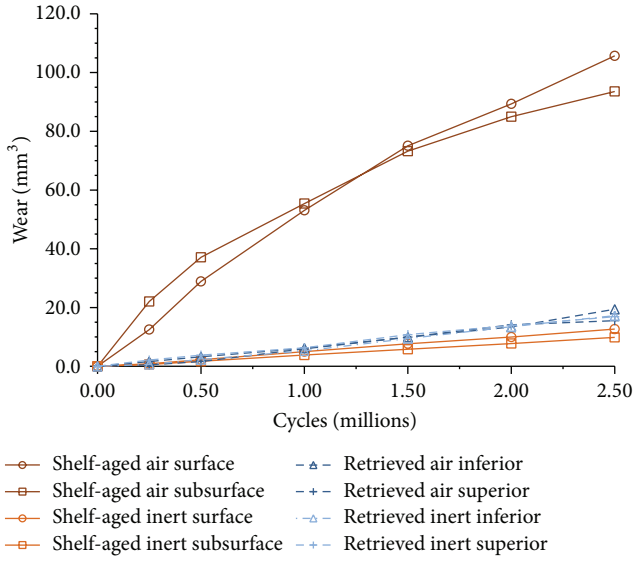

Figure 3: Average volumetric loss versus number of cycles is shown.

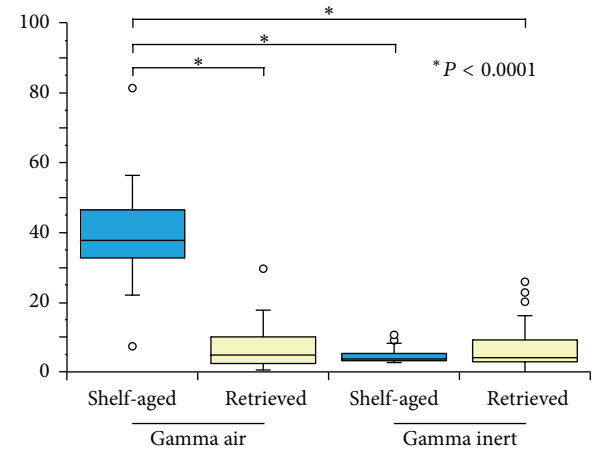

Figure 5: Box plots illustrating the differences in wear rates among the four cohorts. The shelf-aged gamma air pins exhibited the highest wear rates.

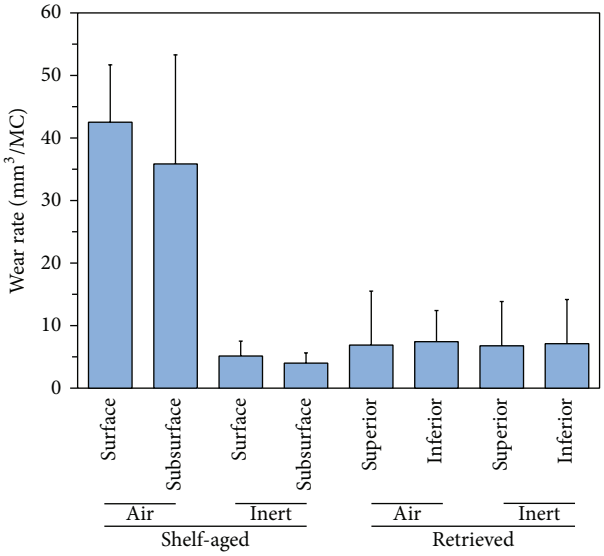

Figure 4: Wear rate of pins grouped by sterilization environment, aging environment, surface/subsurface measurements, and superior/inferior measurements.

significant ($P = 1.0$). The cohort with the least amount of wear was the gamma inert shelf-aged pins (WR = 4.6 ± 2.1 mm^3/MC).

The pins of all specimens showed removal of machining marks as well as burnishing of the articulating surface after 0.5 million cycles of testing (Figure 6). The shelf-aged gamma air pins (both surface and subsurface specimens) showed evidence of both surface and subsurface cracking at the end of the wear test after 2.5 million cycles (Figure 7).

4. Discussion

The results of this study support the utility of using modern, multidirectional pin-on-disk testing with a physiologic lubricant as a novel method for evaluating the wear properties of retrieved UHMWPE components for total joint replacement, which were exposed to *in vivo* conditions. This study also provides independent verification of the reproducibility of the 100-station POD tester, which has been previously studied by its developer using conventional, never implanted UHMWPE materials [18, 21]. The data also supported the hypothesis that wear rates of gamma inert liners were lower than gamma air liners for both retrieved and shelf aging conditions. However,

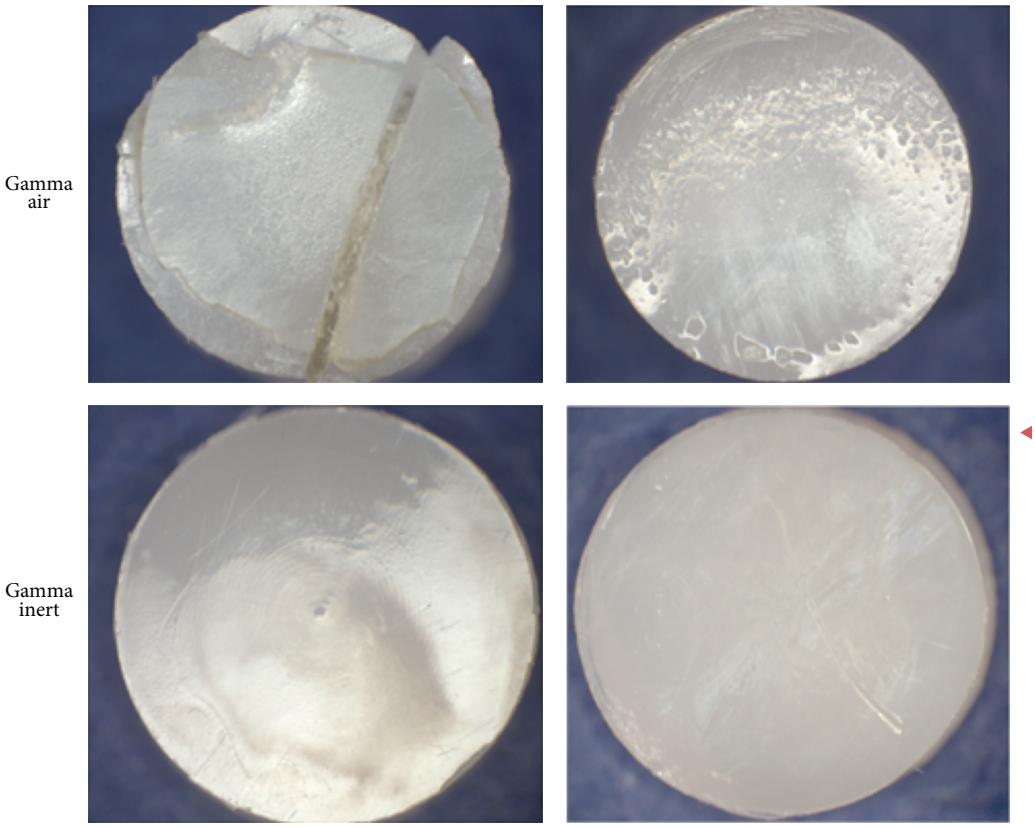

Figure 6: Example pins from the four study cohorts after 0.5 million cycles.

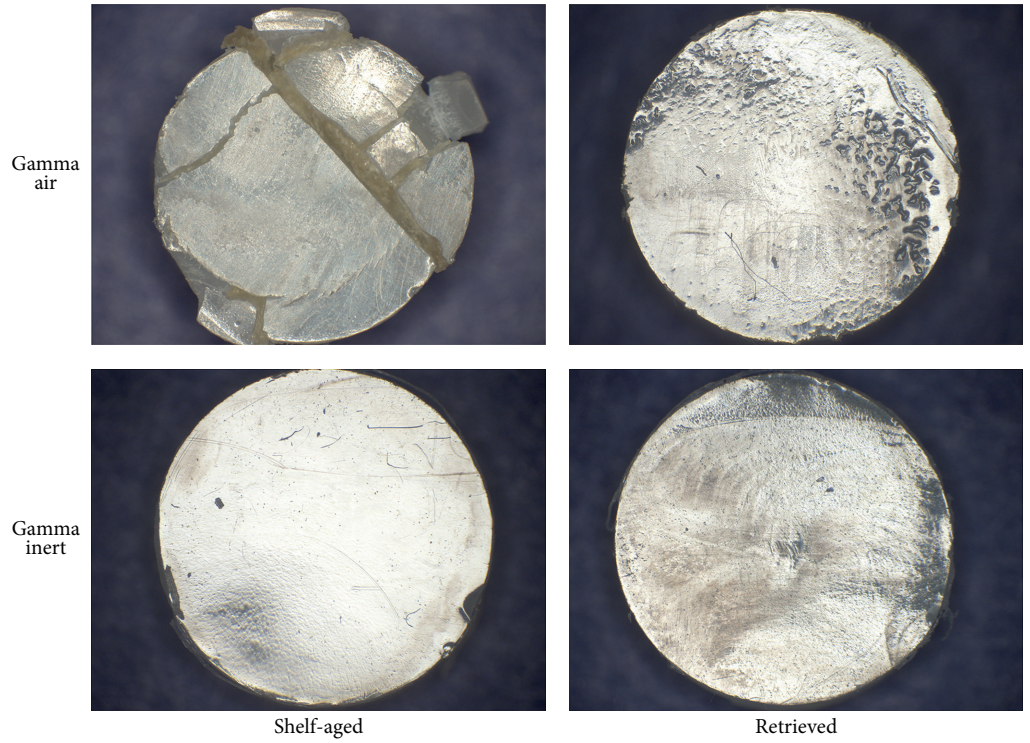

Figure 7: Example pins from the four study cohorts after 2.5 million cycles. Note the extensive cracking in the gamma air, shelf-aged specimen.

this difference was not statistically significant for retrieved condition.

We would like to highlight several limitations of this study for the reader. First, the UHMWPE components in this study were obtained from hip arthroplasty. Although we have no reason to suspect that the mechanism of shelf aging would differ between hip and knee arthroplasty devices [20], the results of the explants may not be generalizable to knee retrievals, which may be subjected to higher contact stresses than in hip replacements [11, 12, 14]. Because of the greater radius of curvature, the hip components represent a worst-case scenario for verification of the coring and pin-on-disk testing approach. It is straightforward to extend the methods of the present study from hips to knees given the encouraging findings of the current experiment. Second, the shelf-aged components that were used for this study were all stored in expired packaging, which typically prescribes 5 years for the shelf-life of gamma sterilized components [20]. Again, we selected these long-term shelf-aged components to provide a worst-case, highly oxidized set of control materials to verify the suitability of the pin-on-disc technique. Thus, the data for these shelf-aged components should not be misinterpreted to represent the behavior of materials that would have been used in patients.

Relatively few POD studies have been conducted on specimens obtained from aged UHMWPE biomaterials [22–24]. Besong and colleagues wear-tested UHMWPE pins fabricated from shelf-aged components and observed that gamma irradiation in air, followed by long-term aging (up to 10 years), as well as the counterface roughness, had a dramatic effect on the wear rate [22]. Muratoglu and colleagues conducted POD tests on specimens following accelerated aging conditions [23]. We found only one POD study, which has been conducted on explanted UHMWPE components. Kwon-Yong et al. tested 12 retrieved hip liners on a pin-on-disk tester. There were two fundamental differences between their study and the current study: (1) the retrievals in Kwon-Yong et al. study were shelf-aged in air 1.5–8 years after surgery before they were tested; (2) the pin-on-disk tester in that study did not produce cross-shear. Ultimately, tribometers employed in these previous tests were capable of evaluating up to 6 specimens concurrently, in contrast with the 100-station apparatus in the present study.

The results of this study mirror findings on retrieved UHMWPE liners. Previously, Kurtz et al. found that the femoral head offers protection to the superior surface from oxygen-containing bodily fluids, resulting in lower oxidation [8]. Additionally, previous studies have found that gamma inert packaging has lower oxidation than gamma air packaging [11, 25]. However, since the polyethylenes are identical (except with respect to sterilization environment), once the gamma inert components are removed from their packaging, they will oxidize at similar rates. This is especially apparent when comparing the POD wear rates between the shelf-aged gamma air and gamma inert cohorts. The pins that were shelf-aged in air had POD wear rates that were approximately 8 times greater than the pins that were shelf-aged in a vacuum-sealed inert environment. Therefore, shelf-life and environment are important factors in *in vivo* oxidation, as well as POD wear rates.

The relative oxidative stability of gamma inert UHMWPE, which has been documented in literature [11, 20], probably contributed to the tribological properties measured in this study. Our second hypothesis that shelf-aged UHMWPE would wear more than *in vivo* aged UHMWPE was supported only in the case of gamma air sterilized components. However, gamma inert shelf-aged components had the lowest wear rates of all the components we tested. This suggests that the sterilization in an inert environment, coupled with effective barrier packaging, is capable of preserving the tribological properties of UHMWPE even after storage on the shelf for more than 10 years.

Another important finding of this study was that long-term aging in air after sterilization in air appears to degrade the wear properties of UHMWPE more aggressively than *in vivo*. This may be due, in part, to the femoral head protecting the articulating surface from oxidizing species in body fluids [8]. Our findings for retrieved conventional liners in the present study will be a useful baseline comparison for evaluating the wear properties of retrieved highly crosslinked polyethylene liners, which were exposed to *in vivo* conditions, in future research.

Conflict of Interests

Drs. D. Baykal and Steven M. Kurtz are employees of Exponent, a scientific and engineering consulting firm. Exponent has been paid fees by medical device companies and suppliers for consulting services on behalf of such companies and suppliers, unrelated to the submitted paper. Dr. Kurtz is a shareholder of Exponent. Dr. Kurtz has received institutional support as a Principal Investigator, unrelated to the submitted paper, from Active Implants, Aesculap/B. Braun, Smith & Nephew, Spinal Motion, Stryker, Zimmer, Biomet, DePuy Synthes, Medtronic, Stelkast, Celanese, Invibio, Formae, Kyocera Medical, Wright Medical, Ceramtec, and DJO.

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Research Article

Wear Behavior of an Unstable Knee: Stabilization via Implant Design?

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Background. Wear-related failures and instabilities are frequent failure mechanisms of total knee replacements. High-conforming designs may provide additional stability for the joint. This study analyzes the effects of a ligamentous insufficiency on the stability and the wear behavior of a high-conforming knee design. *Methods*. Two simulator wear tests were performed on a high-conforming total knee replacement design. In the first, a ligamentous-stable knee replacement with a sacrificed anterior cruciate ligament was simulated. In the second, a ligamentous-unstable knee with additionally insufficient posterior cruciate ligament and medial collateral ligament was simulated. Wear was determined gravimetrically and wear particles were analyzed. Implant kinematics was recorded during simulation. *Results*. Significantly higher wear rates ($P \leq 0.001$) were observed for the unstable knee (14.58 ± 0.56 mg/10^6 cycles) compared to the stable knee (7.97 ± 0.87 mg/10^6 cycles). A higher number of wear particles with only small differences in wear particle characteristics were observed. Under unstable knee conditions, kinematics increased significantly for translations and rotations ($P \leq 0.01$). This increase was mainly attributed to higher tibial posterior translation and internal rotations. *Conclusion*. Higher kinematics under unstable test conditions is a result of insufficient stabilization via implant design. Due to the higher kinematics, increased wear was observed in this study.

1. Introduction

Implant failure due to massive polyethylene (PE) wear and wear-associated aseptic loosening has been one of the main challenges concerning total knee replacements (TKRs) in the past decades [1–3]. This has led to extensive research aimed at increasing the wear performance of TKR. Experimental wear studies showed that improvements in manufacturing, sterilization, and design optimization can be used to increase the wear resistance of TKR [4–7]. Therefore, clinical implementation of these technical improvements should increase the longevity of currently used TKR.

Clinically, failure analysis of currently available TKR confirms a reduction in wear-related revisions [8–10]. Nevertheless, wear remains a critical issue especially for the long-term success of TKR. As wear-related revisions decrease, other failure mechanisms become more relevant. Instabilities have become one of the most frequent failure mechanisms in TKR [8, 11] as they are often seen in the short and midterm (<5 years).

Aetiology of instabilities is often multifactorial, but a relevant portion can be attributed to ligamentous insufficiency [12]. A clinical solution that may address ligamentous instabilities is the use of a high-conforming knee design. However, concerns exist related to the higher grade of coupling. Increased bone-implant loading may be assumed. Additionally, conformity influences contact patterns and consequently kinematics as well as wear of TKR [13–15]. Until now, experimental wear studies cannot clearly answer whether high conformity has beneficial [16] or adverse [17, 18] effects on wear. This is related to the superimposing effects of surface stress, wear area, and resulting kinematics on the wear behavior.

Wear testing should be carried out based on the clinical background of expected loading. Patient collectives designated for the use of a high-conforming knee design differ from

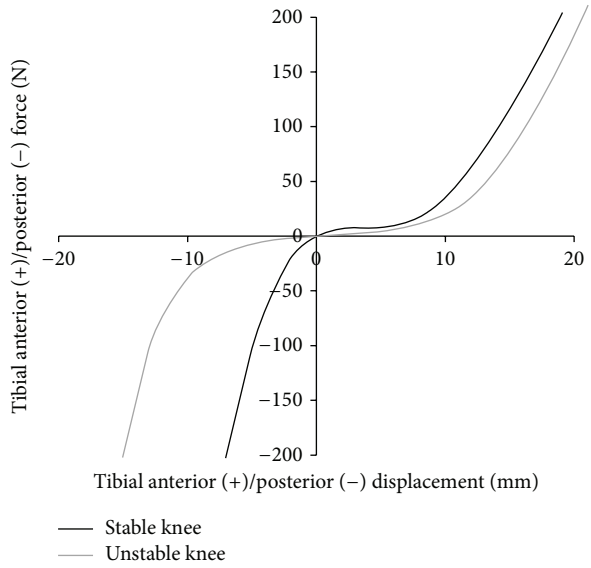


Figure 1: Anterior/posterior restraint in this study based on cadaveric studies [20–22]. The plot shows the level of restraint related to the characteristics of the passive structures (soft tissues, capsule, and ligaments).

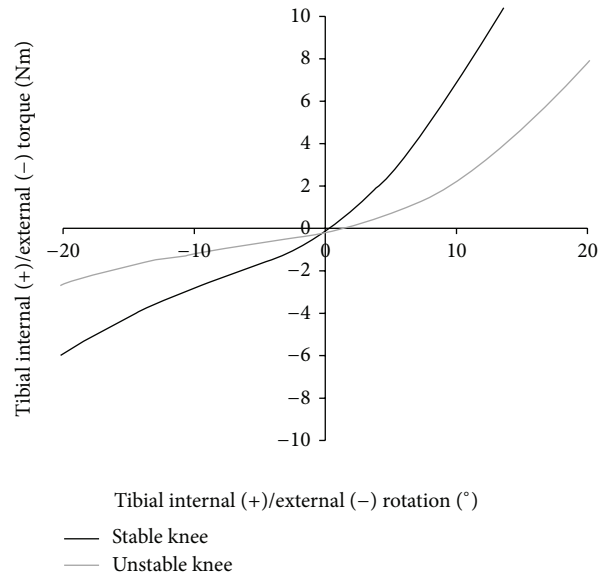


Figure 2: Internal/external restraint in this study based on cadaveric studies [20–22]. The plot shows the level of restraint related to the characteristics of the passive structures (soft tissues, capsule, and ligaments).

patient collectives designated for the use of an unconstrained knee design. The use of a high-conforming knee design may be plausible if a ligamentous insufficiency already exists or is anticipated during one's lifetime. This should be considered during wear testing.

The aim of this study is to analyze the effects of a ligamentous insufficiency on the stability and the wear behavior of a high-conforming knee design.

2. Material and Methods

2.1. Simulation. Two knee wear tests were performed on an AMTI knee simulator (Model KS2-6-1000, Advanced Mechanical Technology Inc., Watertown, MA, USA) using two different restraint characteristics. Restraint characteristics are defined by the restraint of the passive structures (ligaments, soft tissue, and capsule) which are based on *in vitro* laxity measurements [19–21]. In the first scenario, a stable TKR was defined with an absent anterior cruciate ligament and otherwise intact ligament structures [22]. In the second scenario, a ligamentously insufficient stabilized TKR (unstable TKR) was defined with an absent anterior cruciate ligament (ACL), insufficient posterior cruciate ligament (PCL), and medial collateral ligament (MCL). Simulated ligament characteristics are shown in Figures 1 and 2.

Disregarding restraint characteristics, wear tests were run with force-controlled parameters according to ISO 14243-1:2009 with an extension/flexion of 0°–58°, a maximum axial load of 2600 N, anterior/posterior forces of −265 to 110 N, and internal/external torques of −1 to 6 Nm. Axial forces were transmitted with a 7% medial offset of the tibial plateau width in order to achieve physiologically higher forces on the medial plateau.

2.2. Materials. For wear testing, a deep-dished, ultracongruent (manufacturer specification), cruciate-substituting implant design (TC-Plus, Smith & Nephew, Baar, Switzerland) was used. PE-components were irradiated in an inert gas atmosphere (25–37 kGy). The inserts were presoaked in bovine serum prior to the simulation. Inserts were gravimetrically measured on a weekly basis until the incremental increase in weight was less than 10% of the total cumulative weight increase. In detail, components were presoaked for 105 days (stable conditions) and for 132 days (unstable conditions). Every wear test consisted of three specimens plus one axially loaded soak control. Tests were run for a total of 5 million cycles in diluted bovine serum (PAA Laboratories GmbH, Pasching, Austria) with a protein content of 20 g/L. The testing fluid (250 mL) was tempered to 37°C during the simulation. As additives, sodium azide (1.85 g/L) and ethylenediamine tetra-acetic acid (7.44 g/L) were used to prevent bacterial growth and to minimize calcium phosphate layers, respectively.

2.3. Wear Analysis. At intervals of 500,000 cycles, the wear testing was interrupted to replace the bovine serum and determine the PE wear mass. Components were cleaned and measured gravimetrically according to ISO 14243:2:2009. At the end of each test, wear particles were analyzed using acid digestion according to previously published methods [23, 24]. Particles were analyzed on filters with a pore size of 20 nm using high resolution SEM (FEGSEM, Leo 1530,

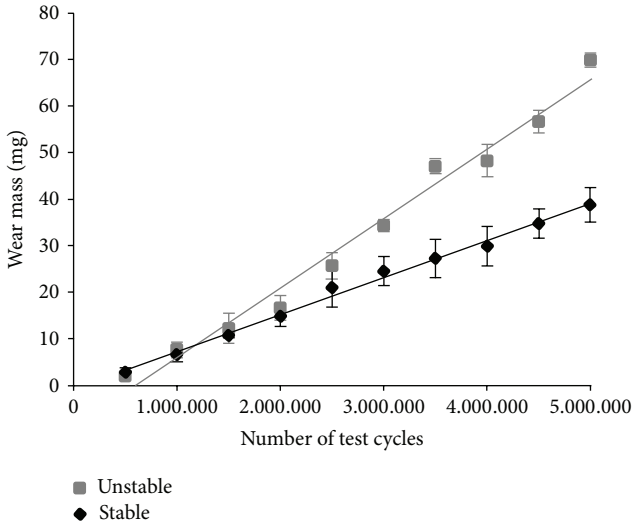


Figure 3: Wear progression for ligamentous-stable and ligamentous-unstable test conditions.

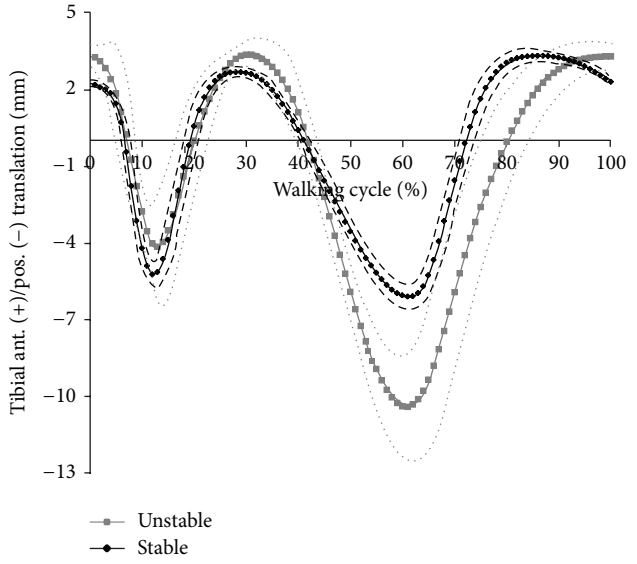


Figure 4: Tibial anterior and posterior translation for ligamentous-stable and ligamentous-unstable test conditions (dashed line = standard deviation).

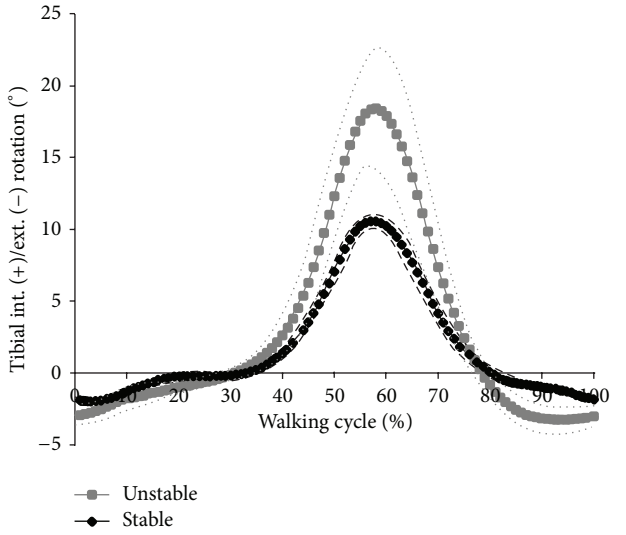


Figure 5: Tibial internal and external translation for ligamentous-stable and ligamentous-unstable test conditions (dashed line = standard deviation).

Leo, Oberkochen, Germany) at a magnification of 25,000. Size, morphology, and number of particles were determined [23–26] using an image analyzing software (Leica QWin V3, Leica Microsystems, Wetzlar, Germany). Implant kinematics (anterior/posterior translations and internal/external rotations) was recorded during the simulation and analyzed in each interval (every 500,000 cycles) using the simulator's own measurement system. Wear areas were documented photographically.

2.4. Statistics. Wear rates and kinematics were compared using Student's t test with a level of significance set at $P < 0.05$. All data is shown with mean ± standard deviation.

Wear particle characteristics are based on a high number of wear particles. Effect size was calculated according to Cohen [27] in order to compare wear particle characteristics between both tests.

3. Results

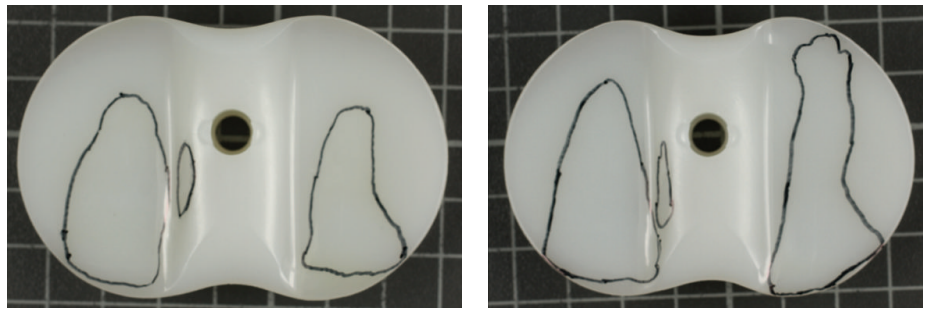
Wear progression of both tests is shown in Figure 3. Simulation under stable knee conditions resulted in a wear rate of 7.97 ± 0.87 mg/10^6 cycles. Simulation of an unstable knee resulted in a significantly increased wear rate of 14.58 ± 0.56 mg/10^6 cycles ($P \leq 0.001$).

Considerably higher kinematics was observed for the unstable knee compared to the stable knee (Figures 4 and 5). In comparison, internal/external rotation significantly increased from 12.62 ± 0.48° to 22.18 ± 4.48° ($P \leq 0.01$). Anterior/posterior translation increased significantly from 9.46 ± 0.29 mm to 14.30 ± 2.03 mm ($P \leq 0.01$). Higher rotations and translations for the unstable knee can be attributed to higher tibial internal rotation and higher tibial posterior translation during simulation. Wear areas are shown in Figure 6. Larger wear areas, particularly on the boundary areas (anterior and posterior) of the lateral plateau, were observed on the PE tested under ligamentously unstable knee conditions. No pitting or delamination was observed on the inserts.

Results of wear particle analysis are shown in Table 1. Wear particles are shown in Figure 7. Unstable knee conditions resulted in a higher number of generated wear particles (effect size 2.23). These particles were greater in size with a higher aspect ratio and a more irregular surface. However, only small effect sizes were determined for wear particle characteristics.

Table 1: Results of wear particle analysis.

	Unstable knee	Stable knee	Effect size
Particles analysed	2016	1510	
Estimated number of particles per 10^6 cycles	$1.09 * 10^{12} \pm 0.14 * 10^{12}$	$0.80 * 10^{12} \pm 0.12 * 10^{12}$	2.23
Equivalent circle diameter	$0.263 \pm 0.160\ \mu$m	$0.246 \pm 0.162\ \mu$m	0.11
Aspect ratio	1.776 ± 0.584	1.700 ± 0.504	0.14
Roundness	0.548 ± 0.151	0.577 ± 0.143	0.20
Form factor	0.657 ± 0.137	0.687 ± 0.120	0.23



(a) (b)

Figure 6: Wear areas on the PE for ligamentous-stable (a) and for ligamentous-unstable knee test conditions (b) (right knee in both figures).

4. Discussion

In this study, the stabilization and wear behavior of a high-conforming knee design with two different ligament settings were simulated. Simulation of ligamentous-unstable TKR resulted in higher tibial posterior translation and higher tibial internal rotation.

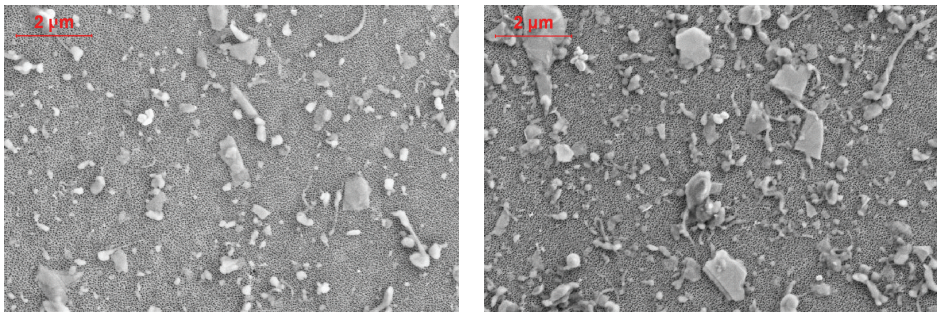
It is known that anterior/posterior translations are mainly constrained by the cruciate ligaments [19, 28–30]. The ACL is the main constraint to tibial anterior translation, whereas the PCL is the main constraint to tibial posterior translation. The MCL is only minimally involved in translation restraint [29]. Higher tibial posterior translation is a consequence of the loss of PCL functionality simulated in unstable knee conditions. However, the high-conforming design was not capable of compensating for this loss of functionality of the PCL.

ACL and PCL participate only to a small extent in rotational stabilization of the knee joint, whereas MCL is a main stabilizer for rotational movements [29, 30]. Due to the insertion points and sense of rotation, the cruciate ligaments are not able to effectively counter rotational torques. In contrast, the collateral ligaments have an appropriate lever arm to withstand rotational torques [30]. Higher rotations under unstable conditions indicate that the high-conforming design was not capable of compensating for the loss of MCL functionality. The high-conforming design was more susceptible to insufficient rotational stabilization (76% increase) than to translation stabilization (51% increase) when comparing both test conditions.

Larger wear areas were observed on the lateral plateaus especially when testing unstable knee conditions. This may be related to the concept of wear simulation. Restraint during simulation is the sum of replicated passive structures, friction of the articulation, and restraint via implant design. Reducing the restraint of the passive structures during simulation will increase kinematics when no substituting via design or friction is occurring. Simulation is run with higher axial loading on the medial plateau. This results in smaller kinematics on the medial plateau (pivot point) and higher kinematics on the lateral plateau. This is a limitation of this study. During simulation only the restraint of the passive structures is replicated. However, ligamentously unstable conditions do alter not only restraint characteristics but also the mechanics (alignment and force transmission) of the joint, which has been neglected in this study.

Results showed that ligamentous-unstable TKR resulted in highly increased wear rates with an increased number of generated wear particles. The increased wear may be due to increased kinematics. Increased secondary movements, especially the cross-shear ratio [31–33], are known to be related to higher wear.

Retrieval analysis of high-conforming TKR has been associated with an increased risk of wear-related failure [34]. Higher delamination and pitting were observed for high-conforming inserts after a short mean implantation duration of 18.6 months. However, this analysis was based on gamma-in-air sterilized PE, which is known to be susceptible to high, oxidation-related wear. In our study, no delamination or pitting was observed after 5 million cycles under ligamentously adverse conditions. Five million cycles correspond to 1–3 years of *in vivo* use based on the activity of the patient [35, 36]. Therefore, this study may indicate an increase in PE quality due to improvements in manufacturing and sterilization techniques.



(a) (b)

Figure 7: Example of analysed wear particles under ligamentous-stable (a) and for ligamentous-unstable knee test conditions (b). Relevant differences were observed in particular regarding the number of released wear particles.

Under standard laboratory test conditions, it remains unclear whether conformity of knee designs results in an increased or decreased wear behavior [16–18]. Thus, the question arises if the increase in wear rates under unstable ligamentous conditions can be considered clinically critical. In a recent publication, Engh Jr. et al. [37] measured wear radiographically in failed and successful TKR. TKRs associated with a lower survivorship had a two-third higher wear rate. Taking this ratio into context of the increase in wear rate found in this study, the unstable TKR conditions may elicit a clinically critical wear performance. However, besides wear rates, biological reactions depend on wear particle characteristics like composition, morphology, and number of particles [38, 39]. Small differences were observed regarding wear characteristics (size and morphology), but relevant differences were particularly found in the total number of released particles. This increase (36%) was smaller than the increase in wear rates, relativizing the poor wear results under ligamentous-unstable test conditions.

Typically, wear testing of TKR is carried out according to ISO standards. In these ISO standards, only the cruciate ligaments (ACL/PCL) are considered (sacrificed/retained). This seems to be appropriate as the ACL is typically sacrificed during TKR implantation and the absence or insufficiency of the PCL is seen commonly in clinical settings. However, deficient ligamentous conditions are clinically often related to traumatic and degenerative changes. Changes to isolated structures, as defined by ISO, are rare. They would mostly occur in several structures (e.g., capsule, cruciate, and collateral ligaments) to varying extents [40–44]. Additionally, in TKR, soft tissues characteristics are altered due to chronic inflammation, chronic tibiofemoral malalignment, and ligament balancing during surgery [40]. Therefore, replication of the complex individual ligamentous interactions is difficult and complicates the establishment of a standardized yet clinically relevant wear test.

In this study, the unstable ligament model was chosen as the worst case scenario since (1) PCL is known for its restraining role in tibial posterior translation [19, 28–30] and (2) the MCL is known for its restraining role against tibial rotation [29]. Recently, the ligament restraint system of the previous ISO standard [45] has been modified. In the new ISO standard [46], a laxer and triphasenal (restraint in two motion directions and neutral zone) restraint model was defined, aiming to better replicate *in vivo* conditions. These more lax ligament characteristics are comparable to ligament characteristics defined in this study, despite both approaches (ISO and this study) replicating different ligament conditions. However, only limited published data is available for wear testing according to the newly introduced ISO standard [32, 47]. Haider et al. [47] reported a high wear rate of 19.88 mg/10^6 cycles for a posterior-stabilized design without reporting the resulting kinematics. Recently, Grupp et al. [32] tested the wear behavior of a posterior-stabilized knee design, comparing the old ISO standard to the recently introduced one. A wear rate more than three times higher was reported when comparing the new to the old ISO standard. Additionally, significantly increased kinematics was observed. Kinematics increased for anterior/posterior translation by up to 41% and for internal/external rotation by up to 131%, when compared to the old, linear ISO standard. Depending on design features of the tested PS design, a mean wear rate of 17.1 mg/10^6 cycles and 18.5 mg/10^6 cycles was reported, which is comparable to the determined wear rate of the unstable knee in our study. However, when comparing kinematics to this study, the unstable knee resulted in kinematics approximately twice as high for translations as well as rotations. Thus, the resulting kinematics of this study is considered to be more critically than the observed increase in wear rates.

5. Conclusion

The tested high-conforming knee design resulted in increased tibial posterior translation and tibial internal rotations under ligamentous-unstable knee conditions. This can be related to insufficient stabilization via implant design. The tested design was not capable of compensating for the insufficient ligamentous stabilization.

The insufficient stabilization was accompanied by an increased wear related to higher kinematics. Increased wear

rates and a higher number of wear particles of comparable size and morphology were observed under ligamentously unstable test conditions.

Conflict of Interests

The authors declare that they have no conflict of interests regarding to the publication of this paper.

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Clinical Study

Serum Metal Ion Concentrations in Paediatric Patients following Total Knee Arthroplasty Using Megaprostheses

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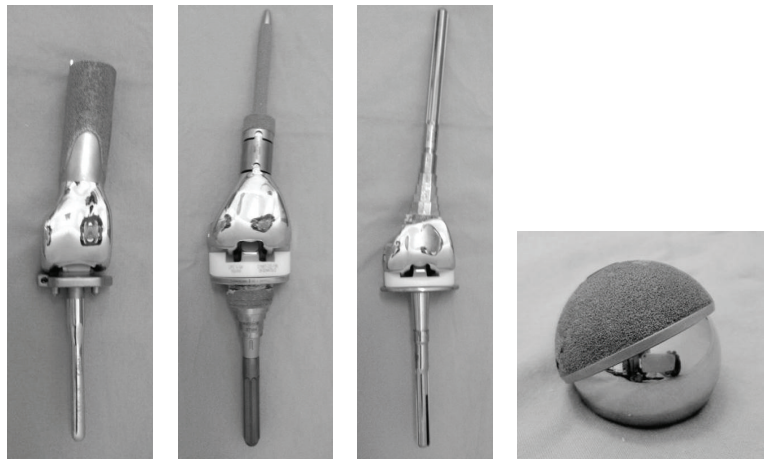
The purpose of this study was to determine the concentrations of cobalt, chromium, and molybdenum in the serum of paediatric tumour patients after fixed hinge total knee arthroplasty. Further, these metal ion levels were compared with serum metal ion levels of patients with other orthopaedic devices such as hip and knee prostheses with metal-on-metal or metal-on-polyethylene articulation to find differences between anatomical locations, abrasion characteristics, and bearing surfaces. After an average follow-up of 108 months (range: 67 to 163) of 11 paediatric patients with fixed hinge total knee arthroplasty, the mean concentrations for Co and Cr were significantly increased while Mo was within the limits compared to the upper values from the reference laboratory. Furthermore, these serum concentrations were significantly higher compared to patients with a standard rotating hinge device ($P = 0.002$ and $P < 0.001$) and preoperative controls ($P < 0.001$). On the other hand, the serum levels of patients following MoM THA or rotating hinge arthroplasty using megaprostheses were higher. Therefore, periodic long-term follow-ups are recommended due to the rising concerns about systemic metal ion exposure in the literature. Upon the occurrence of adverse reactions to metal debris the revision of the fixed hinge implant should be considered.

1. Introduction

The potential harmful effects of elevated systemic exposure to cobalt (Co), chromium (Cr), and molybdenum (Mo) are of increasing concern in the literature, especially following metal-on-metal (MoM) hip resurfacing or large diameter MoM total hip arthroplasty (THA) [1]. Bearing surfaces of implants might wear and release particles depending on the tribological pairing. Metal-on-metal articulations were introduced in an attempt to reduce this wear debris. Nevertheless, against all expectations, the short-, mid-, and long-term results of metal ion measurements following MoM THA as well as resurfacing arthroplasty revealed elevated levels of these metals in blood and urine, which represents the systemic exposure [1–9]. Further, it has been shown that high metal ion concentrations are toxic and known to interfere with biological functions [10–14].

Several studies showed serious local adverse reactions against metal debris (ARMD) such as delayed hypersensitivity reactions (ALVAL), osteolysis, pseudotumour formation, metallosis, and local soft tissue reactions such as inflammation and necrosis [1–5, 15–17]. Furthermore, there are three cases of Co intoxication following THA reported in the literature [6, 7, 9]. Overall, the number of revision surgeries due to high metal ion concentrations is still rising, especially following the recall of the ASR device (ASR XL Head and ASR resurfacing device, DePuy, Warsaw, IN).

On the other hand, there is only little data published concerning metal ion concentrations following reconstructions at other anatomical locations than the hip such as the spine or



(a) (b) (c) (d)

Figure 1: The different devices under investigation: (a) HMRS, (b) LPS, (c) S-ROM Noiles, and (d) ASR XL Head.

the knee joint. There are two studies in the literature reporting metal ion concentrations following total knee replacement [18, 19]. Further, Zeh et al. [20, 21] and Bisseling et al. [22] related metal ion concentrations following MoM total disc replacement (TDR).

Due to the current debate in the literature about potential disadvantages of MoM articulations, we decided to perform this study to evaluate if there is also a high metal ion release following total knee arthroplasty using fixed hinge megaprostheses. The aim was to determine the serum metal ion concentrations in paediatric patients following fixed hinge total knee arthroplasty after wide tumour resection. Furthermore, these concentrations were compared with serum metal ion levels of patients with other orthopaedic devices such as hip and knee prostheses with metal-on-metal or metal-on-polyethylene articulation. Therefore, the Co and Cr concentrations of patients with MoM total hip replacements were used from an ongoing trial as well as their preoperative metal ion levels. We also compared Co and Cr levels from patients with a standard rotating hinge device and patients with rotating hinge megaprostheses.

The hypothesis of the study was that serum metal ion levels in paediatric patients were higher than in patients with MoM THA or in patients with rotating hinge devices due to the fixed hinge metal-on-metal articulation pairing.

2. Patients and Methods

2.1. Study Population. From May 1998 to April 2006, 19 paediatric patients (12 male and 7 female) underwent total knee replacement using the fixed hinge Howmedica Modular Resection System (HMRS, Stryker Howmedica Osteonics, Rutherford, NJ; Figure 1(a)) following wide tumour resection around the knee. There were 14 distal femoral, four proximal tibial, and one total femoral replacement for 13 osteosarcomas and six Ewing sarcomas. All patients got neoadjuvant and adjuvant chemotherapy according to the corresponding protocol (COSS/EURAMOS, EUROWING). The mean age at operation was 14 years (range: 9 to 23) and the mean resection length was 20 centimeters (range: 10 to 45). All prostheses were manufactured from a cobalt-chrome-molybdenum alloy according to ISO 2007-4-211.

At time of evaluation, out of these 19 patients, three had died due to their underlying disease and three patients were lost to follow-up. Two patients did not want to participate in our investigation. Overall, 11 patients with a mean follow-up of 108 months (range: 67 to 163) were available for the current study.

2.2. Control Groups

2.2.1. Rotating Hinge Knee Groups (RHK). The characteristics of these patients have been described in a previous study [18]. There were 17 megaprostheses (Limb Preservation System; LPS/M.B.T., DePuy; Figure 1(b)) and eight standard rotating hinge devices (S-ROM Noiles, DePuy; Figure 1(c)). The mean follow-up was 35 months (range: 9–67 months) and all prostheses were manufactured from an ISO-certificated cobalt-chrome-molybdenum alloy (ISO 5832-4).

2.2.2. Total Hip Arthroplasty Group (THA). Thirty-two patients underwent metal-on-metal large diameter total hip arthroplasty between March 2007 and July 2008 (ASR XL Head, DePuy; Figure 1(d)). Patients' characteristics have been described in a previous study [23]. The prosthesis was manufactured from Co-Cr-Mo alloy according to ISO 5832-4.

For this study, the 12-month data and the 24-month data were regarded as controls because metal ion levels are known to be increased during a running-in period of approximately 6 to 24 months, after which they stabilize. Furthermore, the preoperative baseline metal ion concentrations of these 32 patients were used as controls.

2.3. Blood Collection and Serum Metal Ion Analysis. Blood was taken using stainless-steel needles attached to no additive plastic vacuum tubes (VACUETTE, Greiner Bio-One GmbH,

Table 1: Demographic data of the study population and mean metal ion levels in μg/L (range) in the different prosthesis groups. The P value indicates differences between several implant groups compared to the fixed hinge group. Furthermore, correlations between Co and Cr levels in the implant groups as well as metal ion concentrations and follow-up are shown (THA: total hip arthroplasty; RHK: rotating hinge knee arthroplasty; yr/yrs: year/years; mths: months; FU: follow-up).

	Fixed hinge prostheses ($n = 11$)	Preoperative THA ($n = 32$)	MoM THA 1 yr ($n = 32$)	MoM THA 2 yrs ($n = 32$)	Standard RHK ($n = 8$)	Megaprostheses RHK ($n = 17$)
Mean age (yrs)	14 (10 to 23)	52 (40 to 61)	n.a.	n.a.	73 (60 to 81)	49 (15 to 83)
Sex ratio (m : f)	9 : 2	17 : 15	17 : 15	17 : 15	4 : 4	12 : 5
Mean follow-up (mths)	108 (67 to 163)	n.a.	12 (12 to 12)	24 (24 to 24)	37 (15 to 62)	34 (9 to 67)
Co serum (μg/L)	4.7 (0.4 to 12.8)	0.3 (0 to 5.4)	6.0 (0 to 58.5)	9.3 (0.3 to 78.2)	0.3 (0 to 0.7)	7.5 (0 to 47.0)
Cr serum (μg/L)	4.01 (1.48 to 8.91)	0.68 (0.07 to 7.53)	5.86 (1.11 to 26.56)	8.31 (0.71 to 51.98)	0.33 (0.06 to 0.95)	2.98 (0.12 to 24.90)
P value Co/Cr	—	<0.001/<0.001	0.852/0.731	0.501/0.235	0.002/<0.001	0.312/0.002
Correlation Co : Cr	0.742 ($P = 0.009$)	0.945 ($P < 0.001$)	0.869 ($P < 0.001$)	0.967 ($P < 0.001$)	0.764 ($P = 0.027$)	0.945 ($P < 0.001$)
Correlation Co : FU	0.240 ($P = 0.476$)	x	x	x	0.099 ($P = 0.816$)	0.300 ($P = 0.242$)
Correlation Cr : FU	0.137 ($P = 0.688$)	x	x	x	0.007 ($P = 0.987$)	0.373 ($P = 0.140$)

Kremsmünster, Austria). All needles and tubes were from the same batch. None of the patients had a history of renal impairment. All specimens were centrifuged at 4000 rpm within 2 hours and stored at −10°C until analysis. The concentrations of Co, Cr, and Mo were determined using electrothermal graphite furnace atomic absorption spectrometry (ET ASS) in an external laboratory (Medizinische und chemische Labordiagnostik Lorenz & Petek GmbH, Graz, Austria). The levels of metal ions in the serum were recorded in concentrations expressed as μg/L. The results were analysed in order to calculate the mean level of each ion in the plasma and the detection limits were 0 to 0.5 μg/L for Co, 0 to 1.9 μg/L for Cr, and 0 to 1.0 μg/L for Mo.

2.4. Statistical Analysis. The collected data was processed for statistical differences between the different implant groups. Due to the asymmetric distribution of all parameters nonparametric tests (*Kruskal-Wallis test, Mann-Whitney U test*) were used. Additionally, the correlation between the metal ions was determined using the Pearson correlation coefficient. A P value of <0.05 was considered to be statistically significant. For statistical analysis the PASW Statistics 16.0 program (SPSS Inc., Chicago, IL) was used.

3. Results

The characteristics and results of all implant groups are presented in Table 1 and Figure 2.

3.1. Study Population. The concentrations of Co, Cr, and Mo in the serum of paediatric patients with fixed hinge megaprostheses were 4.7 μg/L (range: 0.4–12.8 μg/L), 4.01 μg/L (range: 1.48–8.91 μg/L), and 0.6 μg/L (range: 0.1–0.9 μg/L). Compared with the upper limits of the reference values from the laboratory, the values for Co (normal range: 0–0.5 μg/L) and Cr (normal range: 0–1.9 μg/L) were increased ninefold and twofold, respectively, while Mo (normal range: 0–1.0 μg/L) was within the physiological limits. Nevertheless, the average concentrations of Co and Cr were within the internationally accepted limits of 2.0 μg/L to 7.0 μg/L at which a regular follow-up is recommended [24, 25].

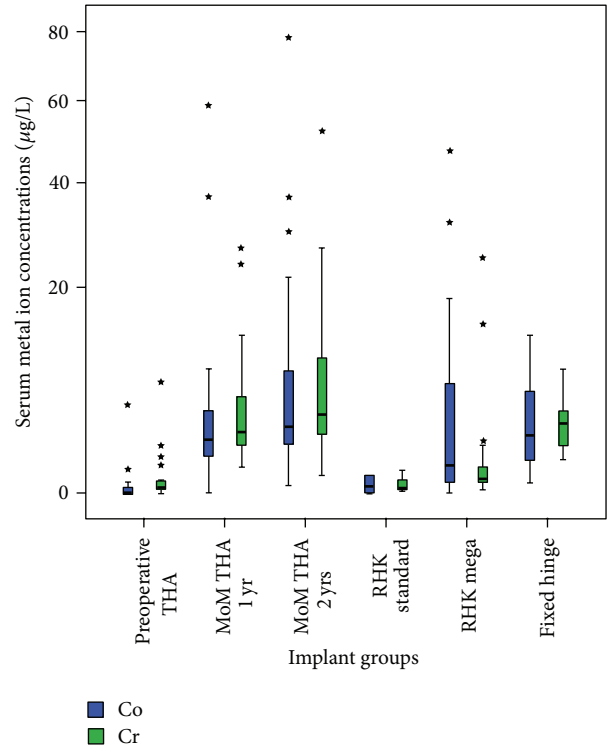


Figure 2: Box plot showing the cobalt and chromium serum metal ion levels in the fixed hinge megaprosthesis group in proportion to the other prostheses and the control group. Patients with fixed hinge devices had higher concentrations of Co and Cr in the plasma compared to preoperative controls and patients with a standard rotating hinge device. These differences reached a statistically significant difference (Table 1).

Statistical analysis showed that there was no correlation between implant length, follow-up, and serum metal ion concentrations neither for Co nor for Cr (Table 1).

3.2. Fixed Hinge Megaprostheses versus Control Groups. The serum concentrations of Co and Cr in the paediatric patients following fixed hinge total knee arthroplasty were significantly higher compared to the preoperative THA controls (Co and Cr: $P < 0.001$, Mann-Whitney U test) and the group with the standard rotating hinge device (Co and Cr: $P = 0.002$ and $P < 0.001$, Mann-Whitney U test, Table 1). On the other hand, the serum metal ion levels of patients following MoM THA were higher at one and two years of follow-up likened to the fixed hinge group, although these differences were not statistically significant (Table 1).

Interestingly, the serum concentrations of Co were higher in the patient group with the rotating hinge megaprosthesis, while the Cr values in this group were lower compared to the paediatric patients with the fixed hinge prosthesis. The difference between the Co concentrations was not statistically significant ($P = 0.312$) while the Cr levels were significantly higher in the fixed hinge group ($P = 0.002$, Mann-Whitney U test, Table 1).

There was a positively significant correlation between serum Co and Cr concentrations in all implant groups under investigation (Pearson correlation coefficient, Table 1).

4. Discussion

The current study revealed increased serum levels for Co and Cr in paediatric patients following fixed hinge total knee arthroplasty using megaprostheses in comparison to several other implant groups as well as the preoperative controls (Table 1). As expected, referring to previous published data, the values for Mo were within the limits [4, 18, 26–29]. On the other hand, patients with rotating hinge megaprostheses and patients with MoM THA revealed higher serum metal ion concentrations compared to the fixed hinge megaprostheses group although these differences were not statistically significant.

Nevertheless, the hypothesis of this study was not supported by the current results. However, continued long-term follow-up is strictly recommended because especially young patients might suffer from possible late effects of chronic, high systemic metal ion exposure with unknown pathologic effects.

Regarding the official guidelines of the EFORT and AAOS societies for MoM THA, the concentrations of Co and Cr were within the accepted limits of 2.0 μg/L to 7.0 μg/L at which a regular follow-up is recommended [24, 25], although there are no standards defined for other orthopaedic devices than the hip. Nonetheless, the authors believe that these guidelines should also be accepted for other orthopaedic devices, especially with metal-on-metal articulation, to perform continued follow-ups with metal ion determination due to the potential harmful effects of high Co and Cr levels. Further, the systemic toxicity of high Co and Cr levels is always the same and is independent of the type of device.

One limitation of the study is the absence of preoperative concentrations of Co and Cr in the serum of patients with fixed hinge and rotating hinge knee prostheses. Another limitation was that only a small number of patients were enrolled in the study but it was not possible to include further patients because the device under investigation has been pulled from the market several years ago. Furthermore, it should be noticed that there are differences between the follow-ups of the different implant groups. Patients with fixed hinge had the longest follow-up but we do not think that this difference is a major confounding factor because all patients have passed the running-in phase of the implant and the metal ion levels must have stabilized. In addition, statistical analysis did not show any correlation between time of follow-up and serum metal ion concentrations in the different groups.

On the other hand, it should be noted as significant benefit that this is the first study evaluating the increase of serum metal ion levels in paediatric patients following fixed hinge total knee arthroplasty using megaprostheses. Further, these results were compared to the concentrations of different other implant groups. All samples of each group were evaluated at the same laboratory using the same study protocol.

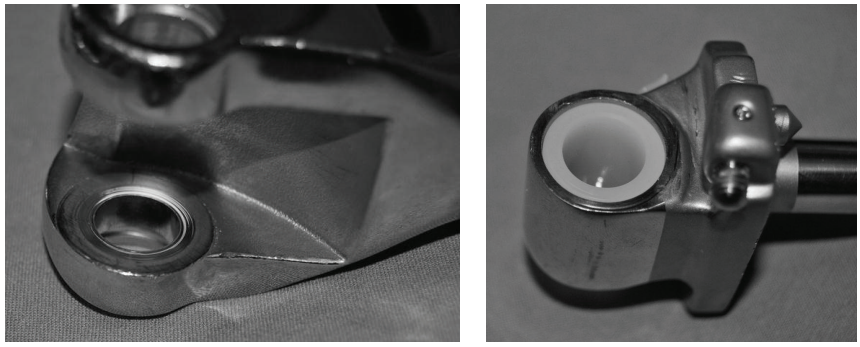
An explanation for the increased concentrations of Co and Cr might be corrosion of the implants, which is known to be proportional to the surface area of the components, and abrasive wear of the soft tissues. Furthermore, metal ions might also be released from the conical junctions of the modular parts from the implants due to fretting.

Our data also shows that the implant's size (mean resection length: 20 cm) might also play an important role, because patients with megaprostheses (fixed hinge and rotating hinge) showed higher concentrations of Co and Cr than patients with a standard rotating hinge device, although there was no correlation between serum metal ion levels and implant size [18].

Another reason for increments of Co and Cr in the fixed hinge group might also be the abrasive wear of the polyethylene bushes at the side of the hinge axle and the direct metal-on-metal contact (Figures 3(a) and 3(b)). Nevertheless, we are unable to provide a safe range of Co and Cr concentrations in the serum because of the wide variation of levels encountered and, therefore, it can be stated that there is a long-term ion release following fixed hinge total knee arthroplasty as observed after rotating hinge total knee arthroplasty [18].

Local soft tissue reactions, delayed hypersensitivity reactions, or development of soft tissue formations like pseudotumours as results of metal ion debris seems to be unlikely following total knee arthroplasty using megaprostheses neither with fixed hinge nor with rotating hinge articulation. Nevertheless, there are two cases of soft tissue masses posterior to the implant following MoM TDR and one case of a wear debris induced pseudotumour seven years following TKA reported in the literature [30–32].

Another observation we made at revision of fixed hinge megaprostheses was periprosthetic metallosis, whereas metal debris can be found in the joint fluid as well as the surrounding soft tissues including the synovial layer and joint capsule (Figure 4).



(a) (b)

Figure 3: (a) The femoral and (b) the tibial component of an explanted HMRS megaprosthesis. At the side of the hinge there is a direct metal-on-metal articulation clearly with signs of metal debris (scratches and striation).

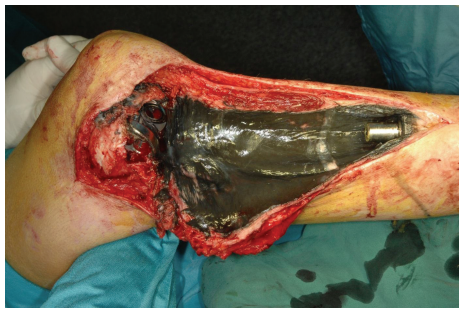


Figure 4: Intraoperative photograph at revision of a fixed hinge megaprosthesis in a 20-year-old male patient showing a marked metallosis in the periprosthetic soft tissues of the lower leg 119 months after implantation.

Significant factors associated with metal wear are patient's activity, weight, type of articulation (constrained versus nonconstrained), implant's design and geometry, bearing surfaces, alignment, and inlay's quality as well as high contact stresses. Furthermore, corrosion of the implant might play another important role for metallosis [32–34] Romesburg et al. [35] related that titanium components seem to have an increased association with metallosis when compared to Co-Cr implants [36]. On the other hand, Willis-Owen et al. [37] reported early metallosis after TKA in 15 Co-Cr knees needing revision of the implant combined with complete synovectomy. In this series, the complications were associated with a failure in manufacturing of the implant.

5. Conclusion

To the author's best knowledge, this is the first study reporting serum metal ion concentrations in paediatric patients and young adults following limb salvage surgery using orthopaedic megaprostheses.

(1) Determination of serum metal ion concentrations revealed significant increments for Co and Cr following fixed hinge total knee arthroplasty using megaprostheses. The measurement values were comparable to the results of rotating hinge megaprostheses despite the different articulation mechanisms. Therefore, we believe that there should be a cause of concern due to long-term exposure to Co and Cr when using this type of prosthesis.

(2) Further, periprosthetic metallosis was observed at revision surgery which might cause problems like osteolysis and aseptic loosening. On the other hand, there was no correlation between implant size and serum metal ion levels, probably brought about by the small number of patients enrolled in the current series. Nevertheless, serum metal ion levels might be used as indicator for periprosthetic metallosis.

(3) Upon the occurrence of adverse reactions to metal debris or intoxications, independently of serum metal ion concentrations, the revision of the fixed hinge implant to the rotating hinge device or another reconstruction method should be considered.

Ethical Approval

This study was approved by the Ethics Committee and informed consent was obtained from all patients.

Disclosure

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this paper.

Conflict of Interests

All authors disclose that there were not any financial and personal relationships with other people or organizations that could inappropriately influence the work.

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Clinical Study

Early Results of a New Rotating Hinge Knee Implant

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Background. Indication for rotating hinge (RH) total knee arthroplasty (TKA) includes primary and revision cases, with contradictory results. The aim of this study was to report prospective early results of a new modular rotating hinge TKA (EnduRo). For this implant several new design features and a new bearing material (carbon-fiber reinforced poly-ether-ether-ketone) have been developed. Furthermore, we tried to establish a new classification of failure modes for revision TKA. *Methods*. 152 EnduRo rotating-hinge prostheses were implanted in two centers. In 90 patients a primary implantation has been performed and 62 patients were revision cases. Knee Society Score (KSS), Western Ontario and McMaster Osteoarthritis Index (WOMAC), Oxford Knee Score (OKS), and Range of motion (ROM) were assessed before surgery, 3 months postoperatively, 12 months postoperatively, and annually thereafter. We defined 3 types of complications: Type 1, infection; type 2, periprosthetic complications; type 3, implant failures. *Results*. KSS, WOMAC, OKS, and ROM revealed significant improvements between the preoperative and the follow-up investigations. There were 14 complications (9.2%) leading to revision surgery, predominantly type 2. *Conclusion*. Our study shows excellent clinical results of the EnduRo TKA. Furthermore, no premature material failure or unusual biological response to the new bearing material could be detected.

1. Introduction

The rate of revision total knee arthroplasties (TKAs) is steadily increasing [1]. The main reasons are infection, aseptic loosening, instability, and microdebris-related osteolysis. With increasing numbers of severe cases with bone loss, instability, and comminuted distal femoral fractures, a more constrained prosthesis such as a rotating hinge TKA is often warranted [2, 3].

Hinged prostheses were first designed and used for reconstruction after wide resection of neoplasms around the knee joint. The initial joint mechanism consisted in a fixed hinge with no rotational motion. This led to high rates of early loosening, osteolysis, and excessive wear due to the highly restricted biomechanics [4–6]. A second generation modified several aspects (rotational axis with a stop, new design of the patellofemoral joint to facilitate patella tracking, use of a metallic tibial baseplate to reduce polyethylene wear, and improvements in the stem design to facilitate osteointegration). In order to avoid torsional stresses on the bone implant interface flexing and rotating models have been introduced. This design aims to avoid early aseptic loosening of the prosthesis [7–11].

There are several indications for the use of rotating hinge knees (RHK). In severe primary osteoarthritis (excessive varus-/valgus deformities, Charcot knees, and rheumatoid arthritis) as well as in revision-cases of TKA rotating hinge prostheses are necessary to compensate for ligamentous instability as well as for severe bone loss [2, 4, 12, 13].

Several authors have studied the results of rotating hinge TKA for various types of prosthesis. However, their conclusions are contradictory. Certain authors seem to consider

such devices to be useful mainly in salvage procedures after numerous failed revisions, whereas others have described encouraging outcomes [6, 14–16]. There are only a few prospective studies with a follow-up of more than two years of rotating hinge TKA in nontumour cases.

The EnduRo prosthesis (Aesculap AG, Tuttlingen, Germany) represents a new modular rotating hinge design. It is characterized by transmission of force from the femoral component to the tibial component via the polyethylene insert with high contact area. Therefore, the hinge is not primary weight bearing. In order to address certain anatomical situations it offers an offset option and wedges for the tibial and the femoral components. Additionally, it contains carbon-fibre reinforced poly-ether-ether-ketone (CRF-PEEK) flanges and bushings firstly used as a bearing material in TKA [17]. Biotribological in vitro studies showed decreased wear for this implant [17]. Furthermore an in vivo murine model showed similiar biological response to CFR-PEEK, if compared to polyethylene debris particles [18].

The aim of the present clinical study was to investigate prospectively the functional and radiographic results of the EnduRo rotating hinge TKA in a short-term clinical follow-up with regard to the newly introduced bearing material. Also, a new classification of failure modes of rotating hinge TKA has been established in order to gain better information about implant survivorship.

2. Patients and Methods

2.1. Study Population. The study received ethical approval from the regional institutional review board (Ref. number 703/2009). An informed consent was given by every patient. Our study is a prospective clinical two-center study. Between November 2008 and December 2012, 152 EnduRo rotating hinge prostheses were implanted at two different orthopaedic centers center 1: ($n = 59$) and center 2: ($n = 93$). Mean age at the time of implantation was 72.3 years (SD 9.3; range 48.0–90.0). Mean body weight was 85.0 kg and height 168.4 cm resulting in an average body mass index (BMI) of 29.8 (SD 6.3, range 15.0–50.0). There were 47 male and 105 female patients. In 90 patients a primary implantation has been performed and 62 patients were revision cases where the EnduRo RHK was used. In center 1 the ratio of primary to revision was 44% to 56% and in center 2 69% of the patients received the device as a primary and 31% as a revision implant. Demographic parameters are illustrated in Table 1. Data collection included demographic information, a complete medical history, and the indication for primary or revision TKA.

Indications for primary arthroplasty with the EnduRo system included severe varus or valgus osteoarthritis (more than 20°) with substantial ligamentous instability, rheumatoid arthritis with ligament laxity, and posttraumatic and postinfectious gonarthrosis. Indications for revision arthroplasty included septic or aseptic loosening as well as instability after primary total knee arthroplasty including flexion extension gap mismatch. Table 1 shows the indications of the patients of the present study.

Table 1: Demographic and indication parameters of 152 study cases.

Age (mean, range)	72.3; 48–90
Body mass index (mean, range)	29.8; 15–50
Male/female	47/105
Primary	**90 (59.2%)**
Severe primary (varus/valgus/instable)	85 (55.9%)
Rheumatoid arthritis	1 (0.7%)
Posttraumatic arthritis	3 (1.9%)
Postinfectious arthritis	1 (0.7%)
Revision	**62 (40.8%)**
Septic loosening	19 (12.5%)
Aseptic loosening	20 (13.2%)
Instability after primary TKA	23 (15.1%)

The diagnosis of septic or aseptic loosening, respectively, was based on a thorough clinical, radiographic, and microbiological examination combined with laboratory studies including leukocyte counts, sedimentation rate, and C-reactive protein. The preoperative diagnoses have been confirmed by histologic analysis and bacterial cultures.

2.2. Type of Prosthesis. The EnduRo prosthesis was used in all patients. It is a modular rotating hinge prosthesis with primary transmission of force from the femur via the polyethylene (PE) insert to the tibial part of the prosthesis. The contact area between the metal and the PE surface is considerably high with a minimum of 800 mm^2 during the entire range of motion (ROM). The axis is not primarily weight bearing but provides stability of the joint in case of severe coronal or sagittal instability. The axes are embedded in bushings and flanges made of PEEK-Optima LT1 (Invibio Ltd., Thornton-Cleveleys, UK) with a carbon-fiber reinforcement containing 30% polyacrylonitrile- (PAN-) based carbon fibers (CFR-PEEK LT1 CA 30) firstly used as a bearing articulation in TKA in order to minimize wear and creep [17, 19]. The prosthesis is designed for a ROM from 3° of hyperextension to 135° of flexion. Augments are available as tibial and femoral wedges in different heights. The prosthesis provides an offset option for femoral and tibial stems. Fixation of the stem is available as cemented or cementless, whereas the epiphyseal fixation of the prosthesis is always cemented.

2.3. Surgical Procedures. All 152 surgical procedures have been carried out through a medial parapatellar arthrotomy. Patients were given a perioperative antibiotic prophylaxis with Cefazolin (3×2 g) or Clindamycin (3×600 mg). In case of two-stage revision arthroplasty due to septic complication antibiotic therapy was chosen according to microbiologic cultures and sensitivity and given for at least 6 weeks between stages and for 6 weeks (range 6 to 13 weeks) after the second stage procedure using the EnduRo RHK. Thrombotic prophylaxis was used with low-molecular weight heparin

(40 mg–60 mg/day) starting 12 hours before surgery continuing for 6 weeks postoperatively. A tourniquet was used before osteotomies have been carried out and released after implant fixation. All implants were implanted in the hybrid technique with cemented femoral and tibial epiphyseal fixation and uncemented stems. Gentamycin containing cement (Palacos R + G, Heraeus, Hanau, Germany) and vacuum cementing technique were used. The patella was routinely resurfaced and a lateral release was undertaken when necessary to achieve satisfactory patellar tracking. The postoperative management was similar for all patients with the use of crutches or a walker as long as needed and with partial to full weight bearing as tolerated.

Primary procedures were carried out in 90 and revision procedures were carried out in 62 knees, whereas in center 1 the ratio primary/revision was 26/33 and in center 2 it was 64/29 (Figures 1 and 2).

2.4. Clinical Outcome and Patients Satisfaction Measures. Clinical outcome of patients was assessed using the Knee Society Score (KSS clinical, function) [20], the Western Ontario and McMaster Osteoarthritis Index (WOMAC) [21], and the Oxford Knee Score, a 12-item patient-reported score [22]. Range of motion (ROM) was measured passively with a goniometer with the patient in supine position. Examinations were carried out before surgery, 3 months postoperatively, 12 months postoperatively, and annually thereafter.

2.5. Radiographic Analysis. Standard anteroposterior and lateral digital projection radiographs of the knees were obtained using Siemens Aristos digital radiographic workplace (Siemens, Erlangen, Germany). All imaging was performed at 57–63 kV and exposure values of 8–12 mAS. (Figures 1 and 2). Evaluation was done by 2 independent observers using standard pacs system (Impax Agfa health care, Mortsel, Belgium). Interobserver reliability was assessed by comparing radiologic reports. Radiographic analysis included assessment of alignment, signs of loosening such as component migration, radiolucent lines of >2 mm, presence of cement fracture or prosthetic/peri-prosthetic fracture, osteolysis, and wear, according to the appropriateness criteria of the American College of Radiology.

2.6. Complications. Complications were defined as complications leading to revision surgery of the involved knee. We defined 3 types of complications: type 1, infection; type 2, periprosthetic complications such as periprosthetic fracture, extensor mechanism failure, patella problems, and wound healing disturbances; type 3, implant complications such as aseptic loosening, wear, implant failure (fracture of axis, bushings, and stem), and instability. Type 1 complications (infections) and type 2 complications (periprosthetic complications) occur with no or little impact of the prosthesis on complications, whereas type 3 complications give information about survivorship of the implant.

2.7. Statistical Analysis. Two-sided tests were used in order to determine statistical significance. The level for statistical significance was set to 0.05 for all tests. Student's t test and analysis of variance (ANOVAs) were performed for continuous variables (age, BMI, hospital stay, and operation time).

Chi-squared tests were used for categorical variables (gender, diagnosis, and complication rate). Survival rates were estimated by Kaplan-Meier method and analyzed by Cox regression. Dunnett's test was used for comparisons of postoperative scores to the preoperative score to control the first type error. All regression analyses were adjusted for age, gender, BMI, and preoperative values. Statistical analysis was performed using SAS 9.2 (SAS Inc. Chicago, IL) and STATA 12.1 (StataCorp, College Station, TX).

3. Results

3.1. Clinical Parameters. Results are presented in Table 2. The outcome scores revealed statistically significant improvements between the preoperative and the follow-up investigations. The WOMAC score was 4.85 (SD 2.06) presurgically and 1.86 (SD 1.60) at 3 months, 1.66 (SD 1.88) at 12 months, and 1.62 (SD 1.67) at 24 months after surgery. The Oxford Knee Score improved from 19.1 (SD 8.1) to 33.0 (SD 8.2), 34.6 (SD 9.0), and 35.8 (SD 8.7), respectively. The Knee Society Score (KSS) improved from 26.1 (SD 16.0) preoperatively to 84.0 (SD 14.6), 85.2 (SD 14.6), and 89.0 (SD 14.7). Knee Society Score function (KSSf) was 38.6 (SD 23.8) prior to surgery and 57.8 (SD 23.2), 64.8 (SD 20.3), and 65.6 (SD 21.3) at the respective timepoints. ROM increased from 94.4° (SD 32.3°) before surgery to 110.1° (SD 14.0°), 114.1° (SD 12.2°), and 119.0° (11.5°). The clinical parameters for primary and revision cases are shown in detail in Table 2.

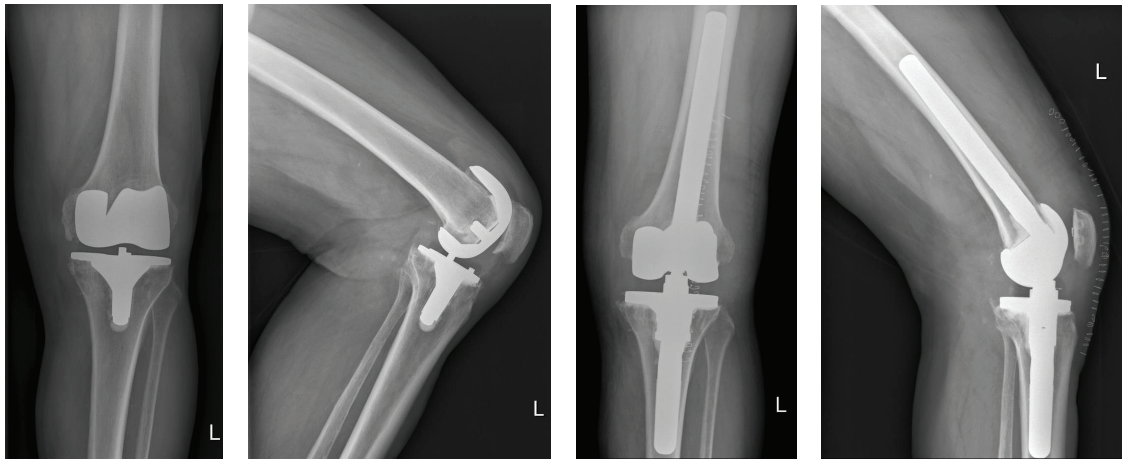
There was a significant influence of the indication for surgery (primary or revision) on the outcome. We found significant better scores preoperatively as well as postoperatively when the procedure was carried out as primary arthroplasty (Table 3).

There was significant impact of gender ($P = 0.043$), diagnosis ($P = 0.006$), and timepoint of followup ($P = 0.011$) on the postoperative improvement in terms of KSS clinical score. Female patients as well as revision procedures showed inferior results (Table 4(a)). For KSS function preoperative score ($P < 0.0001$), gender ($P = 0.018$), and timepoint of followup ($P = 0.011$) had significant influence (Table 4(b)). There was no impact of center and age on KSS.

3.2. Radiologic Results. In our cohort no interobserver variability could be detected. In patients with type 2 (periprosthetic complications) and type 3 complications (implant failure) radiologic irregularities were reported by both observers. In all other patients there were no signs of radiologic complications reported by both observers.

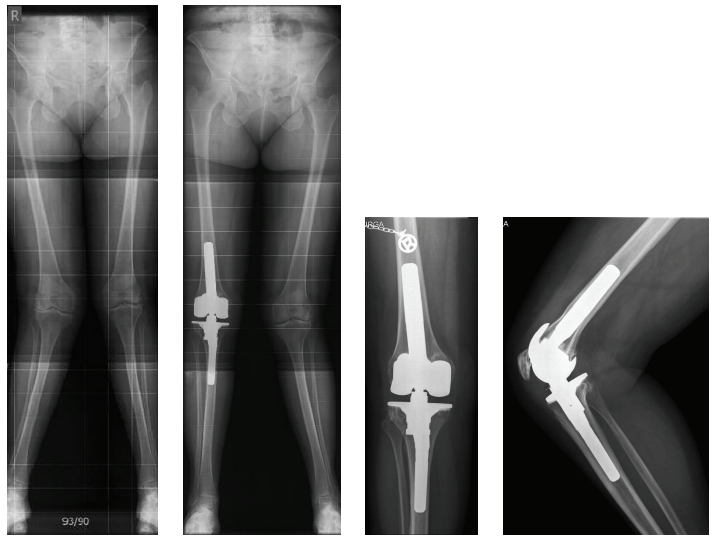
3.3. Complications. There were 14 complications (9.2%) leading to revision surgery.

Type 1. Deep infections occurred in 5 cases (4 patients; 3.3%) and were treated by two-stage revision procedure with implant removal, spacer implantation, and reimplantation of



(a) (b) (c) (d)

Figure 1: (a) Radiographs of aseptic loosened TKA in 77-year-old male—ap view. (b) Radiographs of aseptic loosened TKA in 77-year-old male—lateral view. (c) Postoperative X-rays after one stage revision with EnduRo RHK—ap view. (d) Postoperative X-rays after one stage revision with EnduRo RHK—lateral view.



(a) (b) (c) (d)

Figure 2: (a) Preoperative long standing X-ray of 73-year-old female with 22° valgus deformity. (b) Postoperative longstanding X-ray. (c) Detail X-ray—ap view. (d) Detail X-ray—lateral view.

an EnduRo RHK (4 cases) and 1 tumor prosthesis (distal femoral replacement, Modular Rotating Hinge, Stryker, Warsaw, USA).

Type 2. Complications occurred in 6 patients (3.9%): two periprosthetic fractures have been treated with locking plate osteosynthesis; 2 extensor mechanism ruptures and 2 patella dislocations have been treated by extensor mechanism reconstruction and postoperative immobilisation for 2–6 weeks.

Type 3. Prosthesis complications were seen in 3 patients (2.0%): 2 aseptic loosening of the femur were treated by one stage revision with revision of the femoral part in hybrid technique in one and cemented in the other. One loose tibial rotational axis locking screw was revised by a new fixating screw.

Regression analysis revealed a higher risk of reoperation for revision cases than for primary implantations (HR: 6.00, 95% confidence interval (CI): 1.76–20.47, $P = 0.004$). In revision cases the subgroup of septic loosening showed the highest tendency but no significance for reoperation (HR: 3.14, CI: 0.85–11.54, $P = 0.08$). Furthermore high baseline WOMAC score was associated with a decreased risk for

Table 2: Outcome parameter total and in primary and revision cases.

	Preoperative	3 months	12 months	24 months
WOMAC (mean; STD)	**4.9; 2.1**	**1.9; 1.6**	**1.7; 1.9**	**1.6; 1.7**
Primary (mean; STD)	4.5; 2.0	1.6; 1.4	1.3; 1.5	1.2; 1.2
Revision (mean; STD)	5.3; 2.1	2.3; 1.8	2.3; 2.3	2.3; 2.0
Oxford Knee Score (mean; STD)	**19.1; 8.1**	**33.0; 8.2**	**34.6; 9.0**	**35.8; 8.7**
Primary (mean; STD)	20.4; 7.8	34.9; 7.8	36.4; 8.2	39.4; 6.1
Revision (mean; STD)	17.2; 8.3	29.9; 8.1	31.7; 10.0	30.4; 9.7
KSS clinical (mean; STD)	**26.1; 16.0**	**84.0; 14.6**	**85.2; 14.6**	**89.0; 14.7**
Primary (mean; STD)	22.5; 14.3	86.0; 13.7	87.7; 12.7	94.1; 8.0
Revision (mean; STD)	31.5; 17.0	80.7; 15.5	80.9; 16.5	81.4; 18.9
KSS function (mean; STD)	**38.6; 23.8**	**57.8; 23.2**	**64.8; 20.3**	**65.6; 21.3**
Primary (mean; STD)	43.1; 24.3	61.2; 22.5	66.5; 19.7	72.1; 14.0
Revision (mean; STD)	32.2; 21.8	52.3; 23.6	61.9; 21.1	56.0; 26.4
ROM (mean; STD)	**94.4; 32.3**	**110.1; 14.0**	**114.2; 12.2**	**119.0; 11.5**
Primary (mean; STD)	103.3; 21.2	112.8; 11.2	115.7; 11.4	120.3; 9.1
Revision (mean; STD)	81.2; 40.7	105.8; 17.0	111.4; 12.9	117.2; 14.3

Table 3: *P* values for outcome scores in comparison of primary and revision procedures.

	Preoperative	3 months	12 months	24 months
WOMAC	0.0308	0.0114	0.0083	0.0084
Oxford Knee Score	0.0182	0.0007	0.0072	<0.0001
KSS clinical	0.0006	0.0470	0.0117	0.0006
KSS function	0.0053	0.0368	0.2386	0.0027
ROM	<0.0001	0.0047	0.0777	0.3056

reoperation (HR: 0.656, CI: 0.44–0.96, $P = 0.037$). There was no impact of age, gender, BMI, or center on revision rate.

3.4. Survival Analysis. The overall survivorship with revision for any reason as endpoint was 85.4% (CI: 75.6–91.5) at 2 years. The implant associated survivorship was 92.1% (CI: 81.5–96.8) (Figure 3).

Table 4: Results of regression analyses for the influence of different parameters on the KSS clinical score and function. KSS_f0 (KSS function preop.), KSS_k0 (KSS clinical preop.), DiagKat2 (diagnosis primary or revision), and FUKat2 (timepoint of followup).

(a) KSS clinical

Effect	*P* value
Kss1_k0	0.5238
Age	0.5574
Gender	0.0427
DiagKat2	0.0006
FUKat	0.0109
Center	0.8122

(b) KSS_function

Effect	*P* value
kss_f0	<0.0001
Age	0.2225
Gender	0.0183
DiagKat2	0.1460
FUKat	0.0007
Center	0.1456

4. Discussion

The number of primary and revision TKA is increasing. Many knee surgeons recommend in case of revision surgery designs with the lowest level of constraint possible [6]. Problems with conventional constrained TKA were early aseptic loosening and implant failure due to highly restricted biomechanics. Traditionally, transmission of force was conducted by the hinge axis of the implant. The design of the implant presented in this study addresses this problem by shifting force transmission through the condylar area with additional rotational motion around the tibial axis. Therefore, decreased shear stress is applied to the bone-implant interface. In this prospective study we present early results of a new rotating hinge TKA implant in a fairly high number of patients. The results of the present study reveal favourable results in terms of functional improvement and ROM. The overall survival rate was 85.4%. Patients, who received the implant in revision surgery, experienced a six times higher risk of reoperation than patients after primary implantation. We introduced a new classification for TKA complications to receive more information about prosthesis failure. Type 1 complications (infections) occur unrelated

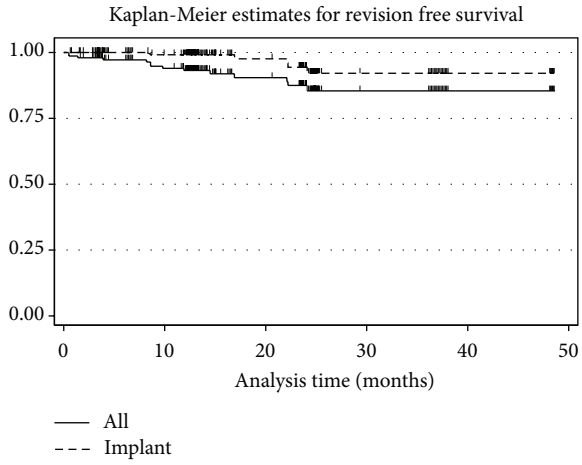


Figure 3: Kaplan-Meier survival curves; total and implant survival.

to the prosthesis. In type 2 complications (periprosthetic complications) surgical technique and tissue quality seem to play a certain role rather than the implant design. Type 3 complications (implant failures) give information about survivorship of the prosthesis. The most common type of complication was periprosthetic complications (type 2). They occurred in 3.9% of our cases.

There are some limitations associated with the present study. First, there is a relatively short follow-up period presented. However, infection, aseptic loosening, and mechanical failure occur most frequently within the first two years after implantation [1, 3, 6, 14]. Therefore, we do think that preliminary results provide reasonable information to the academic community especially when a new implant with clinically unproven design features and CFR-PEEK as a new bearing material is used. Second, we followed only 62 patients at two years, as the other patients did not reach the two-year followup yet. This fact was considered in our statistics and 62 patients represent an acceptable high number especially for rotating hinge studies.

The results of the present study reveal an improvement of KSS from 26.1 to 85.2 and 89.0 one and two years postsurgically, respectively, and of KSS function (f) from 38.6. to 64.8 and 65.6. There was only a slight increase between one and two years postoperatively. Westrich et al. [23] reported in 24 rotating hinge TKAs (9 primary/15 revisions) at a mean followup of 33 months 83 points for KSS and 45 points for KSSf. Whereas KSS corresponds to the results of the present study, KSSf of the present study is superior to the study of Westrich et al. [23]. This may be due to the improved biomechanics of the implant used in the patients of our study. In 2007 Pour et al. [2] found in 44 rotating hinge TKAs (17 primary/27 revisions) at an average followup of 50.4 months a KSS of 73.5 and a KSSf of 43. Again in this study the KSSf presented is inferior to ours. In a recent study Hernández-Vaquero and Sandoval-García [24] found in 26 rotating hinge TKAs (5 primary/21 revisions) 46 months after surgery a KSS of 77 and a KSSf of 51. In a recent study, Yang et al. [11] investigated 50 primary rotating hinge TKAs with a mean followup of 15 years. They found an increase in KSS from 38 to 73 and for KSSf from 36 to 47.

We found a total of 9.2% of complications requiring revision surgery in the patients of the present study. Böhm and Holy [25] reported in 422 rotating hinge TKAs 3.8% infections, 0.7% aseptic loosening, and 0.2% patellar complications at a mean followup of 6 years. Westrich et al. [23] found no aseptic loosening in 24 rotating hinge TKAs after 33 months but 8.3% periprosthetic fractures. Hernández-Vaquero and Sandoval-García [24] found in 2010 in 26 rotating hinge TKAs 3.8% periprosthetic fractures and 7.7% infections.

Recently, van Kempen et al. [26] reported in a prospective study results of 150 revision arthroplasties using a modern semiconstrained implant design. Theoretically, we would expect that functional outcome and complication rate were superior with a less constraint design compared to the results of the present study. In fact, they found a KSS of 76 and a KSSf of 61 points, respectively, at 24 months after surgery. ROM improved from 93° preoperatively to 107° at followup. In their study, 22 complications occured leading to revision surgery resulting in a complication rate of 14.6%. Thus, results are not superior to the results of the present study with a more constrained implant design.

We do think that rotating hinge implants facilitate ROM in severe primary and revision cases and are favourable for all indications of revision TKA. Our results show an increase of ROM from 94° preoperatively to 119° 24 months after surgery. We found 110° ROM 3 months postoperatively with significant increase after 12 and 24 months. There was no revision due to TKA instability in our study, which often occurs within the first two years after TKA.

Biotribologic studies have shown in vitro promising low rates of wear and debris for the EnduRo prosthesis [17]. We were interested if these findings will correlate in clinical outcome. In our in vivo study we found no noticeable signs of biological response to the new CFR-PEEK PAN bearing material. This macroscopic clinical view is also supported by cell culture experiments on L929 and U937 cell lines [27], showing that CFR-PEEK PAN wear particles had no cytotoxic effects and would possibly not cause adverse tissue reactions in vivo. Injecting CFR-PEEK PAN particles intra-articular in a mice model, a similar biological response was found if compared to UHMWPE [18]. A clinical study investigating retrieved tissue of a CFR-PEEK pitch acetabular liner in hip replacement showed a grey synovium due to the CFR-PEEK wear particles but without any serious inflammatory reaction [28].

5. Conclusion

The preliminary results of the present study reveal that the EnduRo rotating hinge TKA yields good clinical, functional, and radiologic results at a short-term followup. Functional results appear to be superior to those reported for other rotating hinge TKA implants. We do believe that this is due

to improvements of implant biomechanics and biomaterials. When applied in revision surgery, there is a six times higher risk for reoperation than in primary use. Long-term results have to be presented in order to draw definitive conclusions regarding the survival rate.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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