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How Has the Introduction of New Bearing Surfaces Altered the Biological Reactions to Byproducts of Wear and Modularity?

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Abstract

Background Biological responses to wear debris were largely elucidated in studies focused on conventional ultrahigh-molecular-weight polyethylene (UHMWPE) and some investigations of polymethylmethacrylate cement and orthopaedic metals. However, newer bearing couples, in particular metal-on-metal but also ceramic-on-ceramic bearings, may induce different biological reactions.

Questions/purposes Does wear debris from the newer bearing surfaces result in different biological responses compared with the known responses observed with conventional metal-on-UHMWPE bearings?

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Methods A Medline search of articles published after 1996 supplemented by a hand search of reference lists of included studies and relevant conference proceedings was conducted to identify the biological responses to orthopaedic wear debris with a focus on biological responses to wear generated from metal-on-highly crosslinked polyethylene, metal-on-metal, ceramic-on-ceramic, and ceramic-on-polyethylene bearings. Articles were selected using criteria designed to identify reports of wear debris particles and biological responses contributing to prosthesis failure. Case reports and articles focused on either clinical outcomes or tribology were excluded. A total of 83 papers met the criteria and were reviewed in detail.

Results Biological response to conventional UHMWPE is regulated by the innate immune response. It is clear that the physical properties of debris (size, shape, surface topography) influence biological responses in addition to the chemical composition of the biomaterials. Highly cross-linked UHMWPE particles have the potential to alter, rather than eliminate, the biological response to conventional UHMWPE. Metal wear debris can generate elevated plasma levels of cobalt and chromium ions. These entities can provoke responses that extend to the elicitation of an acquired immune response. Wear generated from ceramic devices is significantly reduced in volume and may provide the impression of an “inert” response, but clinically relevant biological reactions do occur, including granulomatous responses in periprosthetic tissues.

Conclusions The material composition of the device, the physical form of the debris, and disease pathophysiology contribute to complex interactions that determine the outcome to all wear debris. Metal debris does appear to increase the complexity of the biological response with the addition of immunological responses (and possibly direct cellular cytotoxicity) to the inflammatory reaction

provoked by wear debris in some patients. However, the introduction of highly crosslinked polyethylene and ceramic bearing surfaces shows promising signs of reducing key biological mechanisms in osteolysis.

Introduction

The original biomaterials adopted for use as bearing surfaces in orthopaedic joint prostheses were conventional ultrahigh-molecular-weight polyethylene (UHMWPE) and metal alloys (typically cobalt-chrome [Co-Cr] or stainless steel). It has been recognized since the introduction of total joint arthroplasty that wear will be generated from the bearing surfaces and that wear debris results in inflammatory osteolysis in a percentage of patients. Because a UHMWPE/Co-Cr bearing results in a high volume of debris and most biological responses require a stimulation threshold for tissue reactions to attain clinical significance [26, 41], new bearing surfaces have been introduced to reduce wear volume and the potential for adverse biological responses to debris, thus ameliorating the frequency of osteolysis. These bearing surfaces include hard-on-hard articulating surfaces such as metal on metal (MoM), metal on ceramic, and ceramic on ceramic (CoC) bearing couples, although metal on highly crosslinked UHMWPE and ceramic-on-polyethylene bearing couples also have been introduced into surgical practice. Although MoM cannot be considered a new bearing surface in orthopaedics, its reintroduction in the mid-1990s will be considered novel for the purpose of this review.

There are no biomaterials implanted in the human body that can be considered inert, because there will be both an interaction between the material and the body and an effect of the environment of the body on the material itself over time. Depending on the chemical properties of the biomaterial, there may be breakdown and corrosion products released, which may have both local and systemic effects [13, 32, 40]. The articulation of a joint prosthesis complicates this condition enormously, because the generation of wear is an inevitable consequence of movement at the bearing surface. Wear can arise from four sources: abrasive wear, adhesive wear, corrosive wear, and fatigue wear. A variety of factors influence the outcome of joint arthroplasty including the design of the implant, the alignment of the implant, and based on patient-activity choices. Retrieval analyses have revealed that the quantity, size, shape, material composition, and debris morphology are highly varied between patients receiving the same device, so it is difficult to generalize results to interpret biological outcomes in individual patients, because the morphology of the wear exerts a strong influence on biological responses in addition to the material effects. Given this caveat, we will interpret the biological responses seen

Fig. 1 The literature search strategy for selection of references is shown.

to different orthopaedic biomaterials and contrast them to results accumulated from the classical UHMWPE/Co-Cr bearings. For the purposes of this review, “new” debris from bearing surfaces is considered to be any variation from the conventional or original biomaterial, because the required timespan to evaluate the effects of material change in arthroplasty may take decades.

This systematic review evaluates the following questions: (1) What are the key biological reactions observed in the biological response to conventional UHMWPE debris? (2) Has the introduction of highly crosslinked polyethylene caused variations from the biological response to conventional UHMWPE debris? (3) Does the existence of metals in both ionic and particulate form initiate both innate and adaptive immune responses? (4) Are reduced biological responses to ceramic debris resulting from the material composition or simply low tissue debris loads?

Materials and Methods

Search Strategy and Criteria

An EBSCO host search of Medline with linked texts was conducted in October 2013 using Boolean search strings (text words). The phrases “wear debris” or “nanoparticles” and “biological responses” were input to generate 1804 references. Limits were applied to the data (Fig. 1) to

Table 1. The key biological reactions observed in the biological response to conventional UHMWPE

Macrophage response to debris					
Cell signals	References	Cell signal targets	References	Adverse tissue responses	References
IL-1 β	5, 11, 30, 48, 60, 65, 72, 80	Histiocytes/macrophages	4, 9, 18, 25, 37, 56, 59, 65, 77, 80	Inflammation	8, 25, 27, 70, 77, 80
TNF α	23, 29, 30, 37, 42, 48, 60, 65, 70, 72, 80	Monocytes	4	Osteolysis	5–8, 16, 25, 28, 59
IL-10	11, 54	Osteoclasts	1, 28, 29, 46, 59, 60	Granuloma formation	16, 25
Prostaglandins	19, 45, 48, 72	Osteoblasts	28, 45, 72	Apoptosis	45, 68
Chemokines	11, 27, 43	Lymphocytes	7, 21	Neovascularization	4
Nitric oxide	45, 75	Giant cells	9, 16, 18, 56	Necrosis	8, 9, 25
GM-CSF	6, 29, 48				
MMPs	56				

UHMWPE = ultrahigh-molecular-weight polyethylene; IL = interleukin; TNF = tumor necrosis factor; GM-CSF = granulocyte macrophage colony-stimulating factor; MMPs = matrix metalloproteinases.

exclude papers without abstracts and non-English language papers, yielding 1648 papers. Papers outside of academic journals and papers older than 1996 (to focus the review on new bearing materials) were then excluded, resulting in 1511 publications. Papers were then extracted under the “major heading” subset of prosthesis failure leaving 222 articles. Case reports were excluded (194 papers) and the clinical topics limited to “hip or knee” yielding 127 papers. Papers without biological relevance, papers focused on tribology or methodology, and papers examining materials other than UHMWPE, Co-Cr alloy, titanium alloy, or ceramic materials were excluded, leaving 69 manuscripts. Hand-searching of the reference lists of the selected publications as well as conference proceedings of the American Association of Orthopaedic Surgeons and the Orthopaedic Research Society from 2006 to 2012 supplemented the Medline search. Based on these criteria, 83 papers were evaluated in detail for this review.

Results

What Are the Key Biological Reactions Observed in the Biological Response to Conventional UHMWPE Debris?

The vast majority of wear debris arising from UHMWPE/Co-Cr bearings is polyethylene and the wear rate is considered high. The cumulative biological reactions are diverse (Table 1) and include vascularized granulomatous tissue formation along the implant-to-bone interface [16], influx of inflammatory cells (macrophages, lymphocytes) [4], induction of inflammatory cytokines and chemokines [5, 11, 27, 43, 54], elicitation of antigen-specific immunity

[21], promotion of angiogenic factors [51], bone resorption, and culminating with osteolysis and loss of prosthesis fixation. Although the precise aspects that lead to inflammatory osteolysis are not completely established, two major regulatory factors appear to dominate the process: (1) exceeding a threshold debris load; and (2) the accumulation of biologically stimulatory particles [18, 19, 25, 30, 36, 41]. There is also evidence that the inflammatory factors within this process are under genetic regulation [23] including variants of the mannose binding lectin [46] and transforming growth factor- β 1 signal sequence and interleukin-6 promoter transitions [42]. Reports on the biological activity of UHMWPE by Green et al. [30] have suggested that the particle size range of 0.3 to 10 μ m appears to be the most biologically active with respect to phagocytic cell activation, whereas Matthews et al. [48] have reported that particles in the submicron range (0.1–1 μ m) were the most biologically active. However, factors such as particle morphology (shape and surface texture) can also influence cellular responses to particles with particles classified as sharp or rough exerting the most stimulatory effect on cells [41, 65, 80]. Studies have also shown a variety of cell signaling pathways are involved in the cellular response to debris. These include mitogen-activated protein kinase activation [1], induction of granulocyte macrophage colony-stimulating factor [6], C-C chemokine expression [55], matrix metalloproteinase induction [56], NF κ B activation [59, 66, 72], nitric oxide elicitation [45, 64, 75], induction of apoptosis [74], cytokine activation [43, 78], and direct activation of cyclooxygenase-2 [82]. Although most studies on the etiology of aseptic loosening have been focused on macrophage as the central cell of interest, there is recent interest in examining the role of the fibroblasts in the

Table 2. Highly crosslinked polyethylene variations from the biological response to conventional UHMWPE debris

Cellular responses	Effect	References	Cell signals	Effect	Reference	Tissue responses	Effect	References
Macrophages	↓	7, 8	Cytokines	↑	32	Inflammation	↓	7, 8
Giant cells	↓	7, 8				Necrosis	↓	7, 8
Lymphocytes	↓	40		□		Potential nanoparticulates	?	15, 31, 44, 57, 79

UHMWPE = ultrahigh-molecular-weight polyethylene.

periprosthetic environment and their possible contribution to inflammatory osteolysis [12, 47, 53, 62, 76]. Other cells of potential interest in the pathology of debris-induced osteolysis include osteoclasts [28, 58, 60], osteoblasts [71], lymphocytes [7], and mesenchymal cells [62].

Has the Introduction of Highly Crosslinked Polyethylene Caused Variations From the Biological Response to Conventional UHMWPE Debris?

The introduction of highly crosslinked polyethylene does appear to have caused variations from the biological response to conventional UHMWPE debris (Table 2). The generation of smaller wear debris particles that include nanoparticles [19, 34, 38, 39, 61] suggests that the reduction in osteolytic potential resulting from highly crosslinked UHMWPE could prove to be lower than predicted by the improvement in wear rates. Although interactions with fine and ultrafine particles are mainly confined to phagocytic cells, certain nanoparticles have been shown to accumulate in the cytoplasm of endothelial cells [15], fibroblasts [31, 44], and an epithelial cell line (HeLa cells) [79]. It is now also apparent that nanoparticles may impact the nucleus of the cell [14, 57], and although no overt cytotoxic events resulting from highly crosslinked UHMWPE debris have been reported, we should remain cautious that nanoparticle exposure might result in an unusual effect on cell function and regulation. Early in vitro assessments of the inflammatory potential of highly crosslinked UHMWPE suggested that the particles might be more stimulatory of inflammatory cytokine production [37], but clinical data have not confirmed this observation. Baxter et al. [9, 10] observed the presence of necrosis associated with small wear particles was a dominant histomorphologic change in noncapsular tissues from failed highly crosslinked UHMWPE implants but noted that the quantity of UHMWPE wear debris, and consequently the presence of histiocytes, giant cells, and necrosis, was significantly lower in the highly crosslinked UHMWPE tissues. Inflammatory reactions in tissues containing highly crosslinked UHMWPE debris were reported to be mild and significantly reduced compared with the macrophage responses in response to conventional UHMWPE particles

[10]. Higher numbers of T lymphocytes were also observed in pseudocapsules from conventional UHMWPE when compared with highly crosslinked UHMWPE [45], leading to the overall impression that the use of highly crosslinked UHMWPE has the potential to reduce the potential development of osteolysis. It appears likely that the reduction in overall wear rates using highly crosslinked UHMWPE may result in decreased inflammatory potential in vivo. However, the improvements resulting from material changes at the bearing surface may be compromised by patient factors. For instance, Vasudevan et al. [70] have demonstrated clear differences in the histological lymphocytic responses to polyethylene debris between rheumatoid arthritis and osteoarthritis.

Does the Existence of Metals in Both Ionic and Particulate Form Initiate Both Innate and Adaptive Immune Responses?

The existence of metals in both ionic and particulate form does initiate both innate and adaptive immune responses. Inflammatory, cytotoxic, and immunological responses appear to be interactive, because the exposure of metal debris to the acidic environment of the phagosome [49] or dissolucytosis at the macrophage surface [40] can elevate the generation of metal ions, intracellular metal ions can influence activities relevant to the immunological responses, and local hypersensitivity reactions can increase inflammation and tissue damage (Table 3). Genetic regulation of the responses will affect the overall pathology and outcome to metal debris, and thus it becomes impossible to generalize the outcome of metal debris exposure to the individual patient. The development of metal hypersensitivity appears to follow classical immunological lines and is usually denoted as a Type IV (delayed type or cell-mediated) response. Cytotoxic T cells are frequently CD4+, although CD8+ T cells also participate in the pathology, and there is evidence of skewing of V β T cell subsets in metal hypersensitivity [73]. Metal ions can act directly on immune cells and mediate toxic or stimulatory effects [3] including an increase in T cell costimulatory molecules [13] and elevated expression of the activated (CD3/CD69) T cell phenotype [28] and increased

Table 3. The key biological reactions observed in the biological response to metal debris

Effects of metal debris		References	Effects of metal ions		References
Macrophages	Dissolucytosis and ion release	35, 44	Macrophages	Apoptosis	62
	Inflammation and cytokine release	3, 72		Chromosomal abnormalities	14
			T-lymphocytes	Cellular activation	3, 11, 24, 27, 29
				Reactivity to haptens	45
			B-lymphocytes	Cellular activation	29
				Reactivity to haptens	45

circulating HLA DR+ CD8+ T-cells [32]. The relationship between metal hypersensitivity and implant failure remains uncertain, because the immune response could contribute to the pathology or arise as a result of elevated ion exposure from wear particles generated as a metal component fails. Thus, the contribution of metal hypersensitivity in the pathology of aseptic loosening is controversial [33] and the actual form of the immunological response may extend beyond classical Type IV hypersensitivity to include B cell involvement [34]. A recent paper by Mittal [50] has demonstrated the colocalization of cobalt and chrome ions within synovial tissue determined using Synchrotron X-ray Fluorescence (Spectrosil 2000; Heraeus Quarzglas GmbH & Co, Hanau, Germany) and the overlay of T and B lymphocytes using confocal nuclear density maps. The findings are strongly supportive of the concept of local tissue haptenization resulting in an organized accumulation of sensitized lymphocytes, notably both T and B cells. Animal models of metal debris in inflammatory tissues [3, 77] have demonstrated elevated macrophage accumulation and the induction of inflammatory cytokines and chemokines with a major elicitation of interleukin-1 β the predominant inflammatory feature and expression of CCL2 corresponding with macrophage recruitment. The air pouch model consistently responds with increased cellularity in response to Co-Cr debris, although the response is not elevated over reactions to conventional UHMWPE. Direct effects of metal ions on cellular functions have been reported and include an upregulation of metallothionein I/II and increased catalase and glutathione peroxidase activity in the liver [2, 40], elevated apoptosis in the local tissue [68], and chromosomal aberrations (particularly increases in the percentage of aneuploidy gain) in patients with an MoM bearing [17].

Are Reduced Biological Responses to Ceramic Debris Resulting From the Material Composition or Simply Low Tissue Debris Loads?

Whether reduced biological responses to ceramic debris are the result of the material composition or simply low tissue

debris loads remains unresolved. Investigation of ceramic particles in animal models has indicated a variety of responses dependent on the size of the debris, which may occur in the nanoparticles range [35]. Spinelli et al. [67] observed phagocytosis of small zirconia particles injected intraarticularly into the rabbit knee with some granuloma formation in response to large particles. However, the inflammatory response was limited and without evidence of angiogenesis. In vitro experiments [63] revealed periprosthetic tissue pathology that was not remarkably different from other debris sources with histiocytic accumulation proportional to the tissue debris load and granular wear particles visible as agglomerates phagocytosed within the macrophages. The authors opined that mechanical issues rather than debris-provoked osteolysis were responsible for the development of implant loosening in their patients, in contrast to the findings of Yoon et al. [81] in which a granulomatous response to accumulated ceramic wear debris was observed and considered participatory to the development of osteolysis and subsequent revision arthroplasty. Esposito et al. [20] observed moderate or marked mononuclear macrophage infiltrate with the features of a foreign body response in 21 revision cases using CoC bearings. Inflammation of the residual synovial tissue (which included some neutrophil accumulation) was mostly mild to moderate, and whereas ceramic debris was visible using light microscopy in all tissues, metallic (titanium alloy) debris was also present in most retrieved samples. Ceramic wear has been reported to be less cytotoxic or stimulatory of prostaglandin E2 and interleukin-1 β than UHMWPE or metal particles [16, 22, 52] and generates a lower level of osteoclastogenesis [29]. Tsousi et al. [69] observed no effect on cell viability or growth characteristics using alumina particles in vitro, but both nanoparticles and microparticles increased micronucleated binucleated cells compared with untreated controls. Although no cytostatic effects or clastogenic damage occurred, significant increases in the incidences of chromosome loss and polyploidy were seen using high doses of alumina nanoparticles. The study clearly indicated that the in vitro genotoxicity was significantly lower than that observed using Co-Cr particles, and the overall level of chromosomal events was considered weak.

Discussion

It would be useful to be able to predict the biological response to orthopaedic wear debris to select novel materials for bearing surfaces and identify the appropriate biomaterial for implantation in individual patients. Although a considerable history of adverse responses to orthopaedic wear debris has been published, it should be recognized that the majority of patients do achieve substantial alleviation of pain and restoration of function from the materials currently used for joint prostheses, and because of this, novel biomaterials must be selected with care. In light of that, this review seeks to evaluate changes in biological responses (particularly in the periprosthetic tissues) to debris from materials developed to replace metal-on-conventional polyethylene bearings. The biomaterials investigated are highly crosslinked polyethylene, MoM debris, and ceramics, and the specific questions posed address changes from the biological response to conventional UHMWPE as a result of the introduction of highly crosslinked polyethylene, the occurrence of novel biological responses specific to debris from MoM bearings, and whether reduced biological responses to ceramic debris result from the material composition or simply low tissue debris loads. Recent papers with a focus on immunological reactions to debris [29, 45] are helping the classical views of cell-mediated responses to evolve.

This study had a number of limitations. First, there are numerous factors that contribute to biological responses to wear debris, and each patient generates a unique wear profile. Thus, comparisons within a patient population, let alone across the literature, cannot be considered as the study of responses to consistent stimuli. Patient genetics will inevitably regulate the response to debris, but the genetic regulation of these responses remains largely unreported and it is thus difficult to generalize findings to individual outcomes. Second, among the biomaterials under consideration, there are variations within chemical and physical properties (including variations generated by device manufacturers) that could clearly cause variations to biological responses. This is pertinent for ceramics, in which material-specific changes have been observed using alumina- and zirconium-based materials [34] but not all studies specifically identify the chemistry of the material in clinical use and for highly crosslinked UHMWPE, in which the methods used to achieve crosslinking may generate material differences that could impact the biological responses. Third, it may be difficult to link the observed biological reactions (notably *in vitro* responses) with the pathophysiology of the clinical outcomes. It has taken considerable time for the pathway for wear debris-induced osteolysis resulting from conventional UHMWPE particles to gain general acceptance in the orthopaedic community,

and the current literature generally demonstrates controversy with respect to the interpretation of the clinical outcomes of biological responses to metal debris. This is in part the result of a fourth limitation, which is the extended period of time that usually occurs between surgical implantation and the development of frank clinical failure. Despite over a decade of use of highly crosslinked UHMWPE, there are still limited papers available focused on biological responses to debris from highly crosslinked polyethylene. Nevertheless, the global findings of responses to orthopaedic wear may provide insights into the selection of appropriate materials and permit the elucidations of mechanisms leading to failure at the cellular and molecular level. Although this is reassuring from a clinical standpoint, it limits our knowledge of biological mechanisms in the response to the kinds of debris generated at bearing surfaces that use newer materials. In contrast, publications on metal debris are rapidly accumulating, spurred by an unexpectedly high rate of clinical failure in the new generation of MoM bearings, although the biological processes that accompany poor clinical outcomes have not been conclusively identified.

The key biological reactions observed in the biological response to conventional UHMWPE debris appear reasonably well established. Wear debris that accumulates in periprosthetic tissues is subject to phagocytosis by macrophages. The inability to process UHMWPE particles resulting from a lack of appropriate enzymes and resistance of the material to the acidic environment of the phagosome may lead to broad cellular activation in the macrophage population [16]. Phagocytic cells may acquire an activated macrophage phenotype, leading to a release of proinflammatory cytokines (notably interleukin-1 β and tumor necrosis factor- α) and inflammatory mediators (prostaglandins and chemokines) that create an inflammatory tissue environment [24, 62, 78, 83]. Necrotic cell death may follow macrophage frustration, heightening deleterious tissue effects and failing to alleviate the debris load. Crosstalk between macrophages and osteoclasts through inflammatory cytokines will accelerate osteoclastogenesis, leading to the potential for osteolysis and implant loosening. The precise pathways in this process have been well studied [8, 26, 34, 78] but a number of recent papers indicate that the molecular processes involved in the response to conventional UHMWPE may be broader than originally appreciated.

Our second question, “Has the introduction of highly crosslinked polyethylene caused variations from the biological response to conventional UHMWPE debris?,” is of major importance in the interpretation of material changes on biological responses. The use of highly crosslinked polyethylene as a bearing appears to result in the generation of smaller wear debris particles that include

nanoparticles, provoking the question as to the biological significance of particles that might gain entry into cells without the requirement for a phagocytic process. To date, there is no literature of which we are aware to suggest a novel mechanism (such as cellular transformation) in response to increased levels of nanoparticulate debris, although the active period of study of highly crosslinked UHMWPE in patients is only approximately a decade. Further study is required to identify any rare events that might arise from reactions to nanoparticulate stimuli, and more time is required to provide a convincing association between reduced wear volume using highly crosslinked UHMWPE and reduced revision rates. However, the trend of the studies to date suggests that cellular responses and tissue inflammation are generally ameliorated by the adoption of this new biomaterial (as indicated in Table 2).

The question “Does the existence of metals in both ionic and particulate form initiate both innate and adaptive immune responses?” clearly can be answered in the affirmative. At least three potential factors influencing the overall biological response to metal debris in periprosthetic tissue are recognized: (1) an inflammatory response to particulate debris; (2) an intracellular reaction resulting from the elevation of metallic ions within the tissues; and (3) the development of an immunological response to metal ions behaving as haptens (Table 3). It remains to be determined how these biological responses correlate precisely with clinical outcomes, although the reintroduction of MoM bearings can be considered an orthopaedic failure and it is unlikely that these devices will be used to any great extent in the future. However, further studies into these complex mechanisms should be encouraged, because the use of metal alloys in orthopaedic procedures will continue indefinitely, and the basic effects of metal responses are likely to impact responses to fracture plates and pedicle screws in certain patients.

The question “Are reduced biological responses to ceramic debris resulting from the material composition or simply low tissue debris loads?” remains largely unresolved. The literature on ceramic debris suggests that amelioration of tissue inflammation in periprosthetic tissues may be the result of both a reduction in debris load and a milder cellular response to ceramics but is insufficient to strongly support a majority effect in the mechanisms (Table 4). The relative paucity of papers on orthopaedic ceramic debris as evidenced by the current literature search appears likely as a result of technical difficulties in identifying ceramic debris within retrieved periprosthetic tissues. This may be in part the result of the low availability of clinical specimens from failed ceramic bearings, and it remains to be determined whether the *in vitro* biological responses to the various forms of ceramics actually correlate with reactions in the

Table 4. The key biological reactions observed in the biological response to ceramic debris

Ceramic material	Particle size	Cellular responses	Adverse responses	References
Zirconia	Large	Macrophage/histiocyte	Granuloma formation	67
Alumina	Small	Macrophage	Necrosis/necrobiosis	35
Alumina	Small	Macrophage/histiocyte	Inflammation	20, 63
Alumina	Small	Monocyte and lymphocyte	Inflammation	22
Alumina	Small	Macrophage/histiocyte	Fibrous tissue	81
Alumina	Small	Osteoclasts	Increased TRAP	29
Alumina	Small	Fibroblasts	Genotoxic potential	69

periprosthetic tissues and exert an influence on the clinical outcomes of ceramic bearings.

Overall, the biological responses to wear debris from novel bearing surfaces demonstrate the potential for improvements in the osteolytic potential when compared with conventional UHMWPE on metal bearings. Material changes in polyethylene and the adaptation of ceramics have resulted in a lower rate of wear, which might imply that the threshold to provoke adverse effects has been reduced. However, genetic regulation of the response in patients and as yet unknown responses to nanoparticulates may confound this prediction. In addition, the cellular responses to highly crosslinked UHMWPE and ceramic particles, although not absent, do show some level of reduction in the provocation of inflammation and osteoclastogenesis [7, 8, 20, 63]. The findings for the new generation of MoM bearings have not demonstrated the predicted improvement in prosthesis life expected for a low-wear, hard-on-hard bearing. Most publications conclude that the multiple pathways present in the reaction to metal debris and corrosion products do increase the potential for cumulative adverse reactions that have impacted the revision rates of several MoM devices [3, 11, 24, 72]. Thus, interpretation of changes in biological responses must be interpreted with caution, but our review suggests that highly crosslinked UHMWPE has modestly improved the biological response to UHMWPE debris to date, whereas the presence of metals in both ionic and particulate form in periprosthetic tissue can provoke both innate and adaptive immune responses and elevate the complexity of the biological response.

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