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REVIEW

Biological response to prosthetic debris

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Abstract

Joint arthroplasty had revolutionized the outcome of orthopaedic surgery. Extensive and collaborative work of many innovator surgeons had led to the development of durable bearing surfaces, yet no single material is considered absolutely perfect. Generation of wear debris from any part of the prosthesis is unavoidable. Implant loosening secondary to osteolysis is the most common mode of failure of arthroplasty. Osteolysis is the resultant of complex contribution of the generated wear debris and the mechanical instability of the prosthetic components. Roughly speaking, all orthopedic biomaterials may induce a universal biologic host response to generated wear débris with little specific characteristics for each material; but some debris has been shown to be more cytotoxic than others. Prosthetic wear debris induces an extensive biological cascade of adverse cellular responses, where macrophages are the main cellular type involved in this hostile inflammatory process. Macrophages cause osteolysis indirectly by releasing numerous chemotactic inflammatory mediators, and directly by resorbing bone with their membrane microstructures. The bio-reactivity of wear particles depends on two major elements: particle characteristics (size, concentration and composition) and host characteristics. While any particle type may enhance hostile cellular reaction, cytological examination demonstrated that more than 70% of the debris burden is constituted of polyethylene particles. Comprehensive understanding of the intricate process of osteolysis is of utmost importance for future development of therapeutic modalities that may delay or prevent the disease progression.

Key words: Debris; Adverse reaction; Osteolysis; Macrophages; Cytokines; Chemotaxis; Polyethylene; Phagocytosis

Core tip: After a comprehensive review of joint arthroplasty history, this article outlines the fundamental pathophysiology of the debris-induced biological reaction common to all particles types. Furthermore, specific characteristics of polyethylene, metal, ceramic, and polymethylmethacrylate particles are stated separately with their associated clinical relevance. Lastly, future therapeutic strategies to down-regulate periprosthetic osteolysis are enumerated, including anti-inflammatory agents used to modulate the cytokines release, anti-osteolytic agents used to disintegrate osteoclasts morphology, and antioxidants used to demolish the free oxygen radicals produced by the activated macrophages. The reader will find an extensive literature review encompassing all aspects of the debris-induced hostile cellular reaction.

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JOINT ARTHROPLASTY HISTORICAL REVIEW

As stated by the famous French philosopher of science, Auguste COMTE (1798-1857), we cannot completely know a science without knowing its history.

The first implanted total joint arthroplasty goes back to 1890 where the German surgeon "Themistocles Gluck"[1] performed in Berlin a total ivory prosthesis on the tuberculous knee of a 17-year-old woman. Professor Gluck, whom revolutionary effort was dismissed during his lifetime, was also the first surgeon to use bone cement, about 65 years before Sir John Charnley[2].

Afterward, many biological (fascia lata grafts; pork bladder submucosa; skin) and inorganic materials were used as interpositional layer in an attempt to resurface the arthritic joints: In 1885, Léopold Ollier used adipose tissue and in 1912, Jones used gold foil to perform their "interpositional arthroplasty".

In 1922, the English surgeon Hey-Groves replaced the femoral head by an ivory sphere of same caliber with satisfactory result up to 4 years only. In 1923, the American surgeon "Marius Smith-Petersen" introduced the concept of "mold arthroplasty"[1] where he chose glass as material of his first mold after he removed a glass foreign body from a patient's back and found it surrounded by a synovial membrane. Many other inorganic materials were tried (Pyrex, Bakelite, viscaloid...) without success either because of their fragility or the toxicity of their debris.

In 1936, Venable *et al*[3] discovered the single electrically inert metal alloy, "Vitallium", composed of cobalt (60%), chromium (20%) and molybdenum (5%). Subsequently in 1940, Austin MOORE and Harold BOHLMAN placed the "first metal hip joint" made of Vitallium, in United States, Columbia, South Carolina: one piece femoral head and stem inserted in the intra-medullary canal.

In 1946, the 2 French brothers JUDET conceived the "Plexiglas" [polymethyl methacrylate (PMMA)] femoral sphere attached to a short stem, replacing the hip arthrodesis by hip prosthesis[2]. A short-lived good result was achieved since the PMMA material was extremely fragile and yielded tremendous wear debris.

In 1951 at Norwich (United Kingdom), McKee was the first surgeon to replace both sides of the hip articular surfaces using a metal-on-metal (MOM) prosthesis. Sir John Charnley is considered the "father of modern arthroplasty" where in 1960 at Manchester (United Kingdom), he pioneered the concept of "low friction arthroplasty", called like so because he promoted the use of a small femoral head in order to minimize the wear[1]. In 1962, he finalized his totally cemented prosthesis: a cemented polyethylene (PE) acetabular component and "monoblock" (one-piece) cemented femoral stem with 22 mm femoral head.

The initial work of all these surgeons focused on the design and fixation method of the implants. Once this goal has been achieved with Charnley, more attention was drawn toward the longevity of the prosthesis where "aseptic loosing" started to be noted since the early 1960's[4]. Implant aseptic loosening is the result of the complex intrication of fibrous membrane formation, peri-prosthetic bone resorption and inflammatory cytokines production[5].

Based on the extensive research work performed throughout the historical existence of arthroplasty, especially that of the hip joint, we were able to conclude that an extended longevity of an artificial joint depends mainly on 3 fundamental factors: (1) the durability of implant fixation; (2) the wear rate of the bearing surfaces; and (3) the accuracy of the surgical technique of prosthesis implantation.

This review article will discuss the wear factor stating the different types of generated prosthetic debris (PE, PMMA, metal, and ceramic) along with their specific characteristics (if present) and subsequent host biological reactions. The current knowledge of the adverse biologic reaction induced by different types of wear debris derives from the histo-pathologic analysis of the retrieved peri-prosthetic tissue during revision surgery, from genetic studies or from animal models studies.

At present, more than sixty years after the pioneering of the modern notions of arthroplasty, that underwent an active perpetual progress during this whole period, tens of thousands of hip and knee replacements are performed each year in United States and Europe[1,6]. "According to the Agency for Healthcare Research and Quality, more than 285000 total hip arthroplasties (THA) and more than 600000 knee arthroplasties are performed each year in the United States" (www.AAOS.org). According to the national joint registry (www.njrcentre.org.uk), approximately 160000 total hip and knee replacement procedures are performed each year in England and Wales, with the same number of replaced hip and knee joints. Based on the absolute number of THA performed per 100.000 inhabitants, Germany is the first on the list (296 THA/100.000 residents), followed by Switzerland (287/100.000) and Belgium (240/100.000)[6]. In United States and United Kingdom, 184 and 194 THAs respectively are performed per 100.000 inhabitants[6]. The number of annually performed arthroplasty is worldwide steadily increasing with time.

Building on the brilliant success attained, especially with (THA), the indication of joint replacement surgery was enlarged to include young active patients[1,7] suffering from disabling joint diseases, raising the problem of bearing surfaces wear that induces a chronic

inflammatory reaction leading to osteolysis[4,8] which accounts for the greatest majority of revision surgery that can be sometimes extensive and complicated. In addition, with the advances accomplished in the majority of medical fields, the life expectancy of the general population is lengthened, with more physically active elderly individuals being candidates for total joint replacements[8] with higher stresses exerted on the bearing surfaces for longer periods of time.

For THA, different types of bearing surfaces are available nowadays and can be broadly classified into 2 groups: hard-on-hard surfaces including ceramic-on-ceramic (COC) and MOM, and hard-on-soft surfaces including metal-on-polyethylene (MOP) and ceramic-on-polyethylene (COP). The most widely used bearings are metal-on-polyethylene that showed, since its introduction with Charnley prosthesis, good, cost-effective and predictable outcomes for decades[1] with concordant results whatever school or country is considered: 85% survival rate at 25 years and 78% at 35 years of follow-up[6]. Each couple of bearing surfaces has its advantages and drawbacks. It is incontestable that the development of these materials knew a marvelous evolution during the second half of the 20th century, but yet none can be considered to be absolutely perfect.

PERI-PROSTHETIC OSTEOLYSIS: BASIC SCIENCE

Total joint arthroplasty is considered one of the most prosperous branches of Orthopaedic surgery, where the damaged and painful articular surfaces are substituted by artificial anatomically-shaped components, ameliorating the patient quality of life by providing painless and unrestricted range of motion of the affected joint. Total hip and total knee replacement surgeries are part of the "top 5" surgical interventions in Orthopaedic surgery, alongside with carpal tunnel decompression, arthroscopic meniscal surgery and hardware removal[6]. However, as published by numerous long-term studies, all total joint replacements end up by loosening[4,9-14] with different time-frame longevity for every joint of the body.

The fact that endurance of arthroplasty is not everlasting is due to osteolysis of the bone surrounding the implants; it get established gradually as wear débris (mainly PE particles) are continuously produced by the mobile articulating bearings[5,15], increasing with time[4,9,14,16], with "aseptic loosening" being the end-point of the bone loss. While it is uncontestable that aseptic loosening is the resultant of wear debris production, the exact responsible mechanism and the risk factors are still ill-defined[14]. Likewise, since the adverse biologic reaction to prosthetic debris is not yet elucidated from A to Z, no universal definition for aseptic loosening can be given[14]. Peri-prosthetic osteolysis is rarely limited over many years; most likely, it progresses with time and, if unrecognized, can lead to extensive bone loss, requiring very complex reconstructive revision surgeries with compromised long-term outcomes[9].

Willert *et al*[17] were the first to notice in 1977, the hostile biologic effect associated with the wear débris, which is characterized by peri-prosthetic bone loss. But Salvati *et al*[18] were the first to describe in detail, in 1993, the "debris disease" triggered by PE or metallic debris. Aseptic loosening is the most common cause of arthroplasty failure representing around 75% of cases, with infection (7%), recurrent dislocations (6%), and fractures (5%) accounting for the remaining reasons for failure[10]. Peri-prosthetic osteolysis may be manifested radiographically by radiolucent lines which consist mainly of macrophages incorporating prosthetic debris[9]. As stated by Ollivere *et al*[14], once osteolysis is manifested radiographically, it will be coupled with a more hostile biologic reaction, as it is reflected by the increased cytokines levels. Progression of the radiographic evidence of peri-prosthetic bone loss is a very slow process that is extremely uncommon before 5 years after implantation[9]. This disease can have completely asymptomatic or symptomatic presentations[9]. For this reason, it is extremely important to periodically assess the patients radiographically, especially 5 to 8 years after implantation, looking for subclinical peri-prosthetic osteolysis. Most series have reported increased incidence of osteolysis around 10 years following arthroplasty, but few cases occur before 10 years interval. Symptomatic osteolysis can be manifested by painful loosening and/or fracture.

Foreign bodies particles can be generated from any part of the prosthesis: from the articulating surfaces or from the bone/implant or bone/cement interface[4,19]. These particles accumulate in the joint synovial fluid and may, after stimulation of the host cellular response, get incorporated in the inner aspect of the neo-capsule which is usually formed after joint prosthesis insertion[19]. Consequently, granulomas (nodules consisting of inflammatory cells phagocytizing the foreign bodies) with central necrosis, fibrosis or scar tissue can form within the capsule[19,20].

Osteolysis, originally called "cement disease" since it was first described after revision of cemented prosthesis, is the consequence of the adverse cellular host reaction to wear débris that can emanate from any interface of the prosthetic implants[4,14]. Roughly speaking, all orthopedic biomaterials may induce a universal biologic host response to generated wear débris with little specific characteristics for each material; but some debris has been shown to be more cytotoxic than others[5,14,19]. Likewise, peri-prosthetic bone loss can occur with any fixation method: cemented or cementless prosthesis[4]. The universality of wear debris behavior have been challenged recently where a study conducted on animals has shown that various types of wear particles influence differently the

differentiation and maturation of the osteo-genetic cells and that stimulated bone marrow stromal cells may play a primordial role in the pathogenesis of debris-induced aseptic loosening[21].

Histo-pathologically, the peri-prosthetic tissue is a fibrous granulomatous tissue constantly composed of a complex amalgam of cellular infiltration and particulate debris. The cellular component of this tissue includes numerous cell types: histiocytes, fibroblasts, osteoblasts, osteoclasts, osteo-progenitor cells [adult mesenchymal stem cells (MSCs)], synovial cells, endothelial cells and less commonly lymphocytes[4,5,8,22]. Neutrophils are only found in septic loosening cases[5]. Plasma cells and lymphocytes are found even without evidence of infection; they constitute a sign of humoral immunity defense mechanism[19].

Monocyte/macrophage lineage is the major cell type involved in the inflammatory wear-induced peri-prosthetic osteolysis by their phagocytic role and pro-inflammatory mediator's release[5,14,19,22-24]. Macrophages are one of the first cells to act where 48 h after exposure to debris, their cytoplasm enlarge assuming a balloon-like appearance (diameter size increasing from 10-20 μm to 40-50 μm)[22], and they release different inflammatory biomarkers, like tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1 alpha[14,25]. MCP-1 is one of the most important inflammatory cytokines, playing a chemotactic role where it recruits peripheral monocytes and osteoclasts (that derive from the common cell lineage of macrophages)[14,24]. Many signaling pathways may stimulate macrophages leading to the release of different types of inflammatory cytokines[14]. The classical macrophage activation pathway (M1) is mainly enhanced by T-helper 1 cells (Th 1) and their specific cytokines group, especially interferon-Y, which is normally secreted by microbial activation. This pathway results chiefly in interleukin-1 (IL-1) and TNF-α production by the macrophages. The alternative macrophage activation pathway (M2), which consists of broad spectrum of responses, is mainly regulated by Th 2 cytokines, mainly IL-4 and IL-13. This pathway activation leads to the secretion of different cytokines by the macrophages, like prostaglandin E2 (PGE2), as well as to the stimulation of variant detrimental cellular reactions, such as the nuclear factor kappa-B (NF-κB) apoptotic pathway and the mitogen-activated protein kinases, an intracellular stress and inflammatory signal transduction trail[14].

The alternative macrophage activation pathways, which are the culprit pathogenesis mechanisms of multiple systemic inflammatory diseases (multiple sclerosis, tuberculosis, Gaucher's disease, athero-sclerosis), seem to play a major role also in the wear-induced osteolysis. The knowledge of these alternative pathways is still in its infancy; this may be a rational explanation behind our failure to reproduce *in vitro* the extremely complicated *in vivo* osteolysis process.

Histiocytes are part of the reticulo-endothelial system (AKA lympho-reticular system or mononuclear phagocyte system). Different types of histiocytes exist including macrophages (which main function is phagocytosis), dendritic cells (which main function is antigen presentation) and Langerhans cells. Most of the research investigating the biological response to wear debris has focused on macrophages before clarifying the role of other cell types[8]. Foreign body giant cells (which are fused macrophages generated in response to the presence of a large foreign body) are notably present in the osteolytic tissue surrounding cemented implants; these cells are considered a reaction to the acrylate (cement) fragments[4,19]. All these cell types actively interact with each other, where for example, fibroblasts trigger the formation of foreign body giant cells, and osteoblasts contribute to the differentiation and maturation of osteoclasts[5]. Wang *et al*[26] showed that fibroblasts release osteolytic enzymes in response to debris exposure, especially stromelysin and Collagenase in the presence of Ti particles. However the exact role of lymphocytes is still debatable where the hypothetical synergism between lymphocytes and macrophages in cytokines release could not be demonstrated in one study; T-cells at the interface membrane may alter the cellular response to wear debris[22].

Leukocytes are hematogenous cells produced in the bone marrow, are then transported to the blood vessels and finally to the concerned host tissue containing foreign products, after crossing the endothelial-lining of the vessels wall. Hereafter, endothelial cells represent an active and essential contributor to the transport process allowing the leukocytes to reach the interface membrane[5]. In addition to their role in hemostasis, endothelial cells play an important role in inflammation by synthetizing and releasing von Willebrand factor (vWf) from their intracellular granules, "Weibel-Palade bodies", once they are activated or damaged[5]. The collagen-binding domains of vWf bind tightly to the collagen tissue surrounding the vessels, forming the "peri-vascular cotton wool-like cuff" in the synovium-like interface membrane[5].

Elucidating the specific involvement of each cell type was not of great evidence or ease. It was Kadoya *et al*[27] who first reported that, next to the interface membrane of aseptically loose implants, bone formation was by far more prominent than bone loss; They highlighted the presence of osteoblasts in the reactive tissue and demonstrated that macrophages, not only stimulate bone lysis by releasing cytokines which activate osteoclasts, but also have microstructures that allow them to resorb the bone actively and directly. But actually, it is well known that osteoblasts, beside their role in osteo-genesis, produce Receptor activator of nuclear factor kappa-B ligand ("RANKL") and macrophage colony stimulating factor ("M-CSF") that are cell membrane receptors involved in bone resorption and

release cytokines stimulating osteoclasts formation[5]. In fact few studies explored the role of osteoblasts in peri-prosthetic osteolysis, while numerous studies explored osteoclasts that have been always considered central to the active bone resorption process[14]. Lohmann *et al*[28] demonstrated that osteoblasts may phagocytize prosthetic debris enhancing cytokines expression and release. Osteoblasts originate from the differentiation and maturation of the osteo-progenitor stem cells contained in the periosteum, under the effect of many growth factors like platelet-derived growth factors (PDGFs), bone morphogenetic proteins (BMPs), transforming growth factor beta (TGF-β) and fibroblast growth factors (FGFs)[14]. Osteoblasts can be stimulated differently according to the type and dose of the culprit wear debris[21,28]: low dose of ultra-high molecular weight polyethylene (UHMWPE) or PMMA particles (0.63 mg/mL) displayed strong alkaline phosphatase activity while Co-Cr and Ti particles exhibited minimal effects on the osteoblasts. UHMWPE exposure down-regulate osteoblasts production of collagen type Ⅰ and Ⅲ[14].

The generated débris can have one of 2 different forms: soluble ions or insoluble particles which aggregate with the serum protein forming protein-particles complexes, of different sizes[8,10]. The adverse effect of wear debris is primarily manifested locally by an aggressive inflammation whose maestro is the macrophages[10]. The effect of systemic dissemination of wear debris, especially metal and PE debris is controversial without established risk of toxicity and carcinogenicity to date.

The different orthopedic biomaterial particles, when binding to the serum protein, can change their conformation causing them to be recognized as foreign proteins by T-lymphocytes[22]. To undergo phagocytosis or pinocytosis, a particle should have a size inferior to 10 μm (ranging from 150 nm to 10 μm)[4,8,10]. Once ingested by macrophages or other cells, the wear debris trigger the host biologic response characterized by the release of inflammatory mediators, T-cell activation through antigen presentation, oxidative stress and DNA damage[10]. Cellular activation (mainly macrophages) differs with the engendered form: ions trigger the biologic cascade after they are phagocytosed and non-phagocytosable complexes activate the cell *via* its membrane receptors[8,23].

The debris particles can manifest their adverse effect either directly by eliciting the biologic cascade leading to osteolysis or indirectly by third-body mechanism accelerating the polyethylene's wear once they reach the articulation[4,29]. Third body débris (such as metallic particles, PMMA cement or even cortical bone) can be entrapped between the articulating surfaces of the prosthesis causing "abrasive wear" of both the soft UHMWPE and the hard surface of the femoral head (metal or ceramic)[29]. The relationship between the hardness of the third-body débris and the hardness of the bearing surfaces is the major determinant of the predisposition to abrasive wear[29].

Detailed cytological examination of the lytic tissue demonstrated that 70% to 90% of the debris load is constituted of polyethylene[4,30]. These particles have predominantly a spheroid shape and a size inferior to 1 μm (> 90%) with a mean size of 0.5 μm[4,30]. According to the type of prosthesis implanted, other sorts of particles may be detected in the peri-prosthetic membrane: polymethylmethacrylate, Co, Ti and ceramic. Silicates and stainless steel debris may also be seen but in a small amount since they are most likely contaminants from surgical tools or manufacturing process[4]. It is well admitted that the peri-prosthetic osteolysis does not ensue from the hostile effect of a single type of debris, but rather it is the cumulation of multiple physical, chemical and biologic factors.

The bio-reactivity of wear particles depends on 2 major elements: (1) Particle characteristics (size, concentration and composition); and (2) Host characteristics (genetic variation dictating the immune system reactivity)[4,8,30]. Higher doses and smaller sizes induce more pertinent host response; this response also differs with the particle type where for example, Ti débris are more potent than PE particles of similar sizes[4]. Little agreement exists on what type of biomaterial debris is more bio-reactive, but there is a growing consensus that metallic debris is more pro-inflammatory *in vivo* than polymer debris, despite contradictory statement reported by some authors[10].

Low doses of particles (Co-Cr, Ti and UHMWPE) strikingly promote the proliferation of the bone marrow stromal cells while high doses, mainly of Co-Cr, lead to cell death probably by reaching a toxic level[18,21,31]. The amount of generated wear debris is very critical to the stimulation of biologic response. In general, hard-on-soft bearings produce larger debris than hard-on-hard bearings do, where the average size of metal and ceramic debris is approximately 0.05 μm[10]. The aspect ratio of the debris is also important: elongated particles (fibers) are more potent than round particles in triggering the inflammatory reaction[10]. In general, the intensity of local inflammation depends on several critical debris characteristics: chemical reactivity, aspect ratio and particle load (size and volume)[10]. The critical size inciting the biologic response is one of controversial issues; in general, it is admitted, based on *in vitro* testing, that a particle should have a phagocytosable size to induce an inflammatory reaction (< 10 μm), with (0.24-7.2 μm) size range being the most pro-inflammatory.

Time of exposure is also an important factor contributing to osteolysis[5,31]. In addition, debris bio-reactivity can be determined by the surface charge, energy and roughness as well as the aspect ratio (particle shape), and the composition and nature of the absorbed proteins[4,30]. Despite that particle features are considered to be the main factors controlling the induced biologic reaction, other factors also influence the onset and magnitude of this reaction.

Many radio-stereometric clinical and experimental studies have shown that mechanical instability of the implants is fundamental to induce the inflammatory reaction, where various amounts of different particles were shown to play a secondary role in osteolysis[8,32,33]; in contrary, particles seem to mainly inhibit bone formation around unstable implants more than induce osteolysis. Peri-prosthetic osteolysis could be the resultant of synergy between particulate debris and mechanical instability at the bone implant interface. Motion can lead to fibrous tissue formation that secrete different inflammatory mediators stimulating osteoclasts or can stimulate the extracellular matrix resulting in PGE2 and other cytokines release[32]. Therefore, primary implant fixation or instability portend subsequent clinical failure, result of loosening. Also interface mechanical stability, reflected by bone ingrowth, offers a sealing effect preventing the passage of PE debris from and to the effective joint space.

Interestingly, also the local fluid pressure in the fibrous membrane surrounding loose implants could be responsible of osteocytes apoptosis more than osteoclast activation; a fact that can be supported by the physiopathology of arthrosis-induced subchondral cysts and vascular aneurysms-induced bone erosion[33].

While a consensus about pro-inflammatory parameters, like particle load, has been established, the host reaction variability is still an area of darkness. As stated by Harris[9], many patients with extensive amounts of PE debris may not develop peri-prosthetic osteolysis. Distinct cellular response to prosthetic debris of loosened elbow arthroplasties has been demonstrated between patients with and without rheumatoid arthritis[13]. This different biologic reaction was not related to the amount or type of the prosthetic debris but was alleviated by anti-TNF therapy.

Hence, individual difference in macrophage sensitivity and/or osteoclast/osteoblast reaction, reflecting intrinsic variability in the immuno-regulation, is probably the most important underlying etiology of the debris-induced hostile biologic reaction. Future investigations are warranted to determine whether individual genetic variances is the "maestro" of the inflammatory cascade.

The particle-induced chronic granulomatous inflammation can be of 2 types: non-immune and immune[8]. Non-immune inflammation is a nonspecific reaction stimulating mainly the innate immune system[5,8] where fibroblasts and macrophages are the prominent cell types with scarce lymphocytes; it is specially caused by ceramic and polymeric debris. Immune reactions are induced by excessive metallic ions and particulates that stimulate both the innate and adaptive immune system[5,8]. The immune granulomas are dominated by lymphocytes (B and T) that are widespread, interacting with specific epitopes where they may form the so-called "peri-vascular cuffing"[5,8]. The innate immune system can be activated by the toll-like receptors on the cell-membrane ("Toll" is a German word meaning "great, formidable"), that are one subtype of the specific receptors identifying the "molecular motif"; or it can be activated by the inflammasomes which are oligomeric protein complexes. The inflammasome complexes contain several types of proteins: caspase-1, NALP, PYCARD and sometimes caspase-5; its exact composition changes according to the activator that lead to its assembly. The inflammasome, especially activated by the metal particles[23], maturate the pro-inflammatory factors IL-1 and IL-18 by cleaving their inactive domains once the inflammatory caspase-1 cascade is stimulated[8]. The metallic ions-induced immune reaction has a spectrum of physiopathology ranging from benign fibrosis to severe type Ⅳ T lymphocytes-mediated hypersensitivity reaction leading in some cases to painful pseudo-tumors[8,23,30].

The inflammatory cascade generated once the prosthetic debris activate the cell, is an extremely complex process that is still not fully elucidated. Many older and recent studies have demonstrated the release of different families of inflammatory factors by several cell types of the peri-prosthetic tissue in reaction to all prosthetic debris. Goldring *et al*[34] were the first to state that the bone-implant interface in loose THA is composed of synovial-like membrane made of inflammatory cells producing PGE2 and collagenase.

The key cytokines, released by the inflammatory cells and responsible of bone resorption mainly include: IL-1, IL-6, IL-8, IL-10, IL-11 and TNF-α[4,8,26]. Also many other different factors are involved in this intricate reaction like prostaglandins (mainly PGE2)[4,8], growth factors (PDGF-α and TGF-β)[26], reactive oxygen intermediates (peroxide and nitric oxide)[8,24] and lysosomal enzymes (MMPs collagenase and stromelysin)[4] that are involved in the catabolism and reorganization of the organic extra-cellular bone matrix. Pap *et al*[35] reported that the fibroblasts and osteoclasts of the synovial-like peri-prosthetic tissue exhibit increased expression of several metalloproteinases (MMPs), like MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13 contributing to matrix degradation.

The inflammatory response may be material-dependent where a certain type of cytokine is more released in response to a specific particle, ex: IL-1 predominates the stainless steel-induced reaction and PGE2 and IL-6 predominate the titanium-induced reaction[26].

TNF-α is an essential and extremely potent inflammatory mediator of the particle-induced bone resorption[36]. Merkel *et al*[36] showed, in an animal model study, that TNF-α is a crucial osteoclastogenic agent where "mice failing to express both the p55 and p75 TNF receptors were protected from the profound bone resorption induced by the polymethylmethacrylate particles". This information has a valuable clinical implication, where TNF receptors blockage can prevent wear particle-induced osteolysis.

In the presence of TNF-α and M-CSF, macrophages isolated from the peri-prosthetic tissue may differentiate

to osteoclasts *in vitro*, expressing vitronectin receptor and tartrate-resistant acid phosphatase (TRAP)[26]. TRAP, also known as acid phosphatase 5, is a glycosylated monomeric metallo-enzyme normally highly expressed by activated macrophages, osteoblasts and neurons.

Macrophage interaction with wear debris is constantly the chief phenomenon initiating the complex adverse local tissue reaction (ALTR) that lead to osteolysis and subsequent aseptic loosening. Among the numerous potent inflammatory mediators released, nitric oxide (NO) is copiously produced by the macrophages in a type- and dose-dependent manner of the challenging particles[26,37]. NO production is mainly stimulated by Ti-alloy particles followed by PMMA particles. The role of NO in the wear-induced adverse biologic reaction is not fully elucidated, since few studies investigated this chemical mediator. But it seems that it may play a role in the stimulation of PGE2 release and the inhibition of DNA synthesis[37].

Endotoxin adherence to the wear particles may play a primordial role in increasing the release of inflammatory cytokines in the peri-prosthetic tissue. This fact was demonstrated *in vitro* by several studies, but also was refuted by others[38-42]. Endotoxins, a term used nowadays as synonym for lipopolysaccharides, are large molecules found on the outer membrane of Gram negative bacteria. They are released only after complete destruction of the bacterial cell wall, hence eliciting a potent immune response. Their role in wear-induced osteolysis is still controversial and needs to be more clarified in the future.

Recently, RANKL and osteoprotegerin (OPG) have been shown to play a major role in the initiation and progression of osteolytic lesions[4,8]. RANKL is an osteoblast receptor which activates osteoclasts by binding their surface receptor (Receptor Activator of NF-κB, also known as TRANCE Receptor) "RANK". It is, like osteoprotegerin, a member of the TNF cytokine superfamily. The RANK pathway is the chief regulator of bone turnover (osteolysis) whereas osteoprotegerin is the antagonist of this pathway. Based on many animal model studies, RANK/RANKL/OPG pathway is now considered crucial for the occurrence of osteolysis[14]. The released inflammatory factors can act in a paracrine and autocrine manner[8], up-regulating osteoclast differentiation and maturation and sometimes reciprocally regulating their synthesis (like IL-1 and PGE2)[4].

Normal bone turnover rely on a balanced bone formation and bone resorption which are adjusted in harmony with the homeostatic and electrolytic condition of the organism. Many clinical studies and animal models demonstrated that the particle-induced inflammatory cascade not only up-regulate osteoclast function but also down-regulate the osteoblast and osteo-progenitor cells function[8,16,26,43], resulting in an unopposed bone resorption. In particular, several studies focused of the adverse effect of Ti particles stating that these particles suppress the gene expression and the proteo-synthesis of collagen type I and bone sialoprotein, alter the adhesive behavior of osteoblasts and trigger their apoptosis[26]. Similar sizes of Ti particles and ZrO_2 have different effect on the osteoblastic gene expression: chronic Ti debris exposure, which can be secondary to mechanical instability of the implant, compromise "human MSC differentiation into functional osteoblasts"[26].

Mesenchymal stem cell apoptosis is induced by an increased level of the tumor suppressor proteins, p53 and p73. P53 (also known as p53 up-regulated modulator of apoptosis) may trigger cell death through several long and complex pathways, one of them starts by inhibition of the anti-apoptotic Bcl-2 family proteins, then activation of mitochondrial dysfunction, leading to the release of apoptogenic proteins from the mitochondrial membrane, like second mitochondria-derived activator of caspases, apoptosis-inducing factor and cytochrome C[26]. P53 can lead to cell apoptosis through activation of death domain by soluble TNF cytokine receptors, like TNF-α and TNF-related apoptosis inducing ligand.

In other words, the osteogenetic function of osteoblasts is inhibited at the price of osteoclasto-genesis which is regulated by mediators released by the peri-prosthetic osteoblasts themselves[43]. Hence, peri-prosthetic osteolysis is the resultant of 2 vectors: increased bone resorption by the inflammatory cytokines and the shifted osteoblast function, as well as decreased bone formation by the inhibited osteoblasts/osteoprogenitor stem cells.

The extent of the inflammatory reaction could be not locally confined to the prosthetic joint where debris is generated. Biomaterials debris (mainly PE and metallic) can be detected remotely from the affect joint, in the blood, urine, bone marrow, even in the liver, spleen, kidney, iliac and para-aortic lymph nodes, hair and nails[20,26]. The systemic immune reaction depends primarily on the macrophages chemotactic-function[8,24,44]. After stimulation of local peri-prosthetic cells, peripheral macrophages are recruited exacerbating the osteoclasto-genesis and subsequently peri-prosthetic bone resorption. Foreign bodies' particles can be transported to distant cells of the reticulo-endothelial system *via* the peri-vascular lymphatic vessels; a fact that is supported by the presence of particle-collecting macrophages in the direct vicinity of blood vessels[19,20]. The extent of the distant transportation of wear debris depends on the amount produced as well as the capacity of the peri-articular capsule to transport them[19]. It is assumed that systemic dissemination (mainly of metal particles) occurs when the ability of local cells to store foreign bodies is bypassed.

PROSTHETIC DEBRIS SPECIFICITY

The materials currently available for all prosthetic interface couples were present since more than 40 years but recently, with the advances of metallurgy

processing and tribology knowledge, the manufacturing of these materials has been refined in order to decrease the volumetric wear associated with the traditional surfaces[30]. The new alternative couples nowadays available consist of the metal-on-highly cross-linked polyethylene and hard-on-hard bearing couples. All these new bearings require a meticulous surgical technique, specifically an excellent acetabular positioning in order to avoid the early complications that have been reported: squeaking, chipping or breakage, edge loading and impingement wear (stripe wear) associated with ceramic-on-ceramic couples[8], fracture or rim cracking of the highly cross-linked polyethylene liner and runaway wear and immune system-related complications (hypersensitivity and pseudo-tumors) associated with metal-on-metal couples.

Polyethylene debris

Polyethylene was part of the historical MOP Charnley prosthesis. Even currently, the greatest majority of implemented THA consist of hard-on-soft couples (metal-on-polyethylene or ceramic-on-polyethylene), yet using the newest UHMWPE[7].

Polyethylene debris is considered the main culprit in inciting a hostile biologic response leading to osteolysis and aseptic loosening[4,7,15,20,29,30,45,46]. PE debris can transform appositional bone growth around well-fixed implants to chronic inflammatory tissue with abundant foreign body giant cells[16]. This fact resulted in growing interest in hard-on-hard bearings which have lower friction and wear rates, hence, theoretically, decreased incidence of aseptic loosening.

The wear rate for a "Charnley type" prosthesis couple is in average 0.1 mm/year, thus 1 mm/10 years[6], where the generated debris have a size range of 0.5 to 5 μm, rarely increasing to 100 μm[15,19]. More than 90% of PE debris is smaller than 1μm with a mean size of 0.53 ± 0.3 μm[4,8,10,14,47]. This predominantly tiny size led originally to underestimation of the particles number contained in the peri-prosthetic membrane, until new identification methods came up (electron microscopy, proteolytic enzymes use and density-gradient centrifugation)[14]. Kubo *et al*[48] showed that PE particles of 11 μm size are more biologically potent than larger PE particles; moreover, they showed that the particle's material composition is more strongly related to the histiocytes reaction than the particle size and load.

In a review of PE and metal debris features, Doorn *et al*[47] reported that "approximately 500 billion particles can be produced per year, for a total amount of trillions of particles during the lifetime of a prosthesis".

PE debris is colorless and can have different shapes (flakes, needles, spears): the larger ones have the shape of splinters or plates and the smaller, that of granules or elongated platelets[19,47]. Since the majority (> 90%) of the PE particles is smaller than 1 μm, the spheroid shape is predominant[4,8]. The size could be related to the specific wear mode: smaller particles are generated when the PE surface is rubbing against bone cement or metals[47]. Polyethylene particles are immunologically inert and are not toxic[47].

Willert *et al*[19] noted that, unlike metallic debris, PE debris do not cause necrosis or fibrin exudation of the capsular tissue; but they do produce, as metal products, a marked fibrosis where a meshwork of differentiated collagen fibers form around the foreign body giant cells and phagocytes. According to these authors, this extensive fibrosis is not directly correlated to the embedded PE particles. Plastic particles may travel away from the involved joint occupying the perivascular space[19].

Wear property of conventional PE can be markedly improved by cross-linking of ultrahigh molecular weight PE, either with radiation or with chemical means[49]. Five Mrad gamma radiation treatment lead to 85% improvement of wear resistance of the polyethylene. The improved wear characteristics of UHMWPE were proved in clinical studies as well as in laboratory testing using hip joint simulators. In a laboratory study where crossing-path motion was applied to hip simulator, McKellop *et al*[49] tested the wear resistance of crosslinked PE against extremely damaged femoral ball, trying to simulate extreme *in vivo* femoral head scratch by third-body abrasion. Laboratory crossing-path motion simulates more accurately hip joint *in vivo* than linear motion that could show an erroneous increased wear rate of cross-linked PE[50]. They demonstrated that cross-linked PE, with or without accelerated aging, still exhibit better wear rate than conventional PE even against harshly damaged femoral head[49].

Despite that highly cross-linked polyethylene debris is smaller than conventional PE debris with a critical size range of 0.2 to 0.8 μm[7], they are more bio-reactive; however their decreased volumetric wear prevails over their increased biologic reaction triggering[30]. It is of utmost importance to notice that it is not the wear volume that determines the biologic response but mainly the dose and the smaller size of generated debris[7].

Metallic debris

MOM couple was the first bearing used ever in the literature, first by Wiles, as early as 1938[20] then by McKee in 1940's. Initially, higher revision rate was reported with McKee-Farrar prosthesis than the Charnley low friction arthroplasty. Despite the stated imperfection of the initial design (equatorial contact produce higher frictional torque and wear than polar contact), recent studies have shown good to excellent survival of McKee-Farrar prosthesis[6,15].

MOM bearings had enormously regained interest recently based on their main advantage over MOP bearings, which is a smaller volumetric wear by

more than an order of magnitude (10-40 times less wear for MOM than MOP). Even UHMWPE failed to eliminate the problem of osteolysis and aseptic loosening[20,23,29,30,47,51-53]. In one study, Willert *et al*[20] reported 39-fold higher wear rate for UHMWPE than MOM bearings. As it was once supposed that eliminating cement from THA could address the problem of aseptic loosening, exclusion of polyethylene liners by using MOM bearing was proposed as conceivable solution for osteolysis[47]. Second-generation MOM couples were introduced in the 1990's to eliminate polyethylene-induced osteolysis[12,13]. Commercially available Co-Cr alloys have either low-carbide content (< 0.07%) or high-carbide content (> 0.2%)[12]. Carbide content affects the volumetric wear rate of CoCr alloys but not the particle size or morphologic features of the debris; high-carbide alloys have a wear rate of 2 to 5 μm/year whereas low-carbide alloys show a wear rate of 7.6 μm[12]. Low-carbide content MOM alloys are associated with more prominent immunologic adverse response where in one clinical study[12], extensive necrosis was present in 90% of the interface membrane surrounding failed MOM along with higher intensity of diffuse peri-vascular lymphocytic infiltration.

Although PE particles are considered the main etiology of peri-prosthetic osteolysis, metallic debris have been accused to cause ALTR leading to osteolysis, especially the Ti-alloy implants (Ti-6Al-4 V) more than Co-Cr alloy or stainless steel implants[12,13,26,47,54]. ALTR may cause intra-articular joint effusion characterized by sterile, watery, yellowish or grayish, hazy (tissue debris in suspension), basic (elevated pH) fluid with low cell count (lymphocytes)[54]. In fact, the metal-induced ALTR encompasses a spectrum of histo-pathologic changes including pure metallosis, aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) (detailed later in this paragraph) and granulomatous inflammation; ALVAL represents the precursor of lymphoid neogenesis[55].

The incidence of aseptic loosening leading to early failure of (MOM) TJA was recently estimated to be 4% to 5%, 6 to 7 years after implantation[10]. Metal products can be released from any part of the implant and by different mechanisms: wear, corrosion, stress, fretting and fatigue[56].

On the other hand, the generated metallic particles are smaller in size, of nanometer-order ranging from 30 nm to 200 μm (with majority of < 50 nm)[10,23,30,51]. Willert *et al*[19,20] reported a range size of 0.5 to 5 μm for the metallic wear debris; likewise other authors reported only micron-order size (0.1-1 μm) for the metallic debris with no clear difference between different metal alloys[47]. So despite the decreased volumetric wear associated with MOM couples, the resultant surface/area mass is extensive since the tiny particle sizes of metallic débris are produced at higher rate than MOP bearings[23,30,53]. Nevertheless, macrophage activation and cytokine release can be induced only by high volumetric concentrations of Co-Cr wear particles[51]. If not phagocytosed by macrophages, metallic products can be disseminated to the reticulo-endothelial system *via* the lymphatic vessels[53].

Wear of the metallic articulating surfaces can be manifested macroscopically by delicate scratches (that are sometimes more located in the weight-bearing areas) or polishing of various locations and sizes[20]. However scratches of the prosthesis articulating surfaces are not the primary source of metallic debris, where the anchoring surfaces of the implant represent the more powerful source of debris exhibiting polishing that is secondary to debonding of the implant and its subsequent movement against the bone cements[20]. Only in the circumstance of impingement between the cup rim and the stem neck, metallic wear debris emanates mainly from the articulating surfaces of the prosthesis[20].

Moreover, MOM bearings can undergo corrosion (electro-chemical dissociation) releasing free metallic products that can interact with the surrounding cells of the host tissue and the local body fluids forming complex organic and inorganic metallic products[20,23,30,51]. The process underlying the generation of metal products is ill-defined[30]. The wear debris derived from MOM implants can have one of 2 forms[23]: metal particulates or free metal ions like Cr^{3+}, Cr^{6+} and Co^{2+}. The predominant type of metallic wear particles is nanometer-sized chromium oxide (Cr_2O_3); but chromium particles are not the main offender in triggering the biological cascade[20,25]. In decreasing order after chromium particles, cobalt, nickel and molybdenum debris can be produced[19,20]. But also other soluble metal ions can be formed based on the type of the implanted alloy, like: aluminum, vanadium and titanium[10].

One clinical study found that aseptic loosening of uncemented MOM hip prosthesis result in a significant increase in cobalt serum level but not chromium[56]. The authors reported a 2.8 relative risk of implant loosening for a serum cobalt concentration greater than 9 nmol/L.

Metallic particles have an amorphous, irregular shape (flakes or needles) with sharp edges and a black color staining black the inner layer of the joint capsule[19,20,47]. Submicron sized metal debris procure a blue color to the cellular cytoplasm[47].

The *in vivo* number of metal particles released per year is estimated to range from 6×10^{12} to 250×10^{12} particles[23]. Basic processes of the adverse biologic responses apply also to metal products. Metal debris up-regulate the transcription factor NF-κB and activate the monocyte/macrophage lineage releasing inflammatory cytokines like IL-1β, IL-6, IL-8 and TNF-α. However, metal debris has the specificity of activating the inflammasome danger-signaling in macrophages; this inflammasome activation lead to the maturation of IL-1β and IL-8[10,23]. Once the inflammatory mediators are released, osteoblast inhibition and osteoclast activation ensue, as previously mentioned in detail.

Systemic dissemination of the metallic debris *via* the lymphatic circulation: The cumulative effects of the biological behavior of the metallic debris and their nanometer size range may result in a systemic increase of ions levels, mainly cobalt and chromium serum, urine and synovial fluid concentrations[15,23,30,51,53,57]. Likewise patients with bilateral large-head MOM have higher serum metal ions concentrations compared to the patients with unilateral MOM[23]. To diagnose systemic release of metal ions, normal human serum concentrations of the mostly inserted metals should be recognized: [Cr] = 0.15 ng/mL, [Co] = 0.1-0.2 ng/mL, [Al] = 1-10 ng/mL, [Ti] less than 4.1 ng/mL and [V] less than 0.01 ng/mL.

In one study, there was up to 6- to 7-fold increase in the serologic concentration of cobalt and chromium with small increase in molybdenum level[58]. Another study comparing 4 groups of patients (healthy controls, patients with O.A. without TJA, patients with well-functioning MOP and patients with well-functioning MOM THA), has shown a 13-fold increase in Co and 58-fold increase in Cr concentrations[31]. Several studies reported similar Co and Cr levels in the serum of patients with stable MOM prosthesis and those who do not have any implanted prosthesis[56]. To be noted that there is imperfect correlation between the serologic ion levels, wear rate and incidence of ALTR[54].

The systemic release of metallic ions is a major concern even though acute and forthright toxicity is exceedingly rare, where the incidence of patients necessitating revision for probable hypersensitivity to otherwise well-performing MOM bearings is very low[30]. Even well-performing MOM arthroplasties have shown 3 to 5 times increase in Co and Cr levels[13]. Renal failure can potentiate the detrimental effect of the metallic debris, highlighting the problem of chronic toxicity which is still uncertain nowadays[30,53]. However, it is admitted that the local concentration of metallic debris in the synovial fluid seldom exceed the threshold identified as toxic *in vitro* or dangerous in occupational medicine[53]. Willert *et al*[20] reported a low metal content in the peri-prosthetic tissue of MOM bearings (metal debris representing 0.1% of this tissue), but Huo *et al*[46] reported higher metal and Ba content for loosened implants. The *in vivo* relationship between intracellular debris content and disease development is not fully clear, but toxicity and carcinogenicity of metallic debris have been demonstrated in animal experimental models and in *in vitro* tissue cultures, as well as in clinical studies[57]. Numerous neoplastic tumors have been reported in tissue contiguous to metal prosthesis: lymphomas, malignant fibrous histiocytomas, sarcomas, and haemangio-endothelioma[57]. Likewise, increased incidence of lymphoma and leukemia has been reported after THA in 2 epidemiologic studies[57] but was refuted by other reports[10]. Increased levels of chromium can lead to carcinogenesis, hypersensitivity and nephropathy[57]. Excessive amounts of cobalt can cause hypothyroidism, polycythemia, neoplasia and cardiomyopathies[10]; although Co-induced cardiomyopathy is a theoretical concern, several reports stated that cobalt-containing beer could be the possible culprit of lethal cardiac myopathies[59,60]. Vanadium as well, has been associated with renal and cardiac disorder, hypertension and bipolar psychosis[10]. Nickel and aluminum carcinogenicity to the lung and bladder tissue was reported in industrially exposed workers; nickel is also associated with hypersensitivity and eczematous dermatitis[10,57]. Similarly, increased aluminum level was shown to be a possible etiology of senile dementia, encephalopathy and diminished bone mineral density.

Despite all these literature reports, no clear correlation has been established between metal release from implants and neoplastic, toxic or metabolic diseases. Whenever wear debris are copiously generated, they will exceed the capacity of the local tissue to eliminate them, leading to accumulation and consequently systemic dissemination of these metallic particles which can be, theoretically, harmful to any reached organ. Besides, it has been shown that cobalt chrome alloy-containing prosthesis (whether MOM or MOP) can cause chromosomal aberrations, like translocations (1.5-fold) and aneuploidy (2 to 4-fold) which clinical significance is still unclear[23,30,51,59].

Metal products have a specific biological behavior consisting of triggering a significant and complex immune response involving B and T lymphocytes; this can result in abnormal masses (fibrosis or hystiocytosis), bursa hypertrophy or tissue necrosis[23,30]. A shift in the $CD4^+$/$CD8^+$ circulating lymphocyte ratio was demonstrated in patients with well-functioning implants[5]. It is still unclear if this immune response is the resultant of patient hypersensitivity or increased metal products concentration in the peripheral blood. Recently, Lohmann *et al*[61] stated that the type of tissue reaction in failed MOM arthroplasties may be predicted by the peri-prosthetic tissue metal content and not by the serum metal content. They demonstrated that tissues with higher metal content (222.2 ± 52.9 μg/g) exhibited a predominantly lymphocytic response and those with lower metal content (3.0 ± 0.9 μg/g) showed a non-specific macrophage-mediated granulomatous response.

A long-standing problematic issue was and is still to be "metal allergy" that is irrefutably a real clinical fact but with uncertain prevalence and clinical repercussion[30,31,51]. Evans *et al*[62] were the first to report, in 1974, that metal sensitivity is a cause for bone necrosis and prosthesis loosening where metallic particles released from MOM bearings may obliterate the blood vessels irrigating the peri-prosthetic bone leading to its necrosis. Hypersensitivity can be manifested clinically by urticaria, dermatitis, and vasculitis.

The main metal sensitizers embrace, in order of potency: nickel (Ni), cobalt (Co) and chromium (Cr); Titanium (Ti), vanadium (V) and tantalum (Ta) are exceedingly rare cause of immune hypersensitivity[31]. Nickel is the most potent and most common metal

sensitizer where 14% of the general population has dermal sensitivity to Ni[10]. Dermal metal sensitivity has an estimated prevalence of 10% among the general population, 25% among patients with well-functioning TJA and 60% among patients with poorly-performing TJA[10,31]. In case of early MOM failure, the prevalence of metal sensitivity is estimated to be six-times that of the general population[10].

Metal-induced allergic response is similar to T Lymphocytes-mediated delayed-type hypersensitivity response (type Ⅳ); in this response, T lymphocytes are activated by a primary then secondary stimulus, which are respectively metal ions (or metal particulates-proteins complexes) and danger-associated molecular patterns (DAMPs). DAMPs can be endogenous alarmins released from damaged cells (such as monosodium urate crystals) or exogenous microbial pathogen-associated molecular patterns that can incite innate immunity through Toll-like receptors (TLR) activation. This will lead to a complex interaction between the antigen-presenting dendritic cells that release TNF-α and IL-1 and T lymphocytes that release interferon-γ. A recent *in vitro* study has showed that "Toll-like receptor 4" on the macrophage surface are crucial in mediating the pro-inflammatory immune response to cobalt-alloy particles[23]. TLRs are cell surface receptors expressed in neutrophils, B-cells, dendritic cells and macrophages; More than 10 human TLRs are identified where TLR4 is one of the best described TLR. Particle-challenged human monocytes, beside contributing to other important aspects of the inflammatory response, up-regulated IL-1β, TNF-α and IL-8[23]; and this rise in cytokine release was proportional to particle:cell ratio and was induced either by particle phagocytosis or by extra-cellular stimulation of TLR4. Blocking TLR4 by antibodies before exposure to Co debris caused 46% inhibition of IL-8 mRNA expression and 72% decrease in IL-8 protein synthesis in 24 h[23].

Despite that metal-induced allergic reaction is considered idiosyncratic, some clinical studies could demonstrate dose-dependent reaction intensity with proportional relationship between lymphocyte reactivity levels and serum-metal levels[23,31]. But no clear causativeness could be established between metal-induced lymphocyte reactivity and poor metallic implant performance[31].

Latterly, MOM bearings showed a unique histologic reaction of prominent perivascular and/or diffuse intramural lymphocytic infiltration which is evocative of a cell-mediated delayed-type hypersensitivity response. Willert *et al*[63] termed this response to failed second-generation MOM bearings, ALVAL or "lymphocyte-dominated immunological answer" (LYDIA) which is actually an area of active investigation. ALVAL or LYDIA is an histologic reaction consisting of "diffuse and peri-vascular infiltrate of T- and B-lymphocytes and plasma cells, high endothelial venules, localized bleeding, massive fibrin exudation, accumulation of macrophages with drop-like inclusions and infiltrates of eosinophils and necrosis"[63]. The histo-chemical examination of the macrophages inclusions did not show the phagocytosis of implant-debris but more likely phagocytosis of organic material. The majority of the examined tissue "contained small amounts of histologically visible metal wear particles", suggesting no correlation between the observed immunologic reaction and the particle dose confined in the tissue[63].

Clinically, ALVAL can be manifested by persistent or recurrent pain, soon after primary THA, along with prominent hip effusion, necessitating revision surgery even for well-fixed implants[63].

Based on recent clinical studies, a correlation was established between positive patch test or histologic evidence of ALVAL, and early osteolysis in patients with MOM bearings. Definitely, a poorly-functioning MOM prosthesis produce higher wear rate and subsequently established osteolysis that leads to implant loosening.

Patients with "ALVAL" may experience pain or may develop pseudo-tumors[20,23,64] that are one of the serious consequences of metal debris. Pseudo-tumors, which mechanism of formation is unclear, are complex lesions of lymphocytes, fibroblasts, multi-nucleated cells (with metallic debris inclusions)[20] and granulocytes[23] with significantly high IL-8 (approximately 200-fold higher than IL-1β and TNF-α levels released by the challenged macrophages)[23]. IL-8 is characterized by strong chemotactic effect that may instigate and maintain cellular infiltration leading to pseudo-tumor formation. Pandit *et al*[64] were the first, in 2008, to describe abnormal soft-tissue mass around the hip using the term of "pseudotumors" because these masses are neither infective neither neoplastic. In their large series of hip resurfacings (1300 cases), they observed 12 cases of pseudotumors reporting an incidence of 1% at 5 years; they also stated that some cases were asymptomatic and were discovered incidentally, indicating that the incidence of this abnormal mass, which can be overlooked clinically, could be higher than initially estimated. The most common presentation of pseudotumors was hip discomfort, but also nerve palsy, spontaneous dislocation, rash and obvious palpable mass could occur[64]. To be noted that Boardman *et al*[65] reported, in 2006, a single case of benign psoas mass, secondary to MOM hip resurfacing, that resolved after conversion to conventional THR. Interestingly, a case report was recently published stating pseudo-tumor formation and metallosis in a modular hip hemiarthroplasty where the corrosion products arose from the non-articulating modular prosthetic junction[66].

Since host factors determining the reactivity to wear products are still ill-defined (where some patients develop marked reactivity after a short period of MOM implantation and others can tolerate great debris loads for long period)[31], and since the toxicological implication of high metal ions are not fully elucidated[10,30], patients monitoring, in the circumstance of any clinical or radiographic doubt, with regular metal

ions measurements seems to be judicious[54].

In summary, MOM bearings use in arthroplasty had re-emerged recently after UHMWPE failed to prevent osteolysis. The wear rate of MOM determines the potential of these bearings to trigger the adverse biologic reactions; still to be determined in the future, what wear rate of modern MOM couples is considered safe, precluding the innumerable toxicity associated with metal products. This wear rate, that is by far less than that of plastic, can be further reduced with the use of better design (especially carbon-containing alloy and metal fabrication by forging rather than casting) and larger femoral head with improved radial clearance or perhaps with combination of different hard surfaces[12,15,51,52]. And even when metallic wear is histo-pathologically demonstrated, metal debris do not dominate the adverse histologic reaction[20]. Conformity between the prosthesis components is required, but at least a 0.15- to 0.20-mm clearance should exist between the ball and socket to allow fluid ingress[20]. Despite all the achieved advances in the manufacturing process, creating metallic material with excellent tribologic qualities (wear, friction and lubrication), metal hypersensitivity, toxicity and pseudo-tumors risks remain a dreaded issue which is still not fully controllable.

Ceramic debris

The French surgeon, Pierre BOUTIN, was the first to implement a COC total hip replacement[6]. Since then, COC couples had become an attractive, reliable and more durable alternative to traditional bearings of THA, especially with the design and material improvements accomplished with time (microstructure, density, mechanical strength and surface finish of ceramic materials). Despite their earlier use in Europe, alumina femoral heads were not available in the United States until the early 1980's and Zirconia heads until 1989[15].

Ceramics are stable solid compounds of metals and nonmetals (like oxygen or other anions), with the 2 main ceramic materials, nowadays in clinical use, being alumina (Al_2O_3) and Zirconia (ZrO_2)[15,67]. Ceramics gained interest because of their favorable characteristics of biochemical inertness, hardness (they resist scratching and maintain their polished finishing), wettability, high-strength, corrosion and wear resistance and thermodynamic stability[15,67,68]. Ceramics are considerably harder than both CoCr and Ti alloy tapers[15]. Resistance to abrasive wear is proportional to the hardness of the bearing surface; subsequently ceramic surfaces are more resistant to abrasive wear than metallic surfaces[29]. Laboratory testing had demonstrated that different kinds of wear debris can cause a visible abrasion of all metal surfaces (including nitrogen ion implanted Ti-6Al-4V) but not of ceramic surfaces which, in addition, produce less UHMWPE wear than metallic surfaces[29].

Ceramic compounds are extremely inert biologically and chemically because the reaction of their formation (where base metals, like aluminum, react with oxygen) is highly exothermic, setting these compounds in a very low energy state, hence precluding any further dissociation[67]. Unlike PE that are nonpolar and nonionic molecules, ceramic materials have an ionic structure making their surface hydrophilic; this allows the "polar" water-based fluids to spread over their surface reducing the intimate contact between PE and ceramic[15].

On the other hand, ceramic's brittleness constitutes a drawback which carries a dreaded risk of fracture which cause is, nowadays, attributed to a manufacturing defect[6,67]. The strongest zirconium oxide was introduced to reduce the risk of catastrophic failure (fracture) and to expand the available size range of ceramic components[15]. With the greater fracture toughness (approximately twice that of Al_2O_3) and higher strength of ZrO_2, smaller heads and longer necks could be used but still without attaining the size range available with CoCr heads[15].

Ceramics have exceptional compression strength but poor bending strength making them unable to deform without breakage[68]. The fracture rate reported in the literature varied tremendously from 0% to 13%. Among others, Hannouche *et al*[68] reported an extremely low fracture rate of 0.2% (13 components fracture out of 5500 implanted over a period of 25 years). They recommended a meticulous surgical technique in the use of ceramic femoral head to preclude fracture and stated that this exceedingly rare complication can be overcome by the more common risk of wear and osteolysis associated with MOP or even MOM bearings. Interestingly, Heck *et al*[69] reported that the fracture rate of alumina ceramic is less than PE liner fracture (that represents the weakest link in THA) or metallic stem fracture. Recently, even lower fracture rate has been reported (0.004%)[70]. It is worth to note again that ceramic fracture can be effectively reduced by following a scrupulous surgical technique avoiding excessive abduction of the acetabular component and ensuring a concentric fit of the femoral head on the Morse taper. Before axial impaction, the femoral head should be rotated to guarantee its concentric seating on the trunion to avoid any gouging of the taper by the border of ceramic head[15]. Failure of the Morse taper can be catastrophic leading to fretting corrosion and severe metallosis with metallic embedding in the ceramic bearing surfaces[71].

The wear volume associated with ceramic bearings is considerably less than that of metallic bearings[6,30,31]. PE component in COP bearings exhibits a linear wear that is 5 to 10 fold lower than PE wear in MOP bearings[15]. Because they do not experience surface roughening with time as metal bearings do, ceramics reduce the long-term UHMWPE wear, more than metals[72]. Likewise, COC wear rate is 10-times less than the lowest PE wear rate, being around 0.003 mm/year[15]. This decreased debris generation accounts for the reduced likelihood of adverse biologic reaction and osteolysis with ceramic bearings.

As previously mentioned, bulk form of ceramics is

inert, sparing the environmental oxidative deterioration[30]. On the other hand, once ceramic particles are produced, only in the setting of flawed or poorly functioning components, they induce a cellular response similar in intensity and quality to that triggered by the polymeric and metallic debris[15,30]. A recent study showed that, in contrast to failed MOP bearings, ceramic wear debris and osteolysis are the consequence rather than the cause of COC bearings failure[11]. It is true that the initial design and tribologic material of ceramics were responsible of wear generation and subsequent early failure. But at the present time, early failure of COC is deemed to be secondary to mechanical problems (initial malpositioning or instability) or infection. Hereafter, ceramic bearings are more sensitive to technical errors of implantations than other bearings.

Like metallic products, the ceramic wear debris is small in size, henceforth are produced in greater number, saturating the surface area of the host cells[15]. Some authors reported that ceramic particles size range from 0.13 to 7.2 μm with an average of 0.71 μm[15]; But allegedly, ceramic particles size range is bimodal: nanometer-scale of magnitude for most of these particles and submicron- to micron-order for the remaining part with a mean size of 0.7 μm (as for the polyethylene debris)[30]. Once again, the main biologic factors that determine the cellular response remain to be the particle characteristics (shape, volume and size). But unlike metal products, different ceramic wear products (alumina or Zirconia) do not stimulate the adaptive immune system because they do not experience any corrosion.

Despite the fact that ceramics are considered biologically indolent, ceramics products bio-inertness has been questioned by some studies. Li *et al*[73] showed that alumina and hydroxyapatite have no cytotoxic effects to the *in vitro* cultured human fibroblasts challenged by different particle doses (1-500 μ/mL), while zirconia and tricalcium phosphate inhibited cell viability, where a concentration of about 50 μg/mL decreased cell viability by 50%. Likewise, Lerouge *et al*[74] demonstrated, through an *in vivo* characterization of wear debris generated from COC THA, that ZrO_2 and not Al_2O_3 particles, induce a histiocytic foreign-body reaction and are the major particles responsible of aseptic loosening associated with COC bearings. Alumina oxide particles were found in only 12% of the histologic sections analysis, whereas zirconium oxide debris were by far more numerous and were found in 76%; the third particle type retrieved being Ti alloy debris. In contrast to these studies, a more recent study showed that Al_2O_3 and ZrO_2 do not alter the metabolism of arachidonic acid of synoviocytes cell membrane neither increase IL-1 and IL-6 release[75]. Synovial tissue contains two different cell types: Type A, macrophage-like synoviocytes and, type B, fibroblast-like synoviocytes. The latter are responsible for synovial hyperplasia and are involved in activating the cellular inflammatory reaction by releasing several kinds of inflammatory mediators. Both IL-1 and IL-6 are elevated in the synovial fluid of rheumatoid arthritis (RA) patients. Arachidonic acid metabolites [like (LTB4) leukotriene B4] play a major role in the pathogenesis of multiple inflammatory diseases like asthma, inflammatory bowel disease and RA. A recent *in-vitro* study suggested that biocompatibility of zirconia is greater than that of titanium[76]. Cultured macrophages challenged with both titanium or Zirconia particles expressed increased mRNA for TLRs 2, 3, 4 and 9, and their intracellular adaptors and pro-inflammatory cytokines. However, quantitative differences were evident where zirconia-induced pro-inflammatory gene expression was lower than that provoked by titanium particles.

In summary, COC bearings have the great advantage, over other bearings, of decreased wear rate due to their hardness which resist scratching, making them more suitable for younger patients. Disadvantages of ceramics include their cost[70] and the limited range of neck size available because of the fracture risk. Fracture risk can be tremendously reduced by following a thorough surgical technique and by ensuring an excellent ceramic manufacturing with a quality is nondestructively pre-clinically tested. The increased cost of ceramics seems to be justified, especially in young patients, by the decreased wear rate of COP *vs* MOP, even with traditional PE[70]. Ceramic-on-polyethylene bearings exhibit a wear rate of 0.034 mm/year compared to 0.1 mm/year for metal-on-polyethylene bearings. Ceramic-on-crosslinked PE couples display a wear rate of 0.019 mm/year compared to 0.03 mm/year for metal-on-crosslinked PE.

Polymethylmethacrylate debris

Cemented fixation of both components of THA was the initial fixation method proposed by Charnley[1,14]. In 1989 at Boston, William Harris was the 1st to develop and implement a hybrid hip prosthesis with cementless press-fitted hemispherical metallic cup and cemented titanium femoral stem[6].

It is recommended nowadays not to use a cemented titanium stem because it can generate tremendous amount of Ti debris once loosened, and to use proximally or fully hydroxyapatite-coated cementless titanium stem[6]. Salvati *et al*[18] stated that the synovial fluid contain a significantly higher levels of metal debris with loosened cemented titanium stem (21-fold) than loosened cemented cobalt-chromium stem (7-fold).

The biologic response triggered by PE wear particles is almost similar to that induced by other types of particles. A majority of studies challenged inflammatory cells by different kinds of debris, including PMMA debris, and showed quit identical cellular reaction[21,44]. In fact, PMMA debris are not the sole foreign material found in the peri-prosthetic tissue; based on the type

of implanted prosthesis, other particles can be found (metal, plastic...). Hence, if one of these foreign particles triggers the inflammatory cascade, other particles types perpetuate this adverse reaction[19]. Willert *et al*[20] showed that cement-induced reaction more frequently outweighs metal-induced reaction; but different scenarios may also exist but less frequently.

Macrophages are always the primordial cell type involved in the adverse biologic response, secreting several inflammatory mediators mainly IL-1 and TNF-α. Likewise, PMMA debris recruit peripheral monocyte/macrophages enhancing cell cluttering in the nidus of wear debris, the peri-prosthetic interface membrane[44].

If the cement mantle is macroscopically destroyed or disorganized, PMMA particles may be found within the capsular tissue[19]. Acrylic particles have a size range of 1-2 μm to several hundreds of microns and different shape organization: the smallest ones are dust-like granules and the largest are like pearls clusters or grapes bunch[19,20]. According to their size, PMMA particles can be or not phagocytosed and stored within inclusions in the foamy cytoplasm of macrophages[19]. As previously mentioned, foreign body giant cells predominate in cement-induced aseptic loosening, surrounding the non-phagocytosable large cement fragments. Hence, fibrosis or hyalinization and necrosis of granulomas (formed by Histiocytes incorporating foreign materials) are less common with acrylic particles, as well as plasma cells and lymphocytes infiltration[19].

If the polymethylmethacrylate bone cement contains radio-opaque contrast media, ZrO_2 or $BaSO_4$, traces of these molecules can be detectable in macrophages (or less commonly in foreign body giant cell) inclusions reflecting the disintegration of the bone cement storage in the tissue. The $BaSO_4$ or ZrO_2 particles have an average size of 0.5 to 8 μm[20]. So disintegration of the bone cement can produce PMMA particles and/or ZrO_2 or $BaSO_4$ particles that, besides their direct effect, can cause a third-body wear once they reach the articulation compartment[20].

Aseptic loosening of cemented prosthesis can display one of 2 forms: extensive granulomatosis or non-granulomatous aseptic loosening[77]. PMMA debris can elicit an immunologic-type adverse biologic reaction, a T-lymphocyte mediated hypersensitivity immune response[77]. The bone-cement interface membrane is infiltrated by monocytes-macrophages and multinucleated giant cells encumbered with cement particles. Whereas Santavirta *et al*[77] demonstrated a difference in the immune-pathologic response between granulomatous and non-granulomatous aseptic loosening, Gil-Albarova *et al*[78] showed no difference with increase of both total and activated CD2-positive T lymphocytes in both types of loosening. Likewise, Santavirta *et al*[77] considered these 2 forms of aseptic loosening as 2 different conditions on the basis of the relative lack of fibroblasts in the peri-prosthetic membrane, with activated fibroblasts being the main cell constituent of non-granulomatous aseptic loosening. Gil-Albarova *et al*[78] stated that both histo-pathological patterns have a single systemic immune response and have no difference regarding lymphocytes subtypes (increase in B and T lymphocytes, mainly CD2, CD22 and CD25 positive cells), patch test reactivity and lymphoblast transformation test induced by PMMA material[77].

FUTURE DIRECTIONS AND TREATMENT STRATEGIES

One of the essential repercussions of advanced understanding of the problematical osteolysis process is the development of novel therapeutic modalities that may slow down or prevent disease progression. The pharmacotherapy may target any stage of the intricate inflammatory reaction to wear debris: anti-inflammatory agents may be used to modulate the cytokines release, anti-osteolytic agents to disintegrate osteoclasts morphology, and antioxidants to demolish the free oxygen radicals produced by the activated macrophages. On the other hand, osteolysis may be prevented using osteogenic growth factors that play a critical role in bone formation, remodeling and reparation.

Based on the fact that cytokines constitute the major mediators of the debris-induced adverse response, anti-inflammatory agents have been proposed to down-regulate this reaction. Blaine *et al*[79] reported the modulatory effect of some pharmacologic agents, that alter the intracellular levels of cAMP, on cytokines production (IL-6 and TNF-α) by titanium-stimulated human peripheral blood monocytes[79]. Interestingly, active cAMP analogs (Dibutyryl cAMP) and prostaglandins (E1 and E2) enhanced IL-6 synthesis but inhibited TNF-α production. They showed also that some anti-inflammatory products (indomethacin) may potentiate cytokine production (3 fold increase in TNF-α production). This finding implicate that one should understand the echelon of action of anti-inflammatory medication proposed to delay the disease process, and that the role of culprit cytokines should be stratified by potency weight, since the used agent may inhibit one inflammatory mediator at the price of enhancing other. Likewise, Schwarz *et al*[80] stated that periprosthetic osteolysis and inflammation can be controlled by anti-TNF-α therapy. In an exceptionally novel technique, Keeney *et al*[24] stated that the debris-induced inflammatory response can be modulated by mutant MCP-1 protein delivery from biodegradable layer-by-layer coatings on orthopedic implants. As previously mentioned, MCP-1 is one of the most potent cytokines involved in macrophages recruitment, whose receptors may be blocked using a decoy drug, such as 7nd, a mutant MCP-1 protein. Interestingly, Vallés *et al*[81] stated that simvastatin pre-treatment of human osteoblastic cells down-regulated Ti particle-induced *IL-6* gene expression at mRNA and protein levels. Statins, well-known hypo-lipidemiant

drugs, have anti-inflammatory, immune-modulatory and osteo-anabolic effects where they suppress osteoclastic bone resorption and support osteoblast-precursors recruitment enhancing proliferation, differentiation and mineralization of osteoblasts. Metal debris particularly up-regulate IL-6 release by osteoblasts and peri-prosthetic membranous tissues.

Bisphosphonates have been shown to be potent anti-osteolytic agents that interfere with internal enzymatic cell system disrupting the osteoclast cytoskeleton, effectively used in the treatment of metabolic bone disease with prominent bone resorption, including osteoporosis, Paget's disease and metastatic hypercalcemia[82,83]. Several animal model studies demonstrated the inhibitory effect of bisphosphonates on particle-induced bone resorption. Horowitz *et al*[84] showed that disodium pamidronate is effective in reversing the bone resorption secondary to macrophage exposure to bone cement particles. Similarly, Shanbhag *et al*[85] reported that alendronate, which is integrated in the mineralizing matrix inhibiting osteoclastic activity, reduced debris-induced osteolysis (PE/Ti/Co-Cr) in a canine THA model. A recent meta-analysis, including six randomized controlled trials, suggested that bisphosphonates are advantageous in preserving more peri-prosthetic bone mineral density than that in controls[86]. More recently, a clinical study showed that parenteral (intra-muscular) administration of neridronate, every fortnight for the first three months then every month for the remaining period of 1-year follow-up, reduced pain, improved function and halted the roentgenographic evolution of peri-prosthetic osteolysis, as well as amplified peri-prosthetic bone mineral density as confirmed by DEXA measurements[87]. Since reactive oxygen species (mainly produced by the phagocyte immune cell type) and reactive nitrogen species (a family of antimicrobial molecules derived from NO and superoxide) may mediate aseptic inflammation affecting directly periprosthetic osteolysis, antioxidants use is an attractive manner to modulate the disease process. Antioxidants, such as ascorbic acid[88], bioflavonoid pycnogenol[89], N-acetylcysteine[90], pyrrolidinedithiocarbamic acid[90], are potent free radical scavengers down regulating the phagocytic immune response. Bioflavonoids, class of plant secondary metabolites previously known as vitamin P, have been reported to reduce the gene expression and synthesis of IL-1β and IL-2 by inactivating NF-κB and activator protein-1, two major transcription factors considerably involved in cytokines gene expression[89].

Prevention of osteolysis constitutes the alternative mode of intervention, alongside the down-regulation of the inflammatory process. For this purpose, osteogenic growth factors may be used to locally regulate bone configuration and remodeling. BMPs, insulin-like growth factors (IGFs), and various TGF-β = a known regulator of collagen type Ⅰ represent fundamental local regulators of osteogenesis; most significantly these growth factors interact with nuclear transcription factors (like Core Binding Factor a1) in response to sex steroids, glucocorticoids, parathyroid hormone, or PGE2, which are all well-known controllers of bone turn-over[91]. Hill *et al*[92] demonstrated that osteoblast survival is promoted by IGF-Ⅰ, IGF-Ⅱ, insulin and basic FGF but not the PDGF; however, they stated that PDGFs, even though they have no direct effect on osteoblast survival, they potentiate the survival-promoting effects of IGF-Ⅰ, IGF-Ⅱ, and insulin. The authors concluded that TNF-alpha, a monocyte-derived factor, prominently boosts cellular apoptosis and may negate the osteoblastogenic effects of other unidentified growth factors or components of the extracellular matrix. Dobai *et al*[93] established that, *in-vitro* treatment of osteoblasts with 1α, 25-$(OH)_2$ vitamin D3 (hormonally active form of vitamin D also known as calcitriol) may reverse the particle-induced (Ti/Cr/UHMWPE) diminished osteoblast function of collagen gene expression and synthesis.

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