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PARTICLE DISEASE. A COMPREHENSIVE THEORY OF PERIPROSTHETIC OSTEOLYSIS: A REVIEW

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Aseptic loosening and osteolysis are considered the main long-term problems of hip arthroplasty. Pathogenesis of periprosthetic osteolysis is multifactorial, and both the biological and mechanical factors seem to play an important role. Bearing surfaces continuously generate excessive amounts of micron and submicron particles provoking an adverse inflammatory response of periprosthetic connective tissues. In general, a key role has been attributed to macrophages. Cytokines, growth factors, PGE_2, and enzymes are secreted with activated periprosthetic cells resulting in formation of osteolytic granulomas. The final osteolytic step is taken predominantly by osteoclasts which are getting ready for action mainly by an osteoprotegerin ligand (RANKL) and TNFα. Rankl is expressed by activated macrophages, osteoblasts, and lymphocytes. In parallel, a repetitive hydraulic effect of the joint fluid is manifested on the susceptible bone.

INTRODUCTION

Numerous studies illustrate clinical success of total hip arthroplasty. It is estimated that almost 1 million of total hip replacements are implanted world-wide annually.[3] Surgery is considered as routine with a minimal rate of early complications offering a dramatic pain relief and improvement of the function. However, it remains only a time-limited solution for the damaged hip joint, since up to 30% of the patients can be revised within 10–14 years of the initial surgery.[4]

In the past several years, we have been facing an increasing number of hip arthroplasty revisions (Table 1). According to a report recently published by the Finnish arthroplasty register[43] a 10-year survival rate was observed in 72% and 90% of the patients younger than 55 years and above 70 years of age, respectively. Consequently, subsequent revisions have to be taken into account in younger patients. Aseptic loosening has been recognized as a main reason for revisions.

Osteolysis is almost always associated with aseptic loosening, but it could be seen with stable implants too (Fig. 1). It can be ascribed to an enhanced bone resorption closely related to endoprosthesis functioning. Santavirta et al.[46] defined aggressive periprosthetic osteolysis as the local, progressive, tumor-like aseptic bone resorption which can be easily distinguished from the conventional linear form.

A bone is an extremely dynamic tissue, and the remodelling process is closely controlled at both the local and systemic levels (the genome, hormones, growth factors, cytokines, loading patterns, etc.). There are tight couplings between activities of osteoblasts and osteoclasts and matrix deposition and mineralization. In addition, the actual status of the prosthetic bone bed is influenced by the implant variables (material, design, mode of fixation, surface parameters, etc.).[2] Inherent and/or acquired abnormalities can disturb the balance of the above-mentioned coupling mechanisms and shift them to the excessive bone resorption. **Periprosthetic osteolysis belongs to acquired, local excessive bone resorption provoked by prosthesis functioning,** but this process is also influenced by inborn factors.

Harris et al.[10] reported aggressive osteolysis around an unstable cemented stem in 1976, whilst Jasty et al.[21] observed osteolysis around a stable cemented one. Other authors described several cases with osteolysis around stable cementless implants.[32, 33]

Nevertheless, osteolysis is not the only reason for the periprosthetic bone loss that may be due to other factors, namely the so-called stress shielding and age-related changes.

The research focused on recognizing the natural history of periprosthetic osteolysis is very important, particularly in view of seeking effective preventive measures. Several theories have been suggested to explain the pathogenesis of aseptic periprosthetic osteolysis. They can be simply divided into biological, physical or biophysical according to their scientific roots.

The aim of the present article is to review the "particle disease",[11] a prominent biological theory of periprosthetic osteolysis and aseptic loosening. In parallel, the

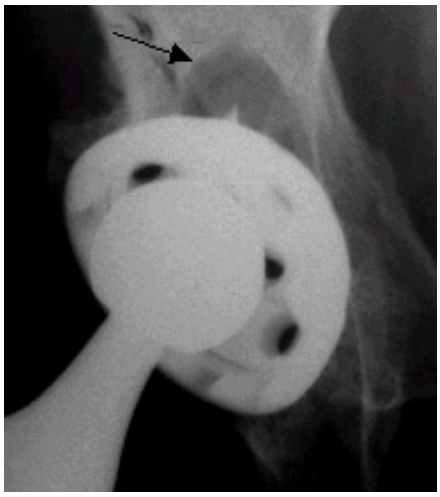

Fig. 1. Retroacetabular osteolysis (arrow) 4 years after primary surgery.

authors' intention is to show the extensive diffusion of fundamental research through the "conventional" orthopaedics.

GENERATION OF PROSTHETIC PARTICLES

A bone is a delicate tissue requiring some vital prerequisites for its fitness, but not the prosthetic detritus. It is a well-known fact that any hip prosthesis generates biologically active particles. Cementless modular implants seem to generate much more particles than cemented ones. There is a clinically evident association between the wear rate and the incidence of periprosthetic osteolysis.[41, 50]

The wear between the primary bearing surfaces is considered the most important source of prosthetic particles (i.e. microabrasions, microadhesions).[47] These micro-separations of the surface material are inevitable for artificial hip and knee joints regardless of a prosthetic design or material characteristics. The wear rates among individual bearers are different in dependence upon implant types, surgical techniques and patient-related factors. Schmalzried et al.[48] strongly argued the wear was a function of the amount and type of use of the prosthesis, not the time in situ. McKellop et al.[36] estimated that a traditional metal-on-polyethylene joint pair (a polyethylene cup-metallic ball) generated several hundreds of thousands polyethylene particles during each gait cycle. More than 90% of these particles are less than 1 μm in diameter with a mean size of 0.5 μm.[34]

The knowledge on polyethylene disease made necessary to develop modern alternative bearing surfaces to eliminate excessive generation of wear debris. It was found out that completely hard pairing (metal-on-metal or ceramic-on ceramic) improved significantly the wear resistance of artificial joints.[18] The same effect has been achieved by means of cross-linked polyethylene either under laboratory[37] or in vivo conditions.[59]

PARTICLE DETERMINANTS

Particles of all biomaterials used up-to-date can provoke an adverse biological reaction of periprosthetic tissues involving the formation of osteolytic foreign body granulomas, inhibition of the bone formation and joint fluid production.[56] The bone resorption leads ultimately to implant loosening. The extension of the bone destruction depends on the number, size, shape and composition of the particles. Hence, the specific biological activity of the debris can be established as the activity per unit volume of the wear material.[18,19]

Today, the standard bearing surface is polyethylene, therefore it can be a starting point. Polyethylene particles of irregular shapes within the size ranges from 0.2 to 7 μm are known to represent the most hazardous fraction.[18] Although Kadoya et al.[23] set up a threshold for polyethylene osteolysis (i.e. 1×10^{10} particles/gram periprosthetic tissue), and others demonstrated that the osteolytic effect was influenced by the size and concentration of the polyethylene particles in vitro[9] or in vivo,[28] still some doubts remain about the rigorous relationship between quantitative parameters and biological reactivity. For example Xing et al.[60] found that particle surface chemistry affected significantly cytokine and enzyme secretion of the activated macrophages.

A great effort is focused on the research of the relative bioreactivity of alternative materials. In 2002 Ingham et al.[19] presented a study confirming that ceramic-on-ceramic articulation had a lower osteolytic potential contrary to a metal-on metal configuration. In addition, it should be emphasized that Co-Cr particles are more toxic than ceramic ones.[19]

PATHOGENESIS OF PARTICLE DISEASE

Willert and Semlitsch[57, 58] and many others documented a foreign body reaction (Fig. 2) and permanent inflammation of periprosthetic tissues in conjunction with the occurrence of a huge number of particles. Sabokbar et al.[45] as well as other researchers validated the particle disease concept through the exact in vitro[39] and in vivo experiments.[13]

Particulate wear debris generated mechanically from prosthetic surfaces can alter the function of a variety of cell types within the periprosthetic space including macrophages, fibroblasts, osteoblasts and osteoclasts by means of phagocytosis or surface activation.[18, 39, 55] At present, monocyte/macrophages are believed to play a key role in the whole process. Mononuclear phagocyte cells attempt to eliminate large amounts of foreign particles in the joint space by means of phylogenetically proof phagocytosis.[18] Small particles are easily phagocytosed, but they are unable to be digested. The inability to degrade the engulfed particles leads to the increased but vain production of numerous mediators and cytokines by stimulated macrophages. The result of this "combat" against particles is excessive accumulation

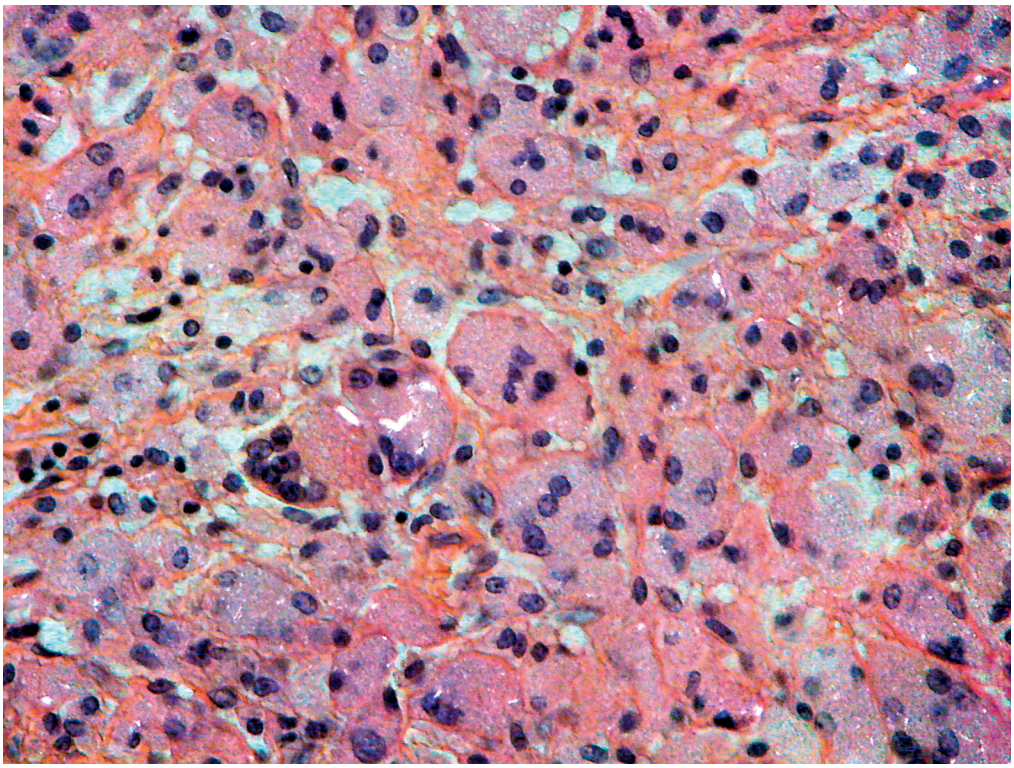

Fig. 2. A pseudocapsula with histiocytic infiltration. Wear particles are engulfed in cytoplasm of mononuclear histiocytes and in the interstitium. Larger particles are visible mostly in histiocytic giant cells. Polarized light. HE×20.

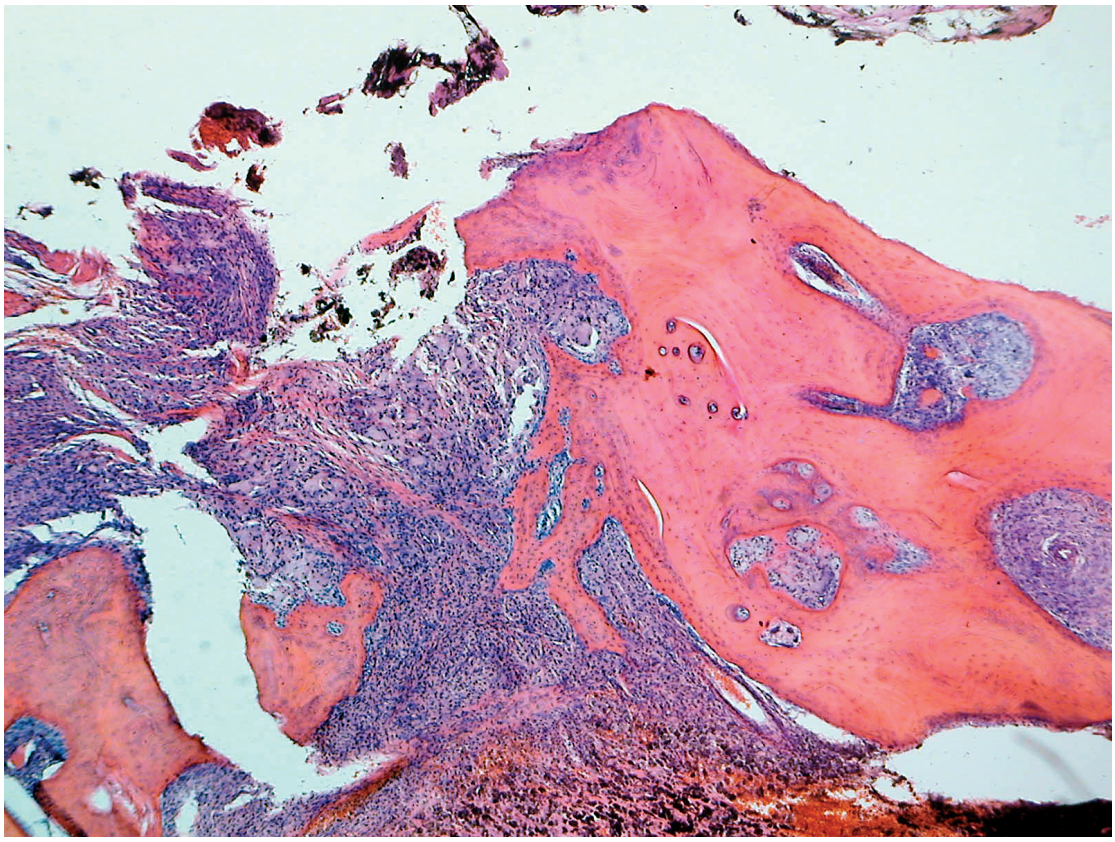

Fig. 3. A bone tissue retrieved during revision of a cementless prosthesis with hydroxyapatite coating. Histiocytic infiltrates are in the intimate contact with the bone trabeculae surface. HE×40.

of bone-resorbing factors and osteolysis, ultimately (Fig. 3). The induction of macrophage apoptosis could be a desirable solution to this situation due to the elimination of the inflammatory reaction power. Petit et al.[42] found the induction of macrophage apoptosis to be more insufficient with polyethylene particles as compared to ceramic ones. In general, the programme for cell death seems to be altered in the chronic inflammatory environment.

Through autocrine and paracrine signalling mechanisms,[55] the cells activated by particles release PGE_2,[7] cytokines and growth factors (i.e. TNF-α, IL-1ß, IL-3, IL-6, M-CSF, GM-CSF, PDGF),[40] chemokines (C-C chemokines,[38] MCP-1[54]), nitric oxide,[15] metalloproteinases,[51,53] and other factors. Among these cytokines, a TNF-α signaling pathway seems to play a key role in the process of periprosthetic osteolysis development since it stimulates osteoclast formation, differentiation and activity.[16,17] This may be through the mechanisms that are dependent and/or independent of the osteoclast differentiation factor (ODF, OPGL).[26] Childs et al.[17] really revealed that etanercept (soluble inhibitor of TNF-α) could inhibit osteoclastic bone resorption induced by the wear particles. The two final proteins controlling recruitment of the functional osteoclasts are a receptor activator of nuclear factor kappa ß-ligand (**RANKL**, ODF, OPGL), and its antagonist **osteoprotegerin** (OPG, OCIF).[6] RANKL stimulates the maturation of osteoclast progenitors by signalling through its membrane receptor RANK. **RANK signalling seems to be inevitable for osteoclast differentiation, activation and survival**.[14] Osteoprotegerin is a TNF receptor-like molecule which inhibits osteoclast maturation and activity by blocking the binding of RANKL to the RANK on the osteoclast progenitor cells.[49] **RANKL** is secreted by activated macrophages, osteoblasts, lymphocytes and other stromal cells.[12,27] Kim et al.[25] demonstrated that osteoprotegerin levels in the failed THA joint fluid were significantly lower compared to the control osteoarthritis group. Similarly, Goater et al.[6] confirmed that osteoclastogenesis was completely suppressed by osteoprotegerin.

The bone resorption is attained by both osteoclasts and activated macrophages. Because macrophages represent a dominant cell type at the bone-osteolysis interface, some believe they are capable of direct bone resorption.[23,24] According to this concept, the osteoclasts execute rapid, extensive bone resorption, whereas the macrophages are engaged mainly in low-grade surface or high-grade lacunar osteolysis.[44] Sabokbar et al.[45] showed arthroplasty derived macrophages could differentiate into multinucleated osteoclastic bone resorbing cells.

Little is known about the role of osteocytes in the process of osteolysis. It has been demonstrated that in vitro polyethylene particles can increase the PGE_2 and nitric oxide production of osteocyte-like cells.[31]

The poor periprosthetic bone quality may further contribute to the development of periprosthetic osteolysis. It was found that periprosthetic bone remodelling was more accelerated in association with an increasing particle-induced adverse host reaction resulting in fragile immature bone formation.[52] Osteoblasts are mainly responsible for the mechanisms of bone formation. Paradoxically, they are able to phagocyte the prosthetic particles as shown eg. by the Chicago research group.[54] The particle-osteoblast interaction results at least in the suppression of type I collagen synthesis and increased release of IL-6 and PGE_2 by activated osteoblasts.[31,54,55] In addition, metallic particles affect osteoblast proliferation and viability, the most toxic being Mn, V, Fe, Cu, Ni, Co.[54] Bi et al.[1] believe that the stimulation of osteoclast differentiation and activity is quantitatively more important for the development of osteolysis contrary to the inhibition or distortion of the bone formation.

It is believed that the primary reaction to the prosthetic debris is a non-specific foreign body reaction, but at least in some patients a specific immune system may be involved in the process of osteolysis and aseptic loosening. Some investigators suggested a participation of T-cell mediated type IV hypersensitivity.[5,8,29] Lymphocytes activation requires a specific antigenic stimulus in conjunction with the "costimulatory" signal presented by antigen-presenting cells (eg. dendritic cells or macrophages). One has to keep in mind that the cytokine milieu during T-cell activation is also important. A possible antigenic stimulus could be either a particle-protein complex[61] or endotoxin adsorbed on the prosthetic particles. Bi et al.[1] found adherent endotoxin to be required for a titanium particle-induced osteolysis in their experiment. According to the "extended self, nonself theory" the professional antigen-presenting cells have to interact with some microbial components to elicit an immune response.[20] The other authors failed to show any active role of lymphocytes in the periprosthetic tissues.[22,30] The controversies could be alleviated by better understanding of the immune system. For example, according to the slightly modified "danger theory" the professional antigen-presenting cells are also under certain circumstances activated by endogenous substances released by damaged bone tissues (eg. heat-shock proteins).[35]

CONCLUSIONS

The principle of periprosthetic osteolysis is based on the permanent interference of a huge number of small prosthetic particles with periprosthetic tissue cells. Phagocytosis of wear particles does not seem necessary for osteolytic cascade induction. The key efferent structures are probably both the activated macrophages and osteoclasts. A repetitive action of the joint fluid and mechanical stresses help destroy the periprosthetic bone bed in conjunction with particle disease.

Table 1. Causes and rates of aseptic revisions of total hip arthroplasty performed at the Orthopaedic Clinic in Olomouc between 1998 and 2001

	1998	1999	2000	2001
Aseptic loosening	46	37	39	37
Osteolysis around stable components	0	4	16	33
Periprosthetic fracture of the femur	3	2	6	7
Dislocations	2	5	8	9
Other reasons	1	1	3	8
Total	**52**	**49**	**72**	**94**

A List of Abbreviations Used:

TNF-α	Tumor necrosis factor-alpha
IL-1ß, IL-3, IL-6,	Interleukins 1-beta, 3, 6
M-CSF	Macrophage colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
PDGF	Platelet-derived growth factor
PGE_2	Prostaglandin E2
C-C chemokines	Conserved – Cysteines chemokines
MCP-1	Monocyte chemoattractant protein-1
OPGL	Osteoprotegerin ligand
OCIF	Osteoclastogenesis inhibitory factor

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