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Review Articles

Bone-Implant Interface Biology —— Foreign Body Reaction and Periprosthetic Osteolysis in Artificial Hip Joints ——

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Aseptic loosening and periprosthetic osteolysis are major problems in artificial hip joint surgery, for which a solution has yet to be found. Biological host response to wear debris combined with cyclic mechanical loading onto the bone bed around hip prosthetic implants has been considered as mechanism responsible for implant-mediated periprosthetic osteolysis. Any type of artificial joint gliding surface continuously produces wear debris, which are derived from implant materials, i. e., ultra-high molecular weight polyethylene, ceramics and metals. Fragmented bone cement between the bone and implants is also a source of debris. Currently, generation of debris is still inevitable, although modern technology provides better biocompatible implants to lessen the debris. Debris induces foreign body reaction in periprosthetic connective tissues. The main loci are synovial regenerating capsular tissues and interface tissues between the bone and implants, where macrophages play an important role. Various cellular mediators and proteinases are produced in the process. The reaction affects periprosthetic bone remodeling and can provoke imbalanced bone metabolism around implants. It weakens the bone and causes periprosthetic osteolysis. In addition, the joint fluid, which is released from the inflamed connective tissues, has osteolytic potential. Pumping effect on gait and poor integration of bone-implant interface allow penetration of the fluid into intact interface, thus enhancing osteolytic reactions around implants. Further studies on interface biology and implant-related osteolysis with modern technique should lead to a better solution to provide longer survivorship of the artificial hip joint.

Key words Foreign body reaction, Macrophage, Periprosthetic osteolysis, Loosening, Wear, Artificial hip joint.

INTRODUCTION

Artificial total hip joint surgery has become an efficient and cost effective procedure in the treatment of patients with painful end-stage arthritis, since the concept of low-friction artificial joint was established[1]. The surgery allows to relieve pain and restore the activity of walking in daily life. Some 800 000 hip joints are replaced annually on a worldwide scale. In successful artificial total hip joint surgery, where the prosthesis remains adequately fixed over a period of several years, the host response has a benign character and signs of immune inflammatory reaction may remain modest. Theoretically, if the mechanical stress is properly transferred to the bone present around the implants, they can support the joint function without loosening and without causing periprosthetic osteolysis, which guarantees a longer and better survivorship. However, loosening and osteolysis of implanted total hip joints occur even if the insertion of the prostheses is technically well performed[2,3] (Fig. 1, 2). A ten-year survival rate of approximately 90% has been demonstrated for total hip joint surgery, and some of them have to be revised due to aseptic loosening and periprosthetic osteolysis. Artificial total hip joints induce a foreign body/host response, including adaptive and reactive processes. They are reflected at the level of the tissue and the joint fluid phase. Debris from implants has been considered as a critical factor

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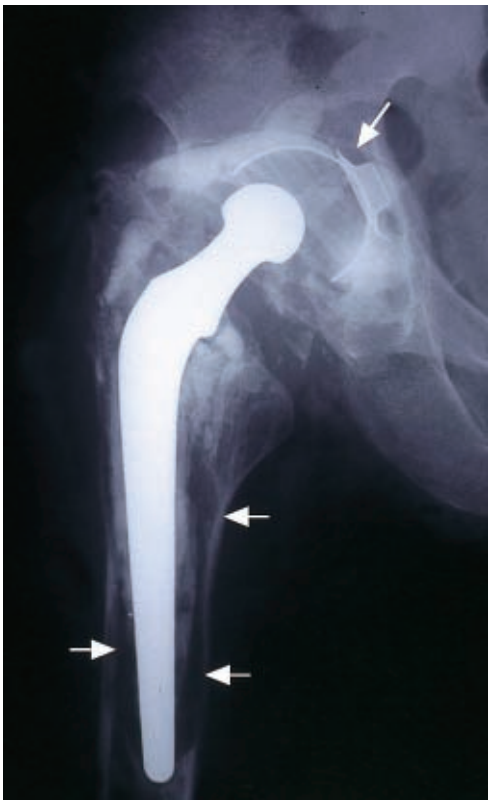

Fig. 1. X-ray picture of a Charnley type artificial total hip system, which was inserted 15 years ago. Periprosthetic osteolysis can be observed both in acetabular and femoral sides (arrows).

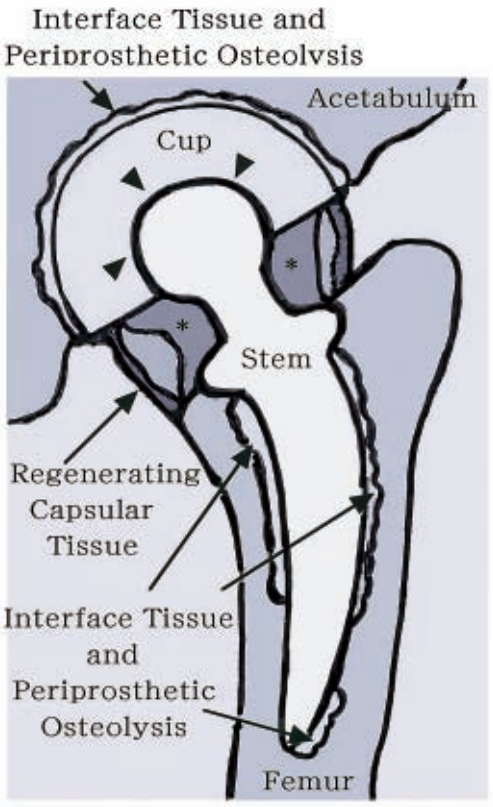

Fig. 2. Diagram of loose total hip joint with periprosthetic osteolysis. A total hip joint system consists of a cup and a stem. In a cement type system, the cup and the stem are fixed to the acetabulum and the femur, respectively, with bone cement. The joint system can move with gliding function between the concave cup and the spherical stem head (arrow heads). The gliding surface produces wear debris continuously. After replacement joint surgery, regenerating capsular tissue is formed. In case of excess production of wear debris, the debris is deposited in the tissues and inflammatory granulomatous reaction become evident. Osteolytic joint fluid is released from the tissues and a fluid retention can be observed (asterisks). An interface tissue is formed between the bone and the implant material/cement. If the implant is maintained with proper biocompatibility, the interface tissue is thin or absent. However, once a local host response to implant occurs, the interface tissues become dense and are recognized as radiolucent osteolytic area of granulomatous reaction between bone and implants.

inducing local host response. It seems to be influenced by multiple factors, i. e., type of material and fixation, design of prosthetic implants, bone quality, and activity and disease status of the patients. This major problem has been a subject of debate for three decades, and there is increasing concern regarding periprosthetic osteolysis and biocompatibility of total hip joint prostheses[2,3,4,5,6].

Inflammatory tissue reaction of regenerating capsular tissues and interface tissues.

Ultra-high molecular weight polyethylene, ceramics and metals are currently used as materials for the gliding surface of artificial hip joints, in order to provide low friction. However, a gliding surface continuously produces wears, although modern technology provides better biocompatible implants to lessen the wear debris. Any type of wear debris is phagocytosed by monocytes/macrophages. It induces macrophage-mediated foreign body reaction in regenerating capsular tissues and interface tissues between the bone and implants (Fig. 2, 3). Bone cement fragments and its small particles are also known to induce the reaction. In chronic local host reaction to debris and/or particles, the cellular response mainly consists of monocytes/macrophages and fibroblasts[6,7,8,9]. Monocytes/macrophages have a remarkable capacity to adapt according to the circumstances prevailing in the micro-milieu. Due to initial tissue damage and the insertion of large foreign body implants and debris, it is not surprising that monocytes are rapidly recruited into tissues surrounding the implants. Monocytes adhere to implants and their debris and are rapidly converted into mature macrophages and multinuclear foreign body type giant cells. They produce various cellular mediators and proteinases in the inflammatory tissues, and contribute to weakening of periprosthetic connective tissue and to process of periprosthetic osteolysis[7]. Fibroblasts are continuously replicating mesenchymal cells, which synthesize the connective tissue matrix and control it via degradative enzymes, including collagenase/gelatinases (a family of matrix metalloproteinases ; MMPs). In implant reactions, many of these enzymes are activated as is reflected by the activation of collagen and collagenolytic enzyme synthesis. In the loosening of implants, there seems to be ingrowth of fibroblasts in the interface between the bone and implants.

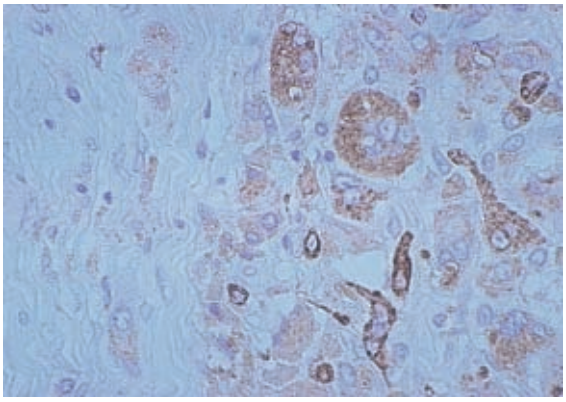

Fig. 3. Immunostaining of CD 68 with nuclear staining of hematoxylin. CD 68 positive monocytes/macrophages and foreign body type giant cells in the interface tissue of loose total hip joint with periprosthetic osteolysis.

To clarify the osteolytic phenomena induced by biological host response, factors relating to osteolysis have been identified in failed artificial total hip joints. Local production of cellular mediators, interleukin (IL)-1s, IL-6, macrophage-colony stimulating factor (M-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), TNF-alpha, prostaglandin E2, nitric oxide, macrophage migration inhibitory factor, cyclo-oxygenase 2, C-C chemokine, and extracellular matrix metalloproteinase inducer (emmprin) was reported as osteolytic mediators by direct or indirect manner in periprosthetic connective tissues[7,11,12,13,14,15,16]. Increased levels of transforming growth factor-beta -1 and -2 (TGF-beta), and acidic fibroblast growth factor (aFGF) in synovial-like regenerating capsular and interface tissues have been reported. These mediators seem to participate in the cascade of pathologic periprosthetic connective tissue remodeling[11]. Thus, various mediators are proposed as key factors of osteolysis and/or pathological connective tissue remodeling around hip implants.

In pathologic connective tissue remodeling, the imbalance between neutral proteinases and their inhibitors is another major event in the process of artificial total hip joint failure. MMPs are known to degrade most components of the extracellular matrix (ECM). It has been reported that protein and/or messenger ribonucleic acid

levels were increased for MMP-1, -2, -3, -7, -8, -9, -10, -11, -12, -14, -15, 16, and -17. Particularly, MMP-1, -2, -9, -13 and -14 seem to be key enzymes in the cascade. MMPs are controlled by tissue inhibitors of metalloproteinases (TIMPs). Increased levels of TIMP-1, -2 and -3 have been reported as local host response to MMPs production, which is postulated as a modulation of MMP activity. TIMP-2 can bind to MMP-2 in the step of enzyme activation. The MMP-14/MMP-2/TIMP-2 complex system can also degrade all the major molecules of the intercellular and periprosthetic matrix components. TIMP-1 and -2 are inactivated by the serine proteinase group, elastase and cathepsin G, which are increased in the periprosthetic connective tissues[7,17,18,19,20]. In the periprosthetic connective tissue remodeling cascade, the characteristics of ECM and ECM receptor proteins are of great interest. Peculiar distribution of extracellular fibronectin, laminin subunits (alpha 5, beta -1 and -2) and their receptor proteins, integrin subunits (beta-1, alpha-1, -2, -3, and -6) was reported. The signal pathway of ECM and ECM receptor interaction may alter connective tissue remodeling around implants[21,22].

Osteolytic joint fluid

Joint fluid is produced by the inflammatory synovial regenerating capsule and interface tissues around failed total hip joints (Fig. 2). Recent research revealed that M-CSF, IL-1 beta and IL-6 were significantly increased and osteoprotegerin (OPG) was low in failed total hip joint fluid. It was able to stimulate mouse osteoclastic bone resorption in vitro. The findings imply that low levels of OPG combined with higher M-CSF, IL-1 beta and IL-6 levels represent potentials for osteoclast differentiation and activation in failed total hip joints. Addition of exogenous OPG can inhibit osteoclastogenesis in vitro. It is proposed that low levels of OPG with elevated bone resorbing cytokines contribute to periprosthetic osteolysis via joint fluid, thus leading to hip implant loosening[11,23].

Joint fluid analysis of MMPs and TIMPs was also performed[24]. Joint fluid of failed total hip joints was characterized as having low levels of MMP-1, but moderate levels of MMP-13 and MMP-14, when compared to inflammatory rheumatoid samples. MMP-2 levels were significantly increased and MMP-9 was modest. TIMP-1 and -2 levels were significantly increased. Thus, the joint fluid contained abundant MMPs and TIMPs, and formation of stabilized proMMP-TIMP complexes enabled the transportation of proMMPs far from their original site of production, which is followed by activation at the inflammatory site and/or intact interface.

Motion-associated cyclic changes in intra-articular pressure, such as pumping effect on gait combined with poor integration of bone-implants interface, allow penetration of osteolytic fluid into the intact interface[25]. These findings imply that the fluid not only reflects the pathologic condition of osteolysis, but may also contribute to the process of periprosthetic osteolysis via bone metabolic factors.

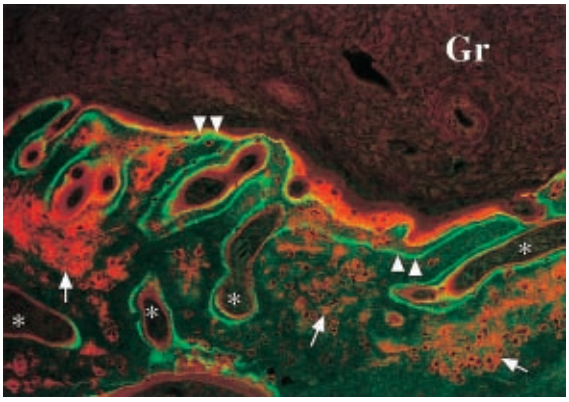

Fig. 4. Periprosthetic bone tissue adjacent to interface tissue with granulomatous reaction by Villanueva bone staining and confocal laser scanning microscopy. In the bony samples adjacent to loose interface, granulomatous connective tissues (Gr), including monocyte/macrophages and fibroblasts were observed adjacent to the retrieved bones, and infiltration of granulomatous cell components into the periprosthetic bone was also found (asterisk). Scattered low-mineralized areas, which were stained in orange, were also found in the green stained mature mineralized bone matrices (arrows). An increase in tetracycline-labeled bone, osteoid (red) and low mineralized (orange) area, and osteoblast lining were observed adjacent to granuloma cell components. Tetracycline deposition was observed as yellow or green-yellow line (arrow heads).

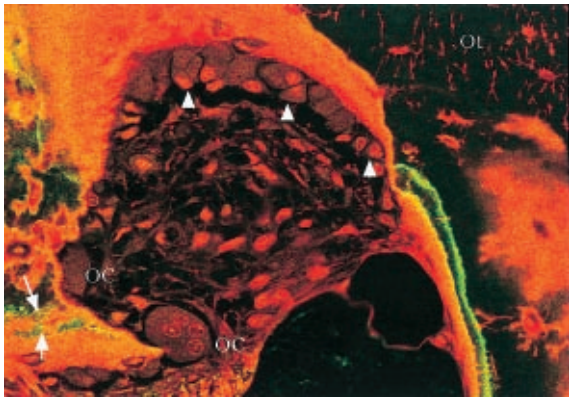

Fig. 5. Osteoid/low-mineralized bone matrix in the interface tissue of periprosthetic osteolysis by Villanueva bone staining and confocal laser scanning microscopy. Wide osteoid/low-mineralized area and osteoblast lining (arrow heads), which are adjacent to monocyte/macrophage sheets. Canalicular development of osteocytes is found in the bone matrix (Ot). Eroded bone surface and osteoclast (OC) containing double tetracycline labeling (arrows). This indicates that bone matrix is resolved soon after formation.

Periprosthetic bone morphology and bone quality supporting implants

Mechanical stresses onto bone bed around implants have been recognized to be important for a longer survivorship of implants and total hip joints. The acetabulum of pelvic bone and femur supports implants. They continuously transfer and/or receive mechano-biological signals via implants depending on daily living activity of the patients.

There were only few studies focused on the investigation of the characteristics of the periprosthetic bone remodeling. However, in recent research, bone histomorphometric analysis combined with confocal laser scanning microscopy system revealed that active coupling of bone formation and resorption in periprosthetic bone of failed total hip joints (Fig. 4, 5). Osteoclastic surface and surface eroded by osteoclasts were evident in the periprosthetic bone from failed total hip joints; increased osteoid/low-mineralized bone matrix and osteoid width were also significant findings in the structural analysis. In addition, an elevated mineral apposition rate was observed, as well as an increased mineralizing surface and bone formation rate. Increased osteocytes with abundant bone canalicular projections and the presence of immature bone matrices (osteoid and low-mineralized bone areas) were also peculiar findings[26]. These results indicate that active osteoclastic bone resorption and/or defective bone formation are coupled with monocytes/macrophages-mediated foreign body type granuloma in the synovial-like interface membrane of failed total hip joints. Thus, this unique high turnover periprosthetic bone remodeling with bad bone quality is probably due to the result of cellular host response combined with inappropriate cyclic mechanical loading. The fragile periprosthetic bone may contribute to hip prosthesis loosening.

It is also of interest that active linear tetracycline deposition and immature bone (osteoid/low-mineralized bone matrix) formation were frequently observed adjacent to monocyte/macrophage cell sheets in the granulomatous tissues[26]. It may suggest bipolar potential of monocyte/macrophages; not only do they produce osteoclastic cytokines such as IL-1, IL-6, TNF-alpha, and M-CSF, contributing to osteoclastogenesis and activation of osteoclast, but they also stimulate osteoblast and woven bone matrix production via IL-1, epidermal growth factor (EGF), TGF-beta, platelet derived growth factor (PDGF), FGFs and insulin like growth factors (IGFs), and increase survival rate of osteoblasts via TGF-beta and IL-6[10]. However, such bone matrices are not sufficiently mineralized and of high enough quality to support implant. In addition, abundant bone canaliculi/projections of osteocytes in low-mineralized area in situ may implicate cell-cell interactions and osteocytic mineral regulation under stimulation of biological mediators combined with mechanical cyclic loading. Such findings indicate a role for osteocytes in situ in various pathologic bone states and in bone turnover. Various types of tetracycline deposition patterns, linear, patchy and diffuse, observed in periprosthetic bone around loosened implants, support the hypothesis that biological mediators combined with mechanical cyclic loading may contribute to disturbances in the local bone turnover. Patchy and/or diffuse tetracycline depositions may represent a repair phase of microfracture trauma, due to fragile bone quality and unfavorable over-

mechanical stress from implant to bone in weight bearing[26].

Bone-implant interface biology in the future

There is increasing concern on wear-resistant materials, implants to obtain proper osseointegration, and to maintain adequate joint function[8,9]. Although etiology of periprosthetic osteolysis is still complicated, intensive study on bone-implant interface biology provides various information on periprosthetic bone remodeling to improve osseointegration of implants as well as a better understanding of osteolysis in failed artificial total hip joints. Trained surgical skill is undoubtedly appreciated, but development of wear-resistant materials and effort on maintaining better bone quality are also important. Application of current study methods in bone-interface biology may, in future, provide useful information in primary total hip joint surgery, as well as reconstruction of total hip joints by new types of implant and/or morselized impacted allo-bone grafting. Therapeutic trials for the administration of systemic and/or local factors maintaining bone bed quality will be performed based on the evidence of bone-implant interface biology research.

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