REVIEW ARTICLE

BONE RESORPTION PROCESSES AROUND STABLE AND ASEPTIC LOOSENED TOTAL HIP ARTHROPLASTIES A REVIEW OF THE LITERATURE

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This review deals with the available literature on bone resorptive processes around stable and aseptic loosened hip prostheses. The clinical and roentgenological appearances of bone resorptive processes are compared with the histological findings and differences between resorptive process around cemented versus non-cemented hip implants are highlighted. The chemical and mechanical contributions to the bone resorptive process are described. The role of macrophages and the chemical mediators they produce during loosening of implants is described. Also the different pathways by which macrophages reach the lesions is discussed. This review ends with recommendations to diminish problems with particulate debris and thereby to improve long term fixation of implants.

Keywords : bone resorption ; macrophage ; wear-particle ; cytokine ; hip prosthesis.
Mots-clés : résorption osseuse ; macrophage ; usure ; cytokine ; prothèse de hanche.

INTRODUCTION

Total hip replacement is generally a very successful operation. However, a major long-term complication is massive loss of bone stock in well-functioning and failed arthroplasties, both in the acetabulum and femur.

Loss of bone stock around arthroplasties is thought to be a multifactorial process. Several studies have been conducted to elucidate the resorption events, which occur in the loosening process. Patient variables, chemi-cal and physical properties of the biomaterials, biomechanical factors and immunological events have all been found to influence the loosening process. There still is controversy about the main factors involved when these processes occur around prosthetic material. This has led to an enormous and still increasing number of different types of prosthetic design and biomaterial-specific modifications, adjusted to the prevailing opinions of the biomedical industry, research group or surgeon.

We reviewed the incidence of resorptive changes around hip arthroplasties. An update is given of basic knowledge about the bone resorption process and the current theories about factors involved in bone resorption processes around stable and aseptic loosened arthroplasties. New approaches to unanswered questions about osteolytic phenomena in prosthesiology and potential interventions in peri-implant bone resorption are discussed.

BONE RESORPTION AROUND ARTHROPLASTIES

Clinical incidence and histological appearance

Charnley (19) was the first to describe periprosthetic bone loss. He observed osteolysis around a few cemented femoral stems and stated that infection, even without bacterial confirmation, was the

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most likely aetiology. Harris *et al.* (46) also published an early report on osteolytic phenomena around cemented femoral prostheses, but their findings suggested a foreign-body reaction in relation to loose femoral stems.

Radiolucencies around prostheses can be observed on an x ray as dark lines or discrete areas between the implant and bone. Localised bone resorption, cystic ero-sion and scalloping are expressions that have been used synonymously to describe well-demarcated local lucencies, which are absent on the direct postoperative x rays (2, 56, 77, 80, 130). Diffuse linear radiolucencies are considered to represent an expansion of the periprosthetic cortical bone (110, 128).

Cemented implants

Bone resorption has been observed around loose (18, 106, 110, 119, 145, 146) and stable cemented implants (2, 64, 86) with cystic and diffuse linear radiolucencies in both conditions. It has been reported that the linear radiolucent areas were distributed along the cemented prostheses with no preferential localization (110, 128). The osteolytic areas were mainly located around the distal stem and on the medial side of the proximal femur, often in cement-deficient areas (2, 14, 56, 77, 80, 86, 130, 152).

In some studies, a correlation was reported between the radiographic and histological features of the bone-resorption areas. In osteolytic areas at cement-deficient sites, granulomatous tissue with wear particles was observed by various authors (2, 14, 77). Longitudinal bone resorption along a loose cemented prosthesis was filled mainly with fibrous tissue, according to Santavirta *et al.* (126) However, in another study with a comparable patient group, duration of implant and linear bone resorption appearance, macrophages and wear particles were observed (128). Tissues derived from focal osteolytic areas of revision specimens were found to contain macrophages and wear particles (128). Retrieval studies also revealed histiocytes and wear debris in tissues obtained from areas of bone resorption far from the articular surface around mechanically stable cemented implants (2, 64, 86, 128). However, other retrieval studies on stable cemented femoral prostheses regarded the linear and cystic radiolucencies as representing osteoporosis of the cortex rather than the presence of fibrous tissue. The cement layer had become enveloped by a neocortex which was connected to the endosteum by thin trabeculae (19, 62, 63, 77). Thus, in the evaluation of linear radiolucencies special care must be taken not to define a well fixed prostheses as being loose.

In 10 to 15 year follow-up studies of successful arthroplasties, the incidence of radiolucencies of any type around cemented femoral components was 20% (9, 66, 149, 152) and 35 to 90% in revision arthroplasties (106, 110). Focal osteolysis started to develop 3 years after insertion of the cemented implant (86, 130). According to Huddleston (56) the cystic radiolucencies tended to expand without exception, whereas Maloney *et al.* (86) observed progression at a variable rate. The presence of focal endosteal excavations had no influence on the risk of aseptic loosening of revision femoral arthroplasties, according to the survival analysis by Retpen and Jensen (115). In primary arthroplasties on the contrary, endosteal cavitations have been identified as a "risk" feature (105). Because the patient groups and analysis methods are not comparable, no conclusion can be drawn from comparing these two studies. It has been demonstrated that extensive linear lucencies are a significant detrimental factor in the long-term survival of cemented femoral implants (72, 117), especially if the lines are divergent from the implant (15). The contra-dictory reports on the appearance of femoral osteolysis with its histological aspects and its influence on the survival time of an implant, emphasise the need for retrieval studies that correlate individual serial clinical radiographs with the corresponding histological findings. These studies should investigate whether or not we are dealing with separate entities of radiolucency with respect to histologic appearance and potency of progression.

Reports on the appearance and progression of osteolysis in studies on the acetabular side are more uniform. Linear radiolucencies of 1 mm or larger around cemented acetabulae are very common

without any sign of loosening. The incidence of this phenomenon varies from 15% at 3 years follow-up (44) to 30 to 60% after 10 years or longer (66, 103, 152). It has been suggested that progression of the larger lesions by more than 2 mm is predictive for acetabular loosening in the future (36, 44, 66). The process of bone resorption starts circumferentially at the intra-articular margin and progresses towards the dome of the implant (44, 129). The superior acetabular margin displays the highest incidence of radiolucent lines (36, 44, 66). The fact that the incidence and size of osteolytic areas increase with time, means that the acetabulum is more vulnerable for failure in the long-term.

Noncemented implants

Initially, the phenomenon of osteolysis was mainly thought to be caused by the cement layer. This concept stimulated the development of cementless osseointegrated implants, which eliminated the use of polymethylmethacrylate as a method of fixation. However, bone resorption also developed around these noncemented prostheses, even in clinically well-functioning implants (11, 30, 31, 68, 85, 121).

Radiographic analysis of clinically well functioning, proximally porous coated femoral components, demonstrated areas of focal and linear osteolysis in 20% of the hips. The osteolytic process started to develop 2 to 3 years postoperatively, mainly in the calcar region and around the distal femoral component (47, 68, 85). Tanzer *et al.* (136) observed more severe osteolysis along loose components, but noted progression in 90% of all their total hip arthroplasties, whether stable or loose. In the study by Brown and Ring (9), fully coated prostheses with stable distal fixation demonstrated severe osteolytic changes in the calcar region. Engh *et al.* (29), on the contrary, observed only slight bone resorption with comparable fully-coated prostheses. An important difference was that the implants used by Brown and Ring had a polyethylene femoral head. Smooth cementless femoral components demonstrated extensive radiolucencies in 20 to 40% of the femoral implants in the calcar and tip region, already after 2 to 6 years follow-up, which correlated with poor clinical results (26, 109). The isoelastic prostheses showed extensive bone resorption in more than 40% of the patients after a follow-up of at least 5 years (122).

Only a few studies made a correlation between radiolucencies around cementless femoral components and the histological features. Studies on stable noncemented implants revealed dense fibrous tissue in non-ossified areas (29). In focal osteolytic areas, histiocytosis and particulate material was observed (84).

Acetabular cystic osteolysis has also been observed in clinically stable noncemented implants ; this developed 1 to 5 years postoperatively. Histologically, these lesions contained macrophages, giant cells and particulate debris of polyethylene and metal (11, 86). Acetabular osteolysis was often located adjacent to screws and was associated with radiographic evidence of gross wear of the polyethylene liner (11, 68, 86). In a comparison between the radiological results of stable retrieval acetabulae and the histological findings, Engh *et al.* (31) observed dense and well-organised fibrous tissue without granuloma formation or wear particles in the diffuse radiolucent areas. Acetabular retrieval studies combined with detailed clinical radiological follow-up are needed, because it is still unclear whether the various types of radiolucency have different clinical implications.

In summary, osteolytic areas with varying appearances, variable progression rates and different histological features have been observed. It is important to extend our knowledge of the radiographic risk factors, i.e. osteolytic appearances, which indicate loosening, so that revision surgery can be planned at the right time. This will prevent not only unnecessary interventions, but also massive bone loss.

Cemented versus noncemented prostheses

Comparison of studies with respect to the incidence, localisation and extension of osteolysis that occurs around cemented and noncemented implants can be biased by multiple variables, such as patient characteristics, surgical technique, and composition of the implants and follow-up period.

Therefore, no comparisons have been made between the cemented and noncemented implants discussed above.

In a retrospective, matched-pair study on the prevalence of femoral osteolysis comparing cemented and noncemented prostheses, osteolysis had only developed in the noncemented group after a follow-up of 4 years (39). In a prospective study by Wixson *et al.* (150), a comparison between the proximal cortical bone resorption around cemented and noncemented prostheses revealed a varying degree of osteolysis, which tended to be more severe around the noncemented femoral stems than around the cemented ones. This difference was explained by the easy access of very small particles into the bone-prosthesis interface, which in turn could stimulate the bone resorption process. This process is explained more extensively below.

Compared to cemented acetabulae, the noncemented showed a lower incidence of radiolucent lines and resorption areas (68, 150, 153, 154). However, post-mortem studies on well-functioning noncemented acetabulae and the findings at revision surgery indicated that routine x rays led to an underestimation of the presence of bone loss and an overestimation of the occurrence of bone apposition. (31, 86).

Granulomatous osteolytic lesions

Aggressive granulomatous osteolytic lesions are described as a separate item, because they appear to have a different presentation compared to the above-mentioned radiolucencies.

Granulomatous osteolysis has a very progressive nature and presents on a standard x ray as localised ovoid tumour-like aggressive bone resorption of periprosthetic bone. It has been observed around both cemented (64, 126, 135) and noncemented prostheses. The lesions are often multifocal, with the proximal femur and supra-acetabular region as common sites, both with cemented and noncemented implants (125, 126, 135). These lesions are responsible for 5% of revision operations for a loose total hip (135, 125, 86) and become visible 3 to 5 years after the primary operation (86, 126).

These cyst-like lesions invariably contain granulomatous tissue with sheets of macrophages, foreign-body giant cells and wear particles, irrespective of whether the prostheses were cemented, noncemented, symptomatic or asymptomatic (64, 86, 126).

The fact that these aggressive lesions have a local presentation and usually appear after only a few years of implantation, allows the surgeon to follow early post-operative radiolucencies with plain x rays without any additional investigations or interventions.

BONE CELLS AND THE LOCAL BONE RESORPTION PROCESS

To better understand the bone resorption process along prosthetic components, it is essential to gain insight into the origin of bone cells and the factors involved in their regulation. This section does not attempt to incorporate all aspects of this topic, but is restricted to specific areas that elucidate the orthopaedic 'osteolytic' literature.

The origin of bone cells

Four types of bone cells can be distinguished in compact and trabecular bone, namely the osteoblast, osteocyte, osteoclast and bone lining cell (fig. 1).

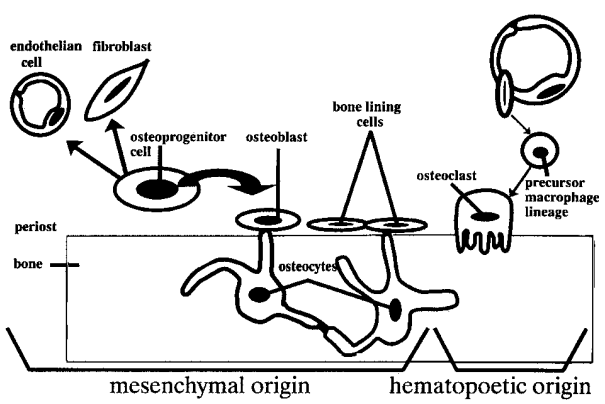

Fig. 1. – Origin of bone cells. Osteoblasts derive from undifferentiated mesenchymal cells. After the osteoblasts are surrounded by mineralised matrix, they are designated osteocytes. Osteoclasts differentiate from precursors of haematopoietic origin. The origin and fate of bone lining cells is not yet established.

Osteoblasts are derived from relatively undifferentiated osteoprogenitor cells of mesenchymal origin. These cells can also develop into endothelial cells, fibroblasts or reticulum cells (the supporting cells of the bone marrow), depending on local physical and biochemical influences (104). When osteoblasts are surrounded by mineralised matrix they are designated osteocytes.

Bone lining cells are flat, elongated cells that cover most of the temporary nonremodelled endosteal bone surfaces. There is still uncertainty about their function and origin, but they may play a role in the functional syncytium of osteocytes because of contact over numerous cellular gap junctions. Their role as a progenitor of osteoblasts has not been established (90).

The osteoclast precursors are of haematopoietic origin and are related to the monocyte-macrophage line-age (92). The initial pathways of osteoclast and macrophage differentiation are identical, but the final pathways of differentiation are different (4, 61). No direct descent of osteoclasts from mature macrophages has ever been demonstrated (13).

The biology of the local bone resorption process

Local physiological bone resorption is influenced by various factors, such as the mechanical loading situation, cytokines, growth factors and systemic hormonal stimuli.

Apart from synthesising bone matrix, osteoblasts also affect the resorption process by means of paracrine mechanisms, which influence osteoclasts (fig. 2). After receiving the signal to initiate the resorption process, osteoblasts show cell retraction, which exposes nonmineralized collagen. This thin osteoid layer is then removed by an as yet unidentified mechanism of collagenase action, which exposes mineralised bone to osteoclasts (16, 116, 141). Osteoclast Activating Factors (OAF's), excreted by osteoblasts, further stimulate the resting osteoclasts to form active multinucleated bone resorbing cells with a ruffled border. As yet these OAF's have not been fully identified, but they are probably metabolites of the arachidonic acid chain (88, 89). Although macrophages and osteoclasts

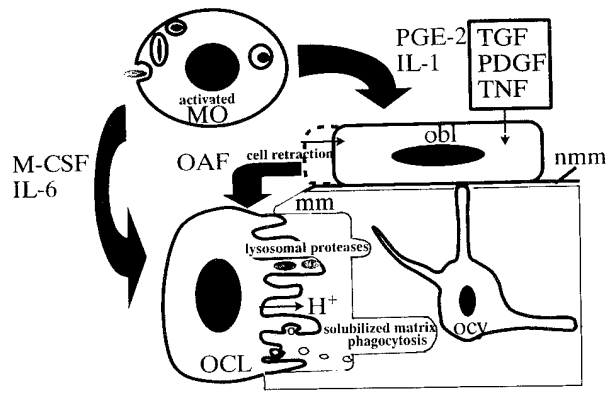

Fig. 2. – Overview of the local bone resorption process. Osteoclast (OCL) activation directly depends on activation by osteoblasts (obl). Also activated macrophages (Mf) enhance the resorption process by stimulating osteoblast activity and osteoclast formation. Several cytokines, growth factors (M-CSF, IL-6, PGE-2, IL-1, TGF, PDGF, TNF) and Osteoclast Activating Factors (OAF's) play a role in the complex interacting system. mm = mineralized matrix.

have a common precursor, living bone is only resorbed by osteoclasts and not by macrophages (13, 106). Dead bone, on the contrary, is readily absorbed by monocytes (91, 13).

Cytokines are short-range soluble mediators that are released by cells, which modulate the activity of other cells. The term cytokines has been used more generally to include products originally described as monokines, lymphokines and growth and differentiation factors. Several cytokines are potent mediators of bone resorption, such as Interleukine-1 (IL-1) a and ß, Tumour Necrosis Factor (TNF) a and ß and Interleukine-6 (IL-6). Transforming Growth Factor (TGF) a and ß and Platelet Derived Growth Factor (PDGF) have also been observed to play a modulating role in the resorption process (93, 116).

In vitro studies have demonstrated that macrophage excretions, such as Prostaglandin E-2 (PGE2) and IL-1 activate the resorption process by affecting the osteoblast. Part of the IL-1 effect on bone is prostaglandine-mediated (94). Macrophages also produce Macrophage Colony Stimulating Factor (M-CSF) (73) and IL-6 (76, 120) that enhance osteoclast formation.

PGs are important local regulators, because every stimulator of bone resorption has been shown to increase prostaglandin production. PGs can act

as a general amplification system for resorption stimuli (70). Local PG concentrations can be raised by hormonal stimuli (70, 111) and by local factors including IL-1 (127, 140), TNF (138), TGF-a (139), PDGF (137) and mechanical force (28, 71, 97). It has not yet been established which bone cells are responsible for PG production (94), but osteoblasts in culture seem to be a likely source of Pgs (32, 100).

PGs can have dual effects in the bone resorption process. *In vitro* studies have shown that, besides its resorptive activities, PGE2 also has a stimulating influence on bone growth, depending on its concentration (21, 112). This phenomenon has also been observed *in vivo* with the factor TGF-ß (87, 99).

Interactions between cytokines are important in modulating bone resorption. Il-1 and TNF can influence the PGE2 concentration. Il-1 can interact synergistically with TNF and TGF-a to increase bone resorption (81, 133).

Local bone resorption with cytokines and growth factors is a complex interaction system. The relationships between the factors involved in this complex biological system have not yet been fully clarified.

Mechanical influences and bone resorption

Mechanical loading plays an important role in the differentiation, growth and remodelling of bone. Numerous mathematical and experimental attempts have been made to describe the relationship between mechanical loading and bone resorption.

Kufahl and Saha (74) developed a mathematical model to describe the stress-induced flow. They stated that a lack of stress-generated intracellular fluid flow, because of nonloaded conditions or interruption of interosteocytic contact could lead to bone resorption. Frost (34, 35) put forward a mathe-matical theory about the 'Mechanostat' according to Wolff's law. The response of bone to mechanical strain is considered an intrinsic property of the bone. He attributed the adaptations of bone architecture and mass to its typical mechanical environment, based on sensor and actor presence in 'mechanical' units. Recently, a model that describes the excitation of osteocytes by bone fluid shear stresses has been developed (144).

Support for these theories can be found in the results of *in vitro* experiments. Several investigations have demonstrated inhibition of the osteoclastic resorption process under intermittent strain induction (13, 71, 97). *In vitro* cyclic stretching of osteoblasts demonstrated a significant increase in mitotic activity, but not in alkaline phosphatase activity (98). Osteoblasts have also been found to respond to cyclic mechanical stretching *in vitro,* with orientation of the cells perpendicular to the strain field applied (10). After mechanical stimulation several nondefined bone resorbing factors are released (124). *In vitro* studies have also confirmed the production of PG's by bone cells after subjection to loading or stretching (8, 28, 112, 113).

Very little is known about cellular interactions during mechanical excitation. Osteocytes, bone lining cells and osteoblasts may communicate via paracrine effects of produced signalling factors. Direct communication may occur via electrical currents and cytoplasmic substances, which are transferred through the syncytium via gap junctions (8, 24).

Although it is still unclear how mechanical stress is transducted into cellular biochemical signals, some models describe hypothetical mechanisms (fig. 3). Stretch-sensitive ion channels, which have been observed in the cell membrane of osteoblasts, could be responsible for the activation of osteo-

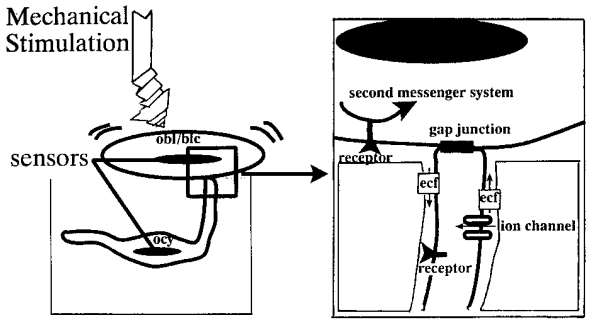

Fig. 3. – Hypothetical mechanism for mechanical stimulation of bone cells. Stretch-sensitive ion-channels or receptors sensitive to force variation can lead to second messenger cascade activation resulting in remodelling activity. obl = osteoblast, blc = bone lining cell, ocy = osteocyt, ecf = extracellular fluid stream.

blasts (25). Another model of transmembrane stimulation was described by Sandy *et al.* (123). By means of *in vitro* experiments they demonstrated that specific receptors, which are sensitive to force variation, activated intracellular messenger cascades in the osteoblast. These sensors could be activated by extracellular matrix proteins, possibly lipoproteins, which extend into the extracellular space and change their special arrangement during elastic deformation of the bone. Moreover, theoretically receptors could be activated by the changed chemical composition during strain induced extracellular flow.

In the above, various factors, such as the monocyte-macrophage system, cytokines, prostaglandins and mechanical loading, have been discussed extensively, to elucidate more clearly in the next paragraph their role in the bone resorptive phenomena along total hip arthroplasties.

FACTORS INVOLVED IN THE BONE RESORPTION PROCESS IN TOTAL HIP ARTHROPLASTIES

Wear particle characteristics and bone resorption

Wear is a process of particle generation from surgical implant materials, owing to contact abrasion between two materials, or material failure because of fatigue, fretting or corrosion (147, 148).

Wear particles around total joint arthroplasties mostly consist of metal, high-density polyethylene (HDPE), polymethylmethacrylate (PMMA) and hydroxyapatite (HA) granules. The particles can be generated between bearing surfaces or between debonded noncemented prostheses and bone (fig. 4). At other interfaces, i.e. bone-cement and implant-cement, particles may also be generated because of slight movements between the surfaces. The new generation of modular implants and the use of fixation screws are also a source of wear particles (7). Entrapment of cement or coating particles between the articulating components of the arthroplasty can give rise to so-called third-body wear (5).

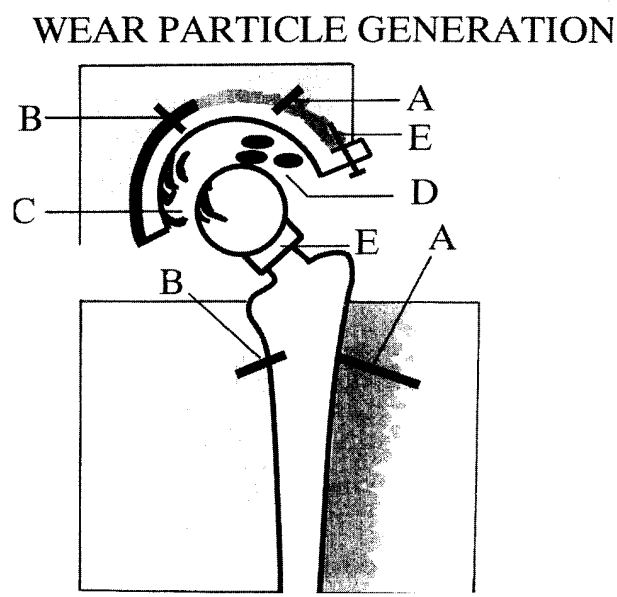

Fig. 4. – Sources of wear particle generation. **A** = cemented interface, bone-cement-metal stem/polyethylene cup. **B** = cementless interface, bone-metal stem/metal backing/porous coating. **C** = articular surface roughness. **D** = third body wear. **E** = modular system/screw fixation.

The release of biomaterials in particulate form is responsible for the increased invasion of phagocytic inflammatory cells and granuloma formation. The periprosthetic particles are phagocytosed by macrophages and giant cells, which leads to the release of soluble inflammatory mediators, such as PGE2, IL-1, IL-6 and TNF (40, 41, 65). Cytokines are known to stimulate granuloma formation (75), and as was described extensively in the former paragraph, they also activate bone cell participation in the bone-resorption process.

Animal experiments have stressed the importance of particle presence in the generation of osteolytic areas along implants. In the absence of mechanical loading, a thin fibrotic membrane was observed around implanted PMMA bulk material with an intact bone mass, whereas a florid foreign body giant cell reaction with osteolysis of the surrounding bone was demonstrated after implantation of the same amount of material, but in a particulate form (42, 43, 55).

Only particles of a certain size stimulate macrophages to phagocytosis and the secretion of cytokines (51, 53, 54, 96). In an *in vitro* study, Glant *et al.* (38) observed a maximal bone resorption response to titanium particles of 1-3 mm with

a concentration of 10 to 15 particles per cell. The surface area of the particles also seems to be important in the ultimate inflammatory response of macrophages. Irregularly shaped PMMA particles elicited a significantly higher cytokine production than spherical particles (37). Also for bulk material evidence was found that activation of macrophages varies with physical properties such as surface energy and roughness rather than chemical nature of the biomaterial (95).

The maximum concentration of particles that stimulate macrophages is different for the various biomaterials (98). The *in vitro* study by Glant *et al.* (38) demonstrated that the bone resorptive activity of titanium particles was significantly higher than that of polymer particles. Howie and coworkers believe that a combination of materials with a pattern of wear and specific number and size of the wear particles have a more adverse affect on the *in vivo* reaction than particulate debris from a specific material (52, 54).

Wear debris induced osteolysis in clinical studies

The results of clinical studies have provided support for the theory that induction of bone resorption depends on the quantity of particles (49, 128). Osteolysis in non-cemented prostheses was found to be directly correlated with the amount of polyethylene wear of the acetabular cup ; this was also verified histologically (68). When the polyethylene wear of a cemented acetabulum exceeded 2 mm, proximal femoral lysis phenomena were present without exception (80, 142). Charnley did not find a relationship between the amount of socket wear and the amount of resorption of the calcar femorale (19).

Several authors have studied the osteolytic potential of tissue obtained from bone resorption areas from cemented and noncemented prostheses, by means of cytokine essays and *in vitro* bone organ culture. The interfaces of failed cemented prostheses demonstrated IL-1, PDGF (65), TNF and PGE2 production (3). The membranes around osteolytic areas of failed non-cemented prostheses contained large quantities of IL-1 (67). A comparative study on noncemented prostheses with or without focal endosteal bone loss, demonstrated more macrophages and small particles and greater Il-1, Il-6 and TNF activity in the group with focal osteolysis (20). Other studies did not find a higher cytokine concentration in particle-burdened tissue (23, 67). In the studies by Ohlin, the mediators released from the joint capsule demonstrated greater bone resorptive activity compared to the bone-cement interface membranes (101, 102). It is possible that the larger particle burden in the capsule was responsible for the greater abundance of activated macrophages and subsequently, higher cytokine production.

Several hypotheses have been put forward in clinical studies to explain the variance in the localisation of osteolysis. Wear particles can be released locally or transported along the bone-implant or cement-prosthesis interface by a pumping mechanism (2, 33, 50, 52, 79, 86, 128). This theory was supported by the findings in a recent study by Goetz *et al.* (39), in which the lower incidence of osteolysis in cemented femoral prostheses was explained by the lack of wear particle access to the periprosthetic interface, because of the tight bone-implant fixation with a third-generation cementing technique. In the same context, several authors observed extensive osteolysis around smooth cementless femoral components with a poor bone-implant fit (26, 108, 121).

The interindividual differences in the quantity and localisation of osteolysis in patients, could also be the consequence of nonphasic fluid flow through the so-called effective joint space. Variation in the intracapsular pressure and obstruction of the flow by local implant-bone connection, may be responsible for different patterns of particle transport along the bone-implant interface (128).

Other authors have hypothesised that wear particle transport along the perivascular lymphatic vessels reaches equilibrium. Once the transport capacity has been exceeded, the particles would remain locally and induce a granulomatous reaction with subsequent bone lysis (82, 145, 148). Recently the histopathology of sinus histiocytosis has been described. The presence of metal particles has been described in the pelvic lymph nodes and lympho-

reticular tissue after metal-on-metal total hip replacement (1, 78).

Herman *et al.* (48) introduced another theory to explain the various osteolysis localisations : the fluid shift theory. Pressure changes in the joint and periprosthetic fluid would facilitate the widespread distribution of bone-resorbing factors.

Mechanical factors involved in the bone resorption process around prosthetic material

Bone cells are sensitive to mechanical load with subsequent biological responses. This is also the case with the bone cells in the changed biomechanical environment around prosthetic material. So far we know very little about the local *in vivo* response of bone cells in changing loading conditions, and it is not possible to predict the bone resorption result from a combined biomechanical-biological point of view.

On the basis of Wolff's law (151), which stated that the structure of bone adapts in accordance with an altered mechanical environment, computer models have been developed, using the Finite Element Method, to predict the long-term behaviour of periprosthetic bone along various types of prostheses (60). In an animal experiment, Finite Element simulations of adaptive bone remodelling processes around noncemented implants showed close similarity to the cross-sectioned animal material (143). In an attempt to validate the prediction of bone loss, human periprosthetic bone of noncemented retrievals described by Engh *et al.* (30, 31), was compared to biomechanical simulation models. Although certain assumptions were made, the same trends in bone loss were observed (58).

A decrease in loading will lead to bone resorption, which is what happens when stress is distributed along the stem to the distal femur. This so-called stress shielding is a process of strain-adaptive bone resorption, in reaction to abnormal stress distribution and leads to bone loss in the proximal femur. The main prosthetic factors responsible are stem stiffness (6, 134) and bonding characteristics of the implant. Human retrievals with a stable cemented prosthesis in situ, which were subjected to strain gauge studies, revealed that there was marked stress shielding in the proximal medial femoral cortex, even long after implantation (83). The cement layer had become enveloped by a neocortex which in turn was connected to the cortex by trabecular struts. There is no evidence that stress shielding limits the longevity of cemented prostheses (45). However, more substantial and extensive bone loss is usually observed around noncemented implants, because they are more rigid, distributing the stress along the stem to the distal femur (29, 57, 121).

In acetabular implantations there is a concentration of stress along the superior edge of the acetabular wall. Interface radiolucency usually starts at the rim of the acetabulum and progresses towards the dome (129). This observation supports the view that resorption and loosening are the consequence of mechanical overload and instability at the rim as well as stress shielding of the subchondral bone in the remainder of the acetabulum (22).

According to some authors, not only bone loss because of stress shielding, but also localised osteolytic areas around prostheses can be explained by changed loading conditions. Micromovements between the cement-implant or implant-bone interface and shear stresses, are the main initiating factors in the osteolytic process. Perren (107) imitated this micromovement-induced bone resorption in an animal experiment. Huiskes and Nunamaker (59) correlated the quantitative interface stress patterns with the histological results in an animal experiment. Mechanical overloading, so-called peak stress, was correlated with resorption phenomena, which depended directly on the design of the prosthesis. The increase in lucent lines along a lateralized femoral component may reflect an increase in shear stress at the bone-cement interface, the latter being generated by an increase in the bending forces due to the longer lever arm of the prosthesis (79). According to Carlsson *et al.* (15) and Huddleston (56), micromovements alone could explain the high incidence of cystic lesions around the distal end of the femoral component if there is insufficient cement. Maximum loading of the metal-bone interface would activate local bone resorption. However, isolated cysts around the

proximal two-thirds of the femoral component and the low incidence of lysis around the proximal edge of the femoral component with loads equal to those at the tip, cannot be explained by this mechanical theory.

The former theories are based on direct mechanical influence of bone cells. However, from a biological point of view focal osteolysis can occur because of mechanical loading, but with an indirect influence on bone cells. Local macrophages that are attracted to the environment around biomaterials with tissue necrosis, a low oxygen concentration and a low pH (131), can be activated by motion, to produce cytokines in the absence of particles (132). Motion between the implant and the surrounding bone and fibrous tissue can also lead to the formation of a pseudosynovial membrane, which consists of cells that resemble synovial lining cells and are capable of producing bone resorptive cytokines in the absence of wear particles (27, 40, 41).

From the enormous amount of literature on this subject, it is not possible to discern what relative contribution micromovements and particles make to initiate the osteolytic response. This can be explained by the fact that when micromotions occur *in-vivo*, conditions are present inherently to promote the production of wear particles. Greater knowledge of how mechanical factors influence the bone resorption process will lead to a better understanding of the influences of implants on periimplant bone cells and macrophages.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE EXPERIMENTS

Osteolysis is a major complication in total hip arthroplasties. In this review various factors involved in the generation and regulation of the bone resorption process were highlighted. A great deal of attention was paid to basic knowledge about the resorption process, the cells involved and cellular factors, because these are the major keys in understanding the detrimental process in periprosthetic bone.

Combining the different views about the osteolytic processes along prosthetic implants led to the generally accepted view that bone resorption along implants is a multifactorial process in which all the recognised biological and mechanical factors play a role in an early or later phase and finally act synergistically in aggravating bone loss (fig. 5).

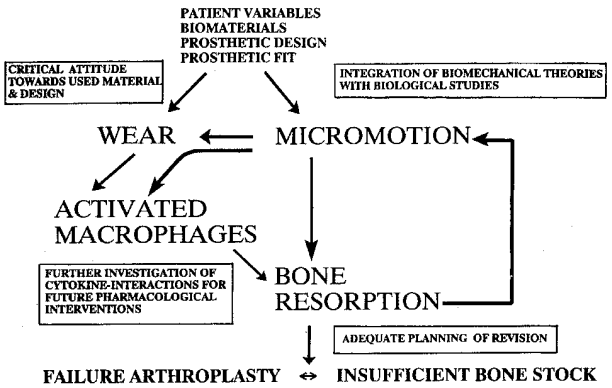

Fig. 5. – Scheme of the multifactorial periprosthetic bone resorption process with fields of attention in rectangular boxes concerning clinical intervention and further clinical and experimental investigations.

Clinical studies were described in which osteolysis was observed along different cemented as well as noncemented prostheses. No difference was observed in the appearance interval and types of osteolytic lesion between the two fixation principles. Generally the local osteolytic lesions contained macrophages with wear particles, whereas linear lucencies were composed of fibrous tissue without wear debris. In clinical follow-up studies, which focus on the osteolytic process, it is important that reports provide definitions of radiographic entities so that clinical and histological results of similar publications can be compared.

Extensive analysis of the sequence of osteolytic events in retrieved material with information on relevant

biomechanical and biological influences, will throw more light on the *in-vivo* behaviour of the biomaterial and periprosthetic bone mantle. The observation of cortical osteoporosis, the presence and relevance of which was explained from different viewpoints, requires integration of several concepts.

Biomechanical theories should be integrated with biological studies, in order to validate the mathe-

matical predictions.

Improvements can be made on the *in vivo* mechanical and chemical stability and the reduction of wear particle production via factors such as the constituents, manufacturing and prosthetic design. In addition, care must be taken when choosing modular systems for long-term arthroplasties.

Current knowledge about the cytokines, their reaction sequences and dual effect should be further extended. An important field of investigation comprises interactions between the different cytokines that mediate bone resorption processes around prostheses. We could then explore the potential of pharmacological interventions to directly or indirectly affect active cytokines, for example by the selective inhibition of bone-resorption mediators and retardation of the loosening process after the development of osteolytic areas. Indomethacine (38, 69), selective osteoclast inhibitors (116) and proton pump inhibition, which have all been found to prevent osteoclasts from generating an acid environment for bone resorption, are all nonsurgical treatments that may delay the detrimental process and therefore deserve more attention in the future.

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SAMENVATTING

N. M. P .LAMERIGTS, P. BUMA, T. J. J. H. SLOOFF. Botresorptie rond heupimplantaten. Een overzicht van de literatuur.

Dit review geeft een overzicht van de literatuur betreffende botresorptie rond heupimplantaten. Een onderscheid wordt gemaakt tussen klinisch goed functionerende stabiele implantaten en losse implantaten. Dit review gaat verder in op de potentiële verschillen tussen gecementeerde en ongecementeerde implantaten. De chemische en mechanische componenten in het proces van botresorptie zijn beschreven. Met name de rol van macrofagen, de mediatoren die deze cellen uitscheiden na het opnemen van allerlei slijtage partikels en de routes waarlangs de cellen en mediatoren de resorptieplekken bereiken is verder uitgewerkt. Dit overzicht eindigt met aanbevelingen om de productie van slijtage partikels te verminderen en op deze wijze de lange-termijn performance van orthopedische implantaten te verbeteren.

RÉSUMÉ

N. M. P. LAMERIGTS, P. BUMA, T. J. J. H. SLOOFF. Les processus de résorption osseuse autour des prothèses totales de hanche stables ou présentant un descellement aseptique. Revue de la littérature.

Les auteurs passent en revue la littérature consacrée aux processus de résorption osseuse autour des prothèses de hanche stables ou présentant un descellement aseptique. Ils étudient la relation entre les aspects cliniques et radiologiques des processus de résorption osseuse et les observations histologiques ; ils font ressortir les différences entre les processus de résorption qui s'observent autour d'implants cimentés ou non cimentés. Ils décrivent les facteurs cliniques et mécaniques impliqués dans les processus de résorption osseuse. Ils décrivent le rôle des macrophages et des médiateurs chimi-ques qu'ils produisent, dans le descellement des implants. Les différentes voies par lesquelles les macrophages parviennent au site des lésions sont également étudiées. Cette analyse se conclut par des recommandations en vue de réduire les problèmes liés aux particules d'usure et d'assurer une fixation durable des implants.