

**Bone Remodelling, Particle Disease and Individual Susceptibility to
Periprosthetic Osteolysis**

Mini-review

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Short title:

The Pathophysiology of Periprosthetic Osteolysis

Summary

Bone remodelling is a tightly coupled process consisting of repetitive cycles of bone resorption and formation. Both processes are governed by mechanical signals, which operate in conjunction with local, and systemic factors in a discrete anatomic structure designated a basic multicellular unit (BMU). The microenvironment around total joint arthroplasty is a dynamic and complex milieu influenced by the chemical and physical stimuli associated with servicing the prosthesis. A key factor limiting the longevity of the prosthesis is polyethylene wear, which induces particle disease, and this may lead to increased and prolonged activity of BMUs resulting in periprosthetic osteolysis. Several pathways regulating BMU function have been reported in the past, including RANKL/RANK/OPG/TRAF6, TNF- α /TNFR/TRAF1, and IL-6/CD126/JAK/STAT. Moreover, the expression and functional activity of all these molecules can be affected by variations in their genes. These may explain the differences in severity of bone defects or prosthetic failure between patients with similar wear rates and the same prosthesis. Simultaneously, this data strongly support the theory of individual susceptibility to prosthetic failure.

Key words

Periprosthetic osteolysis, particle disease, basic multicellular unit, osteoclast, osteoblast

Total hip arthroplasty (Figure 1) continues to be one of the safest and most effective surgical therapies. Nevertheless, the long-term outcome of this procedure is gradual deterioration over time in service resulting in increased rate of revisions due to aseptic loosening and osteolysis (OL). Both mechanical and biological factors trigger a cascade of events leading to the distortion of local bone homeostasis in favour of resorption. At least two types of periprosthetic OL may be distinguished: linear and the aggressive. The former demarcates prosthesis with either a thin or a heavy fibrous membrane lying as a pad on the sclerotic bone surface. The latter differs from the former by lacking sclerotic adaptation of the bone surfaces. Poorly organized fibrous tissues may fill the bone lesions; thus, OL may be associated with loosening of the prosthesis.

Particle disease theory was coined to explain the pathophysiology of OL and prosthetic loosening (Harris 1994). This is based on the evidence that macrophages and other cells of mesenchymal origin release a multitude of cytokines, chemokines, metalloproteinases, and other agents after stimulation by prosthetic wear particles (Purdue *et al.* 2006). Ultimately, these substances mediate increased local concentration of mature and functionally competent osteoclasts that execute bone resorption. Simultaneously, prosthetic particles and substances of particle disease suppress osteoblast activities. Concurrently, mechanical factors such as excessive forces generated at the prosthesis-bone interface and joint fluid produced by surface macrophages of the synovium are involved in the aetiology of OL (Sundfeldt *et al.* 2006). Both can lead to direct bone resorption independently of other factors.

The aim of this mini-review is to present particle disease as a deviation in the balance of osteoblast-osteoclast interaction within the BMU (basic multicellular unit). Further, the concept of individual susceptibility to periprosthetic OL is introduced to explain the varying degrees of OL in patients with similar wear rates and prosthesis design. We believe this could lead to the development of more effective preventive and therapeutic strategies in the future.

Particle disease: macrophage over-stimulation by prosthetic particles

Briefly, prosthetic particles are released by the artificial joint surfaces through the mechanisms of wear. In the case of polyethylene (PE) cup and metallic ball the rate of release has been estimated at 100 000 - 500 000 micron-sized particles for each step the patient takes (McKellop *et al.* 1995). After opsonization by plasma proteins or directly, prosthetic particles are phagocytosed by macrophages, which are then activated to release matrix metalloproteinases, chemokines, and cytokines (Purdue *et al.* 2006). The released factors increase vascular permeability, recruit other monocytes, activate innate and adaptive immunity, and support multinucleated osteoclast formation and activation – all of them leading ultimately to a shift in bone homeostasis towards resorption. In reality, macrophages are not the only cells endowed with the ability to phagocytose wear particles. Interface tissue fibroblasts (ITF), osteoblasts, and some other cell populations have the same ability. If particle size is over the phagocytosable limit, multinuclear foreign-body giant cells are formed (Ma *et al.* 2005). It remains to be elucidated whether the multinuclear cells represent a source of alternative osteoclast precursors induced by non-phagocytosable wear particles, or if they play another role in particle disease.

The monocyte/macrophage cell line is not only an initiator of osteoclast differentiation. It also serves as precursor for osteoclast lineage. The most important pathway involved in osteoclast maturation and activation is mediated by receptor activator of nuclear factor- κ B (RANK) and RANK ligand (RANKL) (Boyle *et al.* 2003). Activation of RANK by its ligand leads to the initiation of osteoclast-specific genes. Both TNF- α (tumour-necrosis factor) and IL-1 (interleukin) promote RANKL expression on marrow stromal cells, T-lymphocytes, ITF, and osteoblasts and this appears to be an inevitable precondition for osteoclast maturation (Figure 2). In contrast, osteoprotegerin (OPG) blocks osteoclast

formation by binding to RANKL (Boyce *et al.* 2006). The most potent secretors of OPG are dendritic cells, ITF, osteoblasts and their precursors (Koreny *et al.* 2006). A number of studies have recently shown that the local ratio between RANKL and OPG significantly influence the size of periprosthetic OL (Holding *et al.* 2006; Mandelin *et al.* 2003; Veigl *et al.* 2006). Using cDNA microarrays, induction of gene expression in macrophages and other involved cells has been found to be much more extensive and more complex than had been thought until recently (Garrigues *et al.* 2005; Guenther *et al.* 2005). Further progress may be expected in relation to pathway-focused DNA microarrays designed specifically for studying gene expression associated with particle disease.

Pure particle disease theory, however, cannot explain irregularities such as different rates of failure (OL) in patients with the same prosthesis and wear rate (Gallo *et al.* 2006; Wilkinson *et al.* 2005). Surprisingly, the number of particles released into the periprosthetic tissues can achieve levels in the order of 10^{12} even if the rate of prosthetic wear is 0.1 mm per year (Pokorny *et al.* 2006). Such a quantity of particles would undoubtedly trigger particle disease. Thus, not only particles per se but also other factors must also be involved in the pathophysiology of OL. These may include hypersensitivity to prosthetic materials (Willert *et al.* 2005) or polymorphisms in the genes encoding for molecules involved in the pathways associated with OL (cytokines, enzymes, chemokines; Ambruzova *et al.* 2006; Malik *et al.* 2006; Wilkinson *et al.* 2003). In addition, adherence of endotoxins to prosthetic particles markedly increases their biological activity. Hence, Nalepka *et al.* has proposed low-grade sepsis or systemic bacteriemia as another important factor in OL development (Nalepka *et al.* 2006).

Bone remodelling: lessons learned from academic discussions

Bone remodelling is the process by which the bone adapts its shape to external forces. It takes place at the bone surface, and key players are osteoblasts and osteoclasts (Sims and Baron 2002). The complete bone remodelling cycle consists of activation-resorption followed by activation-formation sequences both of them closely coupled and balanced at each BMU, thus guaranteeing the functional capacity of the bone under physiological conditions (Parfitt 2002). Formerly, it was thought that osteoblasts control the formation and activity of osteoclasts, and “make all decisions” in the BMU. Recently, it has been postulated that osteoclasts also contribute significantly to the local homeostasis by stimulating the osteoblast cell lineage (Martin and Sims 2005). Osteoblasts, osteoclasts, their precursors and other present cells are engaged in cell-cell interactions via a variety of mechanisms including secretion of long-range (hormones) and short-range signalling molecules (BMP-2, Wnt, M-CSF, RANKL, IL-6, IL-1 β , and IFN- γ), and direct cell-cell contact (communicating gap junctions, RANKL:RANK) (Stains and Civitelli 2005). In addition, each BMU is influenced by the immune system through both soluble and membrane-bound cytokines, and growth factors (Yeung 2005).

In contrast, uncoupling occurs when the balanced link between formation and resorption is disturbed (Martin and Sims 2005). In this regard, particle disease may be an example of a factor that profoundly changes parameters in favour of resorption. Within the context of particle disease, the final degree of bone loss depends on the number of uncoupled BMUs present at one time. Theoretically, this may be brought into effect by either *increasing the lifespan of existing BMUs* and/ or the *origination of new BMUs* (Parfitt 2002). Thus, the underlying mechanism for uncoupling of bone resorption from formation may lie in the number of functional osteoclasts and osteoblasts inside each BMU, which depends on perturbations in cytokine/ chemokine milieu, vascular supply and concentration of osteoclast precursors in the blood.

Apoptosis is the key mechanism of cell number regulations with many positive and negative regulators including the above-mentioned soluble signals and cell-to-cell interactions. PE-particle induced cytokines such as IL-1, M-CSF, and notably TNF- α and RANKL support osteoclast survival mostly by stimulation of TRAF activated pathways (NF- κ B, ERK, PKB/Akt) (Blair *et al.* 2005; Xing and Boyce 2005). This stimulation may be so strong that can even protect osteoclasts from bisphosphonate-induced apoptosis (Zhang *et al.* 2005). Moreover, TNF- α induces apoptosis much easier in less mature osteoblasts than in mature ones (Xing and Boyce 2005). Simultaneously, prosthetic particles and agents of particle disease suppress the osteogenic activity of residual osteoblasts. In addition, prosthetic particles provoke the expression of chemokines MCP-1, MCP-2, IL-8, which attract monocytes, T cells, and neutrophils. Intense local accumulation of such cell types creates conditions not only for continuation of inflammatory pathways but also increase in level of tissue damage caused by necrosis.

Osteoblasts

Osteoblasts are bone-lining cells derived from mesenchymal stem cells of the bone marrow stroma or periost (Sims and Baron 2002). They never act individually but in groups when they synthesize a number of substances, including bone matrix constituents, and participate in several pathways through regulating immune and non-immune factors (IL-6, IL-8, MCP-1, CXCL-12, COX-1, COX-2, PGE2, M-CSF, FGF-2, RANKL, OPG, Wnt) (Krishnan *et al.* 2006). Among other signals, osteoblasts activity are strongly regulated by surrounding pH and growth factors released from resorpted bone matrix that stimulate osteoblasts to promote bone formation (coupling concept).

In vitro experiments have shown that wear debris alone or in conjunction with TNF- α or IL-1 β stimulate mature osteoblasts toward the expression of chemokines MCP-1, IL-8, and

CXCL-12 via a NF- κ B pathway (Fritz *et al.* 2006). Osteoblasts can participate in the initiation of local inflammation by attracting monocytes, T cells, and neutrophils. Moreover, low concentration of particles, TNF- α and IL-1 β may stimulate osteoblasts toward expression of the membrane-bound or soluble RANKL, and M-CSF thus participating in osteoclast recruitment, maturation, and activation (Boyce *et al.* 2005; Tanaka *et al.* 2005). On the other hand, the same cytokines can also induce expression of OPG, IL-6, and Wnt in osteoblasts (Krishnan *et al.* 2006) resulting in inhibition of cathepsin K (CATK) and tartarate-resistant acid phosphatase (TRAP) expression in mature osteoclasts via the JAK/STAT pathway (Rakshit *et al.* 2006). In fact, Wnt serves as an autocrine stimulator of OPG expression in osteoblasts. Furthermore, osteoblasts can actively bind immune cells (T cells) by surface expression of adhesive molecules ICAM-1 and ALCAM-1 (Stanley *et al.* 2006).

Osteoclasts

Osteoclasts are multinuclear giant bone resorbing cells that are usually located one or two per one resorption site (Sims and Baron 2002). Early osteoclast mononuclear precursors differentiate from haematopoietic progenitors of the monocyte/macrophage lineage (GM-CFU) under specific local milieu, which includes the presence of specific cells, and soluble factors (SCF, M-CSF, TNF- α). Once progenitor lineage cells differentiate to early osteoclast precursors they express RANK on their surface (Boyce *et al.* 2006). Binding of RANKL to RANK molecule stimulates further differentiation toward osteoclasts. RANKL exist in both surface-bound and soluble form. The former is expressed on the particle-stimulated osteoblasts and ITF (Mandelin *et al.* 2005). The latter is secreted by several cell lineages (T cells, osteoblasts, stromal cells) after stimulation by particle-induced TNF- α , IL-1 β and PGE2 (Boyce *et al.* 2005). At this stage, the osteoclast precursors may be activated to further differentiation by IL-1 β (Blair *et al.* 2005). Simultaneously, macrophage and T cell

recruitment is reinforced by chemokines MCP-1, MCP-2, MIP-1, and IL-8 released from BMU cells. These interactions result in a cascade of positive feedback further supporting osteoclast maturation and activation (Figure 3), eventually leading to high concentrations of mature and active osteoclasts with prolonged survival in BMU.

This differentiation and activation process is down-regulated by soluble RANKL-decoy factor (OPG), IL-6, IFN- γ , IL-4, and other as yet not well-understood factors (Blair *et al.* 2005). OPG is secreted predominantly by regulatory-acting dendritic cells, ITF (see below), and osteoblasts as the negative feedback response to increased surrounding concentration of TNF- α and IL-1 β . OPG secretion is also stimulated by regulatory anti-inflammatory cytokines TGF- β , IL-4, and factors such as hormone 17 β -estradiol or differentiation factor Wnt (Krishnan *et al.* 2006). The high affinity of binding RANKL to OPG precludes a dispersed osteoclastogenic environment, supporting somewhat, the hypothesis that for effective osteoclast formation, direct cell to cell contact between RANKL-positive cells (ITF, osteoblasts) and precursor cells expressing RANK is required in interface tissue (Stains and Civitelli 2005).

A gradual increase in expression of osteolytic substances (CATK, TRAP) during osteoclastogenesis is possible, owing to the large number of transcription factor binding sites in regulatory sequences of respective genes (Blair *et al.* 2005; Boyce *et al.* 2006). These binding sites are cumulatively occupied by transcription factors (PU.1, Mitf, NFATc1, AP-1, and NF- κ B) whose intracellular level increases during the monocyte to osteoclast differentiation and activation. Down-regulation of CATK and TRAP transcription has been observed during osteoblast IL-6 secretion; interestingly, IL-6 may be expressed by macrophages and ITF as well. Another down-regulator is IFN- γ , which stimulates the JAK/STAT pathway after binding to osteoclast surface receptor CD119 as does IL-6. However, direct binding of wear particles on osteoclast surface, which causes the induction of

various MAP kinase pathways, regulating JAK/STAT cytokine response, may dampen the interferon-suppressive effect. It has been shown that IL-6-induced JAK/STAT signalling is suppressed by the p38 MAP kinase pathway, which is activated by RANKL and IL-1 TRAF6-mediated activation (Rakshit *et al.* 2006). Thus, the wear debris is not only a stimulus for inflammatory and osteoclastogenic response. It also suppresses the naturally evolved homeostatic regulatory mechanisms directing the BMU (Figure 3).

Interface tissue fibroblasts (ITF)

Fibroblasts are dominant cell type at the interface tissue membrane that play important role in the control of osteoclastogenesis after direct particle-induced or indirect stimulation (hormones or cytokines) resulting in secretion of chemokines including MCP-1, MCP-2, IL-8, matrix metalloproteinases, and cytokines such as TNF- α and RANKL (Koreny *et al.* 2006). Recently, *in vitro* experiments confirmed that the only factor that consistently increased RANKL production in ITF was not TNF- α or IL-1 β but 1 α , 25-(OH) $_2$ vitamin D $_3$. In contrast, OPG expression was effectively regulated by hormones and cytokines including TNF- α (Mandelin *et al.* 2005). ITF participate also through cell-to-cell interactions with osteoclast precursors. Moreover, they can contribute to lower pH and produce CATK (Mandelin *et al.* 2005). On the other hand, ITF can down-regulate osteoclast activation by IL-6 production (Konttinen *et al.* 2002). As a result, ITF actively contribute to both up- and/or down-regulation of the osteolytic microenvironment between prosthesis and bone.

Lymphocytes

Perivascular infiltrates of lymphocytes have been observed in tissues from patients with aseptic loosening or osteolysis (Willert *et al.* 2005). Wear particles-activate macrophages which secrete MIP-1 and MCP-1 and these attract lymphocytes into the BMU (Purdue *et al.*

2006). Revell et al founds IL-15 transcription in macrophages retrieved from interface membrane suggesting specific stimulation of attracted T cells (Revell and Jellie 1998). *In vitro* experiments have revealed active interaction between osteoblasts and T cells mediated by adhesion scavenger molecule CD6 and integrin LFA-1 (CD11a/CD18) on the side of T cells with their ligands ALCAM (CD166) and ICAM-1 detected on osteoblast surfaces (Stanley *et al.* 2006). During this interaction, T cells augment IL-6 expression in osteoblasts resulting in the above-described down-regulation of osteoclastogenesis. On the other hand, T cells can influence BMU by expressing RANKL and TRAIL, which stimulate osteoclast maturation (Lee and Lorenzo 2006). RANKL expression on the surface of T cells is upregulated by TNF- α and IL-1. However, other studies deny any role for T cells in OL (Li *et al.* 2001; Taki *et al.* 2005) demonstrated OL in lymphocyte-deficient mice. Although the RANKL/RANK/OPG pathway is a clear molecular link between the immune system and particle disease, the role for the clonal immune system in OL development remains to be elucidated.

Possible sources of individual susceptibility to OL

Although this may appear like looking for the proverbial needle in the haystack, detailed knowledge of OL pathophysiology may facilitate a more effective choice of treatment and preventive targets. In this context, the large individual variation in outcome for the same prostheses under comparable conditions (e.g. similar wear rates) strongly suggests a genetic component to OL. Thus, a search for the “candidate” genetic markers (polymorphisms) has already been initiated. Theoretically, any part of any pathway involved in OL may be affected by nucleotide variation in individual genomes. Wilkinson et al have conducted to date, the largest study in which they found carriage of the TNF- α -238*A allele was associated with an increased incidence of periprosthetic OL compared with non-carriage

(OR=1.7; Wilkinson *et al.* 2003). Moreover, they found this variable was an independent risk factor for OL. Recently, an association between homozygous genotype A/A for the OPG-163 and both the aseptic (OR=3.76) and septic failure of THA (OR=3.42) was confirmed (Malik *et al.* 2006). Additionally, a relationship between homozygous genotype T/T for RANK+575 and aseptic failure of THA (OR=1.77) was found. Recently, in our pilot collaborative study we reported an association of particular variants of IL-1 α and IL-6 genes with susceptibility to / protection against OL (Ambruzova *et al.* 2006). Despite these promising results, we should bear in mind the complexity of OL pathophysiology and the hierarchical nature of numerous pathways, predispositions and conditions.

Therapeutic implications for the future

Understanding the cascade of events that follow polyethylene wear exposure of periprosthetic tissue may lead to the development of new preventive and treatment approaches. The potential of bisphosphonates, RANKL antagonists, and anti-inflammatory agents are in focus at present (Childs *et al.* 2001; Shanbhag 2006; von Knoch *et al.* 2005; Yang *et al.* 2004). Unfortunately, there is not enough evidence that such approaches work when applied to patients with existing periprosthetic OL. Moreover, there are concerns about the systemic administration of some drugs and some kinds of gene therapy. As a result, there is not approved pharmacological treatment of periprosthetic OL so far.

Conclusions

The main problem in total hip or knee arthroplasties is polyethylene wear resulting in development of OL. Prosthetic wear debris influences periprosthetic environment complexly and there is strong evidence that monocytes/macrophages are central in these processes. Stimulated macrophages trigger a large number of pathways leading ultimately to uncoupling

of the osteoblast/ osteoclast balance, and OL. Individual host response may explain why comparable bone defects are not observed in individuals with similar prosthetic wear rate. Preventative measures such as preoperative identification of patients at high risk of early OL development (individual susceptibility) may be possible in the future. It could be based on identification of relevant functional alleles for above mentioned cytokines, adhesion molecules, prostanoids, or any proteins involved in osteoclasts maturation and activation pathways associated with increased OL risk.

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Abbreviations

Akt – serine/threonine protein kinase; AP-1 – activator protein-1 (complex of transcription factors cJun, cFos); BCL-6 – antiapoptotic protein (transcriptional repressor); BMU - bone multicellular unit; CATK – cathepsin K - degrades collagen type I at several sites in the triple helical region; c-Jun NK – c-Jun N-terminal kinase; COX-1 – cyclooxygenase 1; c-Src – cellular unmutated form of Rous sarcoma virus oncogen – tyrosine kinase; ERK – extracellular signal-regulated kinase; FOXO4 (AFX) – ALL1-fused gene from chromosome X (member of “O” subfamily of Forkhead box transcription factors Fox); IF- κ B – inhibitor of NF- κ B; IF- κ BK – IF- κ B kinase; IL-1R – IL-1 receptor; IL-1 α , IL-1 β , IL-6, IL-4, IL-11 – interleukins; JAK – Janus tyrosine kinase - associated with cytokine receptor; mi/Mitf – transcriptional regulator microphthalmia transcription factor; NFATc1 - nuclear factor of activated T cells (NFAT) c1 (transcription factor); NF- κ B – nuclear factor kappa B (complex of transcription factors p50, RelA, p52, RelB or p50, p65); OPG – osteoprotegerin, protein - inhibits osteoclastogenesis; p38 – protein kinase; PE – polyethylen; PGE2 – prostaglandin E2; PI(3)K – phosphatidylinositol 3-OH kinase; PKB - protein kinase B; RANK – receptor activator of nuclear factor- κ B; RANK-L – ligand for RANK, osteoclast differentiation factor (TRANCE, TN-FSF11); SCF – stem cells factor; STAT – signal transducer and activator of transcription - transcription factors family; TNFR – TNF receptor; TNF- α – tumour necrosis factor; TRAF - TNFR-associated cytoplasmic factor; TRAP – tartarate-resistant acid phosphatase; Wnt/ β -Catenin pathway: low-density lipoprotein receptor–related protein (LRP), frizzled signaling induces preosteoblast replication, osteoblastogenesis, inhibits osteoblast or osteocyte apoptosis.

Figure 1

Total hip replacement and periprosthetic OL. Acetabulum after removing of femoral hip moiety (A) is prepared – white dotted line (B) to fit with cementless cup which is positioned (C) before assembling total hip replacement (D). In case of OL the wear debris and proinflammatory and osteoclastogenic substances are spread out over the prosthesis (E) resulting in development of osteolytic granuloma that causes OL - as demarked by red arrows in perioperative picture (F) or in X-ray photograph (G).

Figure 2

Schematic representation of pathways participating in development of periprosthetic OL.

Microenvironment of the bone multicellular unit (BMU) is regulated by signals arising either from BMU cells (osteoblasts, osteoclasts, stromal cells) or from attracted cells (macrophages, lymphocytes, neutrophils, ITF and dendritic cells). These signals can either stimulate (M-CSF, RANKL, TNF- α , IL-1 β , wear particles, CD40L) or dampen (OPG, IL-6, IFN- γ , TGF- β , Wnt, BMP-2, IL-4) the osteoclasts formation and activity. Separately prostanoid pathway components (PGE2, COX-1, COX-2) involved in osteoclast stimulation and chemokines (MCP-1, MIP-1, IL-8, CXCL-12) attracting immune cells are depicted.

Figure 3

Induction of the osteoclast differentiation, survival, and activity. Osteoclasts differentiate from GM-CFU progenitor in bone marrow. First osteoclast precursors begin to express RANK and migrate to ossificated bone (BMU) under specific signaling where the differentiation is completed. Mature osteoclasts require extracellular signals for survival and activity that is associated with osteolysis.

Figure 1

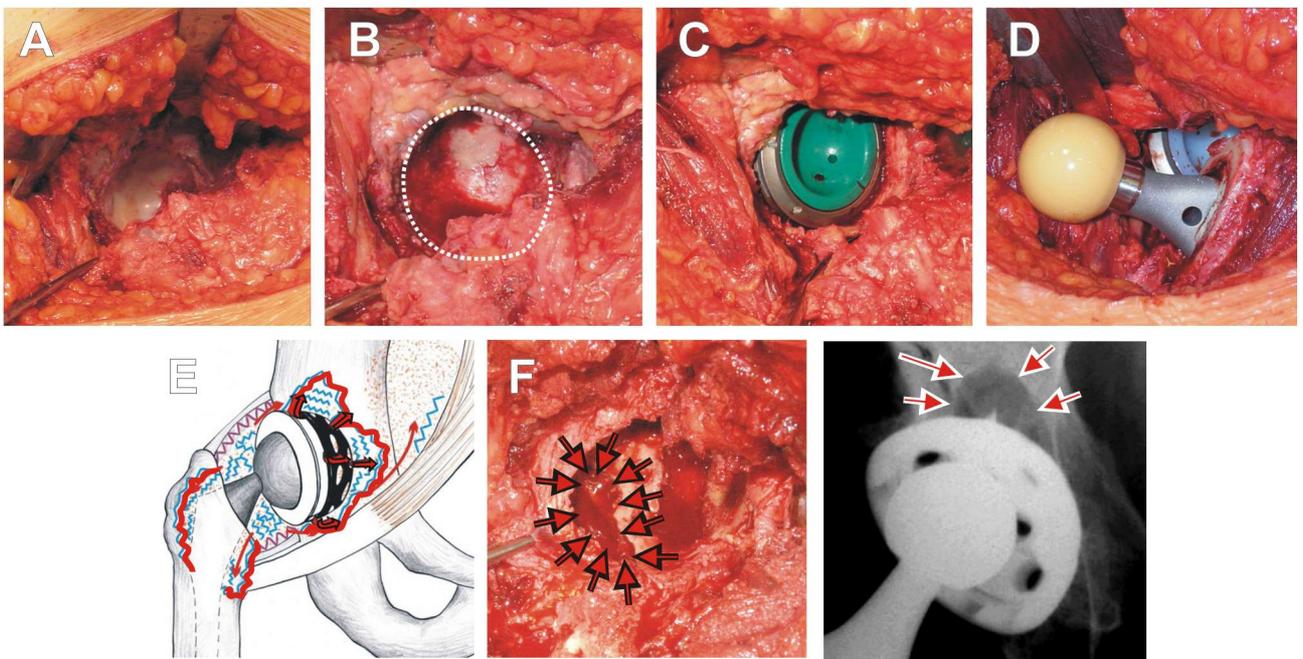


Figure 3

