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The Role of Aluminium Ceramics in Total Hip Arthroplasty

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1. Introduction

The investigation into the reaction of tissues on organic and inorganic particles is the topic of a multitude of medical disciplines. In the area of hygienics, industrial medicine and pulmonology for instance, the effects of fine dust particles in the lungs are examined (Wottrich et al. 2004). In the field of oncology, now and then the possible influence of nano foreign-body particles on carcinogenesis is being investigated (Jacobs et al. 1998). From the viewpoint of the immunologist, the different attitudes of cells and variable receptor activities during the phagocytosis of foreign bodies are of interest (Sun et al. 2003).
In the region of surgical disciplines like orthopaedics, trauma surgery or maxillary surgery, particle studies that investigate the influence of the abrasion of different prosthetic materials on the peri-prosthetic tissue have been undertaken in order to get evidence on their respective biocompatibility. In orthopaedics, this question is of importance mainly in the field of the total endoprosthetic hip replacement. Hip joint prostheses rank as most frequently performed implantations of biomaterials in orthopaedics and are particularly affected with regard to the formation of wear debris and loosening because of their exceptional mechanical use.

2. The development of the artificial hip joint replacement

At about 1.3 million implantations of biomaterials worldwide per year, the artificial replacement of the hip joint counts among the most frequent operations in the frame of orthopaedic surgery (Harris et al. 1995). In Europe, 500,000 hip joint prostheses are implanted annually. In Germany, there are about 200,000 every year including up to ten percent replacement of an already existing prosthesis (Özkir et al. 2007). In the USA, 600,000 total hip arthroplasties (THA) are implanted yearly at present. Up to the year of 2030 the annual requirements of primary THA will probably rise from 209,000 to 572,000, an increase by 174%. The future need by patients younger than 65 years will presumably come to 52% of the primary THA. The annual hospital expenses for primary THA will rise to 17.4 billion US$ up to 2015. According to estimations the number of THA revisions will increase from 40,800 (year 2005) to 96,700 (2030) in United States. The expected rise of THA revisions will be at 137% (Kurtz et al. 2007).
The idea of an artificial hip joint can be traced back to design drawings made by Gluck at the end of the 19th century. The first translation of this idea into action took place by Hey-

Groves in 1922, who used an implant from ivory as a femur head prosthesis. The first metallic total hip arthroplasty – consisting of an acetabulum and a femur head fastened to the neck of the femur by a bolt – was implanted by Wiles in 1938.
Today, the fixation occurs in the femur by an intra-medullary metallic stem. The first operation that was performed this way was done by Moore in 1940.
The results of the hip joint replacement, at first scanty concerning durability and load capacity, could be improved in 1959 by the introduction of bone cement (polymethyl methacrylate, PMMA) by Sir John Charnley (Herren et al. 1987).
Today, the most frequently used materials in hip arthroplasty are titanium alloys (e.g. titanium-aluminium-vanadium, TiAlV) or cobalt-chromium-compounds, polyethylene (e.g. ultra-high-molecular-weight-polyethylene, UHMWPE), and aluminium ceramics (Al_2O_3).

2.1 The significance of aluminium ceramics in hip arthroplasty

Bio-ceramics are an alternative to metal alloys for total hip replacement. Alumina is the most widely used oxide ceramic material for orthopaedic implants. Alumina ceramics are manufactured from powdered aluminium oxide which is mixed with an organic binder and pressed into a mold. The material is then dried to evaporate the water and calcinated to burn the organic binder. The quality and purity of the powdered raw material and the temperature of calcination determine the microstructure of ceramics (Hannoche et al. 2005).
Ceramics became of great interest in hip arthroplasty (Manley et al. 2008) as they promised a solution to the problem of aseptic loosening. Clinical and experimental studies showed that pairings of alumina ceramics in comparison to the widely used polyethylene/metal pairings lead to less debris. Wear particles can stimulate osteoclasts around the implant resulting in particle-induced osteolysis – the major cause of long time failure in hip arthroplasty (Sunfeldt et al. 2006).
Many authors concluded that the number of revision surgeries of ceramic/ ceramic pairings due to aseptic loosening is lower compared to polyethylene/ metal pairings (Clarke et al. 1994). Until 2001, more than 3 million ceramic prosthetic heads and more than 300,000 ceramic acetabular cups were successfully implanted worldwide (Thompsen et al. 2002). The combination of a ceramic head combined with a polyethylene cup reduces the particle wear by half compared to a metal/polyethylene pairing. (Hannoche et al. 2005) The combination of a ceramic head and a ceramic cup can further reduce the particle wear by ten times (Hannoche et al. 2005). Nowadays, the most widely used combination in total hip arthroplasty is that of a ceramic head with a polyethylene cup (Rössler and Rüther 2005).
The idea to use ceramic materials for hip replacement comes from the French surgeon Pierre Boutin. In 1970, he implanted a cemented ceramic cup combined with a ceramic head for the first time. In 1974, Peter Griss and Heinz Mittelmeier introduced the regular use of ceramic heads and cups in Germany. Meanwhile, most ceramic materials are based on alumina (Al_2O_3) (Hannoche et al. 2005). An advantage of using ceramics in hip joint replacement is that laboratory experiments showed ceramics to be bio-inert. The material does not corrode, it is well tolerated by the surrounding tissue and produces significantly less wear than current alternative materials of ultra-high molecular weighted polyethylene (UHMWPE) and titanium aluminium vanadium TiAlV (Manley et al. 2008, Warashina et al. 2003).
Ceramics possess advantageous tribological characteristics (Bierbaum et al. 2002). In-vivo experiments showed that the ceramic surface forms a lubricating protein-rich film after implantation that works as sliding layer (Christel 1992).

In the 70ties, so-called monolithic or bloc cups entirely made of ceramics were used at the beginning. They demonstrated good bio-inert characteristics and a high corrosion resistance but a poor osteo-integration. A fibrous tissue was frequently found between implant and bone leading to migration and loosening of the prosthesis due to change of position of the components and resulting in increased abrasion (Willmann1998). Therefore, the results in the early era of ceramic hip implants have been poor. Many studies from this period reported revision surgeries in 30 % of the patients after 5 years compared to significantly better results of metal / polyethylene combinations (Mahoney et al. 1990). Furthermore, the initial poor performance of ceramic hip joints is attributed to the mechanical characteristics of ceramics. The brittle, inelastic material can hardly compensate forces by deformation. Therefore, fractures of ceramics, mostly found in the femoral part, were more frequent than in prostheses out of polyethylene or titanium alloys (Manley et al. 2008). Ceramic implants demand an experienced surgeon as the positioning of the implant e.g. inclination, ante-version, offset and neck length, is of great importance for the long-term results. The correct positioning of cup and stem reduces asymmetric strain on the implant, avoids an impingement and reduces the material abrasion and fracture. Hamadouche et al. published excellent long-term results in correctly positioned ceramic prosthesis (Hamadouche et al 2002). Savarino et al. recently published a study showing that trauma, infection, mechanical instability and incorrect positioning mostly lead to implant failure of alumina ceramic on alumina ceramic hip prosthesis. They pointed out that particle-induced osteolysis was no longer the number one reason of long-term failure (Savarino et al. 2009).

Another reason for the improvement of durability of alumina ceramics was a constant development of the material. First generation alumina ceramic materials consisted of large (7.2 micron particle size), less strong (400 MPa) and less dense (3, 94 g / cm ^{3}) crystals and showed impurities of up to 5 percent by volume. Currently, third generation alumina ceramics consist of crystals with a much finer grain size (1.8 microns). They have a higher density (3.98 g / cm ^{3}), higher stability (580 MPa) and impurities of less than 0.5 percent by volume. (Hannoche et al. 2005)

In addition to the improving surgical technique and the higher quality of the raw material, the geometric shape of the femoral head and acetabular cup were optimized leading to a significant increase in the longevity of ceramic prosthesis (Thompsen et al. 2002). Clinical outcome studies confirmed that a total hip prosthesis made of alumina ceramic has good durability and low particle wear. Rousseau et al. (2004) reported of an average survival rate of 62.8% after 11 years of cemented alumina ceramic on alumina ceramic hip replacements. Lusty et al. (2007) found a survival rate of 99% after a mean of 7 years in cementless alumina-on-alumina ceramic hip replacements.

2.2 The aseptic loosening of the hip prosthesis

While in the early times of hip arthroplasty secondary complications were most frequently caused by material fatigue, inaccurate implantation techniques, and infections, today – following improvements in the methods of operation, sterilisation, and material development – the aseptic loosening of the prosthesis is the most common reason for orthopaedic revision operations (Sundfeldt et al. 2006).

During the aseptic loosening of a prosthesis, there is a progressive periprosthetic osteolysis in the course of time leading to a growing instability and increasing wear triggered by the advancing mobility of the prosthesis. In the long term, this results in the loosening and

dislocation of the prosthesis. A reason for the limited durability of the endoprosthesis is therefore caused by the composite of the implant and the surrounding bone tissue. In addition, the aspect of material wear plays a role. For the patient the loosening of the prosthesis appears in the form of pain following exercise or on movement (Rössler and Rüther 2005). As things develop revision operations are often inevitable. They weigh heavily upon the patients and are susceptible to risks because of peri- and postoperative complications (e.g. embolism or infections). Moreover, the secondary implant requires a greater intramedullary volume at each replacement of a hip prosthesis. Thus, the durability of the replacement prosthesis is significantly reduced in comparison to the first implant and the number of possible replacements is limited (Callaghan et al. 1985, Hanssen et al. 1988).
The real cause for the formation of periprosthetic osteolysis followed by aseptic loosening is still disputed. There is a multitude of theories:

2.2.1 Bone resorption induced by wear debris

Many authors in the contemporary technical literature assume that the wear debris generated by the abrasion of the prosthesis is phagocyted by cells of the surrounding tissue, thereafter activating these cells and giving rise to an aseptic reaction by release of different messenger substances (e.g. cytokines like interleukins or TNF-α), eventually causing the osteolysis of the surrounding bone. A significant role in this connection is assigned to the macrophages activating already present osteoclasts in the described manner or stimulating precursor cells to become osteoclasts or even further differentiating themselves into osteoclasts (Fujikawa et al. 2005). Furthermore, studies are mentioned in literature stating that other tissue cells, e.g. osteoblasts, are also able to phagocyte wear particles and to react to them (Lohmann et al. 2000). The cellular response caused by the wear debris and the connected bone resorption are dependent on different physical characteristics such as the material the particles are made from as well as their size, amount and morphology.
Schmalzried et al. (1992) consider that the aseptic loosening of the femur shaft is mainly due to mechanical reasons, while merely the loosening of the acetabulum, mostly consisting of polyethylene, is caused in the manner described above by bone resorption induced by wear debris.

2.2.2 The hydrostatic pressure

Schmalzried et al. (1992) and Aspenberg et al. (1998) regard an increased intracapsular pressure as an important factor in the origin of aseptic osteolysis. According to their theory the intra-articular cartilage in normal joints prevents the contact between bone and synovial fluid. As part of a disease or a trauma, a damage of the cartilage and consequently a loss of its osteoprotective properties is however possible. There will be an inflammation of the joint with the development of more intra-articular liquid. The result is an increased intracapsular pressure which reduces the blood circulation to the bone and leads to the ischaemic death of osteocytes consequentially leading to increased bone resorption. This theory is supported by studies of Robertsson et al. (1997), who discovered an increased intracapsular pressure in 18 implanted hip joints shortly before a revision operation because of aseptic loosening, compared to 34 clinically and radiologically stable hip joint implants. In addition, Aspenberg and van der Vis (1998) were able to show in a rabbit experiment that an oscillating intracapsular liquid pressure results in osteolysis and the death of osteocytes.

2.2.3 Endotoxic contamination of implants and particles

Hitchins and Merritt (1999) consider bacterial cell components attached to the hip joint implants (lipopolysaccharides, endotoxins) to be responsible for osteolysis. This theory is also supported by Akisue et al. (2002), who incubated macrophage-like THP-1 cells with titanium particles and endotoxins and observed almost no effect of endotoxin-free titanium particles on the expression of cytokines in their experiment.

2.2.4 Genetic predisposition

Matthews et al. (2000) pursued observations where certain patients showed no failure of their implant in spite of massive polyethylene abrasion, while in other patients with only small wear amount the implants failed with a distinct osteolysis. In a cell culture study, where macrophages from three different donors had been incubated by endotoxin-free polyethylene particles, they discovered a high variability of the macrophage cytokine expression induced by particle contact dependent on the donors. A similar discovery was made by Hatton et al. (2003), who incubated peripheral blood monocytes from six different donors with particles of aluminium ceramics and observed significant differences between the donor cells in the release of TNF-α. Genetic investigations on the correlation between genetic nucleotide polymorphisms and aseptic hip prosthesis loosening are currently under way (Wedemeyer et al. 2009, Bachmann et al. 2008).

2.3 In vivo and in vitro studies on wear particles

Until now, a lot of studies to clarify the morphological characteristics of wear particles have been carried out. It turned out that the peculiarity of the wear debris and hence the amount of wear particles in the periprosthetic tissue was dependent on the used material of the prosthesis.

Different methods have been used for the quantitative investigation of wear debris. These include calculations in the frame of radiographic studies and recently also calculation models with the help of prosthetic simulators. The latter have also been used to determine morphology and amount of the wear particles arising over time. At the same time there were clinical studies analysing the intra-operatively recovered particles afterwards, e.g. during a revision operation or the replacement of a loosened prosthesis.

The above mentioned investigation methods showed the highest rate of wear debris (6 to 140 mm^3 per year) for polyethylene in comparison to other materials (Livermore et al. 1990). On the other hand, for prostheses made from ceramics comparatively little wear debris is described. Lusty et al. (2007) mentioned a mean abrasion of 0.2 mm^3 per year. You et al. (2005) were not able to ascertain any wear debris in their radiological study, whereby in this case the assessment took place five years after the implantation of the prosthesis.

Concerning the size of the particles found in vivo, there is a dependence on the used prosthesis material, too, but like in the abrasion rate there are differences between authors also concerning the particles' size. Maloney et al. (1995) generally observed a mean particle size of just below 1μm for non-cemented polyethylene and metallic prostheses and an absolute number of 1.7 billion particles per gram tissue. Studies by Lee et al. (1992) on tissue recovered from cemented prostheses during revision operations yielded a similar particle size for metallic particles (TiAlV, CoCr, steel) between 0.3 and 1.8 μm and for polyethylene particles a magnitude between 2 and 13 μm.

During electron microscopic analysis of wear particles from Mittelmeier-prostheses (ceramics on ceramics) Yoon et al. (1998) found sizes between 0.13 and 7.20 μm (mean 0.7 μm). Hatton et al. (2003) on the other hand identified particles from ceramics in two magnitudes by a laser-based micro-dissection method (likewise on failing Mittelmeier-prostheses), one group with a mean diameter of 0.503 μm, while the other group showed a diameter on the nanometre scale (24 ± 19 nm).

The signalling pathways that have been investigated until now in cell-particle co-culture systems mainly contain cytokines (interleukins, TNF-α), prostaglandins and recently the RANK(L)/OPG-system, too, which so far, however, has only been tested on metallic and polyethylene particles (Baumann et al. 2004) and not as yet on aluminium ceramics. On this occasion, an increased expression resp. release of the corresponding messenger substances was connected with growing particle concentration and also in these cell culture studies polyethylene and different metallic particles induced a more distinct cellular response than particles from aluminium ceramics (Sterner et al. 2004). Concerning the influence of the particle size, however, different effects have been observed. For instance Sterner et al. (2004) described a proportional correlation between the size of aluminium ceramics particles and the release of TNF-α in macrophage-like cells, while Yagil-Kelmer et al. (2004) as the only authors so far concluded from their studies that smaller ceramics particles in single individuals might have a more significant biological answer than particles of the same material but with greater diameter.

Catelas et al. (1999) investigated the impact of aluminium ceramics particles on cell death mechanisms (apoptosis versus necrosis) in macrophage cultures and reported on a volume effect where cells showed apoptotic changes dependent from a combination of size and concentration of the deployed particles.

In a co-culture with a murine macrophage cell line, Petit et al. (2006) examined the influence of bisphosphonates on the release of TNF-α and the induction of apoptosis. It turned out that only the TNF-α-release induced by polyethylene (UHMWPE) particles could be inhibited, not the one induced by particles from aluminium ceramics and that bisphosphonates lead to an induction of apoptosis in the cells.

2.4 Monocytes and macrophages

Monocytes are mononuclear phagocytes circulating in the blood. They represent precursors of macrophages. In particular at inflammatory processes in the neighbouring tissue, monocytes are caused by chemotaxis to enter the tissue concerned where they differentiate to macrophages under the prevalent humoral stimuli and are able to survive there for a period from a few days up to several months. During this time the macrophages are performing most diverse functions: By secretion of messenger substances (cytokines, leukotrienes, prostaglandins, proteases, complement factors, etc.) for instance, these cells initiate inflammatory reactions as well as conversion and repair processes in the surrounding tissue. They phagocytose very different organic and inorganic materials, both foreign-bodies and own tissue, whereby the phagocytosis is being facilitated by previous opsonization of the materials being phagocyted by antibodies or complement proteins. The macrophages participate in immunological processes (immune defence) by antigen presentation at lymphocytes (Schiebler et al. 2002).

Within the framework of the particle-induced periprosthetic osteolysis the macrophages have a special significance in double regard: on the one hand, especially these cells react to

the particles by introduction of a pro-inflammatory signalling cascade, which eventually leads to an increased activation and recruitment of osteoclasts. On the other hand, the wear debris is able to inhibit the effect of osteoprotective mechanisms, e.g. the release of the osteoprotective interferon-gamma, whereby a differentiation of macrophages into osteoclasts is being facilitated (Purdue et al. 2006).

2.4.1 The THP-1 cell line and cell-particle co-culture systems

Tsuchiya et al. (1982) established this cell line and were able to verify their numerous monocytic properties, especially the potentiality for phagocytosis of foreign-body particles. Furthermore, the authors demonstrated that a treatment of this cell line by the phorbol ester phorbol-12-myristate-13-acetate (PMA), also called 12-O-tetradecanoylphorbol-13-acetate (TPA), results in a further differentiation along the monocytic development line up to macrophage-like cells (Tsuchiya et al. 1982). This happens via a signalling pathway mediated by protein kinase C, where PMA functions as an analogue for diacylglycerole, the physiological activator of protein kinase C. Schwende et al. (1996) observed a significant amplification of characteristics typical for macrophages if THP-1 cells were stimulated by PMA in a concentration of 10 nmol over 72 hours: This includes an increased expression of the surface proteins CD14 and CD11b typical for monocytes and especially macrophages and an intensified potential for the secretion of oxygen radicals. Additionally, they concluded that the PMA treatment induces an increase of TNF-α-cytokine release from the cells, inducible by lipopolysaccharides. Further observations showed cells stimulated by PMA are able to phagocytose about ten times more latex particles than unstimulated cells, and the morphological development to macrophages reached by the PMA treatment is quasi accompanied by a termination of the very high cell division rate known from the untreated cells. Beside different humane and murine cell lines, fresh peripheral blood monocytes (PMBC) extracted from donors have often been used (Yagil-Kelmer et al. 2004). There are only occasional reports about PMA stimulated THP-1 cells used for the analysis of osteolysis inducing properties of biomaterials. More often particle studies have been carried out with THP-1 cells using other substances than PMA for the stimulation to macrophage-like cells. A research group from Würzburg, Germany, used THP-1 cells which had been pre-treated by a granulocyte macrophage colony-stimulating-factor (GM-CSF) and vitamin D_3 (Baumann et al. 2004).

2.5 TNF-α und das RANK(L)/OPG- system

2.5.1 Osteoprotegerin (OPG)

The identification and characterisation of the RANK(L)/OPG system began in 1997 by discovery of Osteoprotegerin (OPG). It just happened by accident at the AMGEN company where cDNA from rat intestinal tissue had been characterised in a study. The researchers were looking for TNF receptor-like molecules, hoping for their therapeutic benefit. Certain transgenic mice which overexpressed the gene for OPG attracted attention because of a distinct osteopetrosis (Simonet et al. 1997). It was discovered that this was due to a decrease of the number of osteoclasts in the mouse skeleton and it was concluded that OPG plays a key role in the regulation of the osteoclastogenesis.

Apart from that, a Japanese research group discovered osteoprotegerin almost at the same time. Here, they were searching specifically for an undiscovered factor produced by

osteoblasts and stromal cells which they awarded regulatory features concerning the osteoclastogenesis and hence the bone resorption (Yasuda et al. 1998).
In detailed analyses of OPG, it turned out that OPG is a peptide comprising 380 amino acids. OPG is secreted as a 401 amino acids-long peptide where a propeptide of 21 amino acids is being split off (Simonet et al. 1997, Yasuda et al. 1997). It represents the only protein of the TNF receptor super-family which does not possess transmembrane and cytoplasmatic domains and which is secreted as a soluble protein. Using OPG-knockout mice, it was found that OPG apparently plays an important role in other organ systems, too. This is because a suppression of the OPG in the mice not only culminated in strong osteoporosis but also in changes in the vascular system, e.g. calcifications of the large arteries, proliferations of the intima and media and aortic dissections. Meanwhile, it is known that OPG-mRNA is being expressed in almost all organs (Simonet et al.1997, Yasuda et al. 1997).

2.5.2 Receptor Activator of Nuclear Factor kappa B Ligand (RANKL)

Soon after the discovery of OPG it became apparent that a protein already known concerning its ability to stimulate dendritic cells, the RANKL, works as a ligand of OPG. For this reason it is also called osteoprotegerin ligand (OPGL). In the presence of a low M-CSF level, RANKL is necessary and sufficient for the complete differentiation of osteoclast precursor cells to mature osteoclasts (Lacey et al. 1998).
Again during knockout mice experiments it was demonstrated that the elimination of the RANKL gene entailed a strong osteopetrosis and a total missing of osteoclasts (Kong et al. 1999). RANKL has been identified as a peptide with a length of 317 amino acids. It exists in a membrane bound and also in a soluble mode. The latter emerges through separation of a peptide part at position 140 or 145 (Lacey et Al: 1998).

2.5.3 Receptor Activator of Nuclear Factor kappa B (RANK)

By the discovery of RANKL as a potential ligand for OPG, it was concluded that also RANK, an already known receptor for RANKL, should play a crucial role in osteoclastogenesis and bone resorption.
The absence of RANK in knockout mice induces a distinct osteopetrosis, attributable to the complete missing of osteoclasts (Kong et al. 1999). Detailed analyses of RANK showed it to be a peptide with a length of 616 amino acids. It is composed of a signal peptide with 28 amino acids, an N-terminal extracellular domain, a short transmembrane domain of 21 amino acids and a large C-terminal cytoplasmatic domain. It is mainly expressed on monocytic cells and macrophages and also on pre-osteoclasts, B- and T-cells, dendritic cells and fibroblasts (Anderson et al. 1997).
The signal transduction running via RANKL and RANK eventually ends with the regulation of the nuclear transcription factor NF-kB. In its inactive form, NF-kB is bound to different inhibitor proteins in the cytoplasm. In the case of activation, these are degrading and the NF-kB molecule is able to translocate to the nucleus where it controls the transcription of a multitude of genes and, besides the osteoclastogenesis, it also regulates significantly apoptotic, inflammatory and autoimmune modulatory processes (Holt et al. 2007).

2.5.4 Tumor Necrosis Factor alpha (TNF-α)

The cytokine TNF-α is being secreted mainly by activated macrophages and owns a multitude of functions. Through its capability to stimulate osteoclasts, it is a potent mediator of bone

resorption (König et al. 1988) and it also plays an important role in the frame of inflammatory diseases and post-menopausal osteoporosis (Komine et al. 2001). The role of TNF-α in bone resorption has been studied by means of a knockout survey: Merkel et al. (1999) observed a hardly detectable bone resorption after elimination of the TNF-α receptor in mice following subperiostal implantation of bone cement particles. Furthermore, it could be noticed that TNF-α not only shows a synergistic effect to RANKL, but it also initiates a signal cascade via its receptor leading again to the activation of the transcription factor NF-kB.
The stimulation of osteoclasts, however, is not due to TNF-α alone. The presence of M-CSF is needed, too. Both factors together ensure a differentiation of haematopoietic progenitors to dendritic cells and hence an enlargement of the pool of pre-osteoclastic cells (Udagawa et al. 1990).

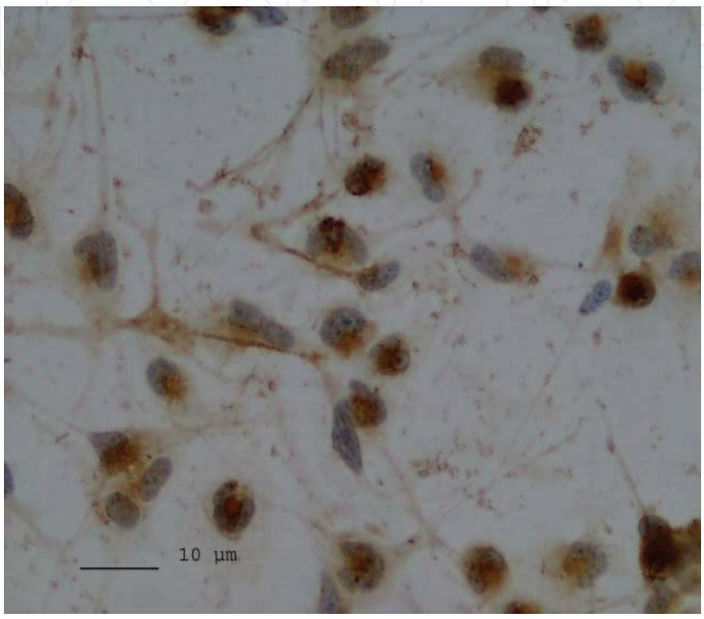
2.5.5 The RANK(L)/OPG system and TNF-α in the particle-induced osteolysis

Because of the affiliation of RANK and OPG to the TNF receptor superfamily, the following synonyms exist in the current nomenclature: RANK is also called Tumor Necrosis Factor Receptor Superfamily, member 11A. For RANKL there is the synonym Tumor Necrosis Factor Receptor Superfamily, member 11 and OPG is also considered as Tumor Necrosis Factor Receptor Superfamily, member 11B.
Like a multitude of other pro-inflammatory proteins (e.g. interleukin-1), TNF-α is in the position to stimulate the osteoclastogenesis via an activation of NF-kB. However, these cytokines do not belong to the final step of the signal cascade. This is rather composed by the RANK(L)/OPG system (Holt et al. 2007).
Because of the observations made so far, RANK must be the only receptor for RANKL on the cell surface of osteoclast precursors. OPG, which may be bound by RANKL, but with an opposite effect in bone metabolism, hence turned out as a soluble "decoy receptor" catching RANKL in the intercellular space without bone resorption resulting from this binding.
The relation of RANK and RANKL on one hand and OPG on the other is decisive for the way (construction resp. resorption of bone) and the extent of bone metabolism because of the above mentioned observations. The relevance of this relation has been confirmed in the area of the particle-induced aseptic osteolysis. During analyses of periprosthetic tissue surrounding loosened hip joint prostheses, a strong increase of RANK and RANKL expression could be found and in comparison a low expression of OPG (Mandelin et al. 2003). A further conclusion that could be drawn from this study was the fact that an imbalance in favour of RANKL and to the detriment of OPG induces the enhancement of osteoclastogenesis and hence loosening of the prosthesis.

2.6 THP cells and ceramic particles

We recently performed a study to illuminate the effect of alumina ceramic particles with different diameters and concentrations on the mRNA expression of certain key regulators in particle-induced aseptic osteolysis (RANK, RANKL, OPG, and TNF-α) in THP-1 macrophage-like cells (Bylski et al. 2009). Titanium particles were used as a positive control. RNA was analyzed by quantitative RT-PCR. Our results demonstrate that alumina ceramic particles, regardless of particle size, caused only slight up-regulations of RANK, TNF-α, and OPG mRNA, whose levels were significantly lower in comparison to those of titanium particles ($p < 0.05$). The continuous increasing tendency to time-dependent and particle-dependent mRNA-expression of all the parameters stimulated by titanium particles was not

found after stimulation with ceramic materials. Even after the concentration of ceramic particles was increased, only a mild up-regulation of mRNA-expression was found. Furthermore, we observed that the bio-inert characteristics of ceramic particles did not change much in diameters ranging from 0.5 to 1.5 µm. At most of the measuring time points, there was no significant difference between the reactions of the large and small particles in this range. Our results support the theory about the relative bio-inert characteristics of alumina ceramic particles.



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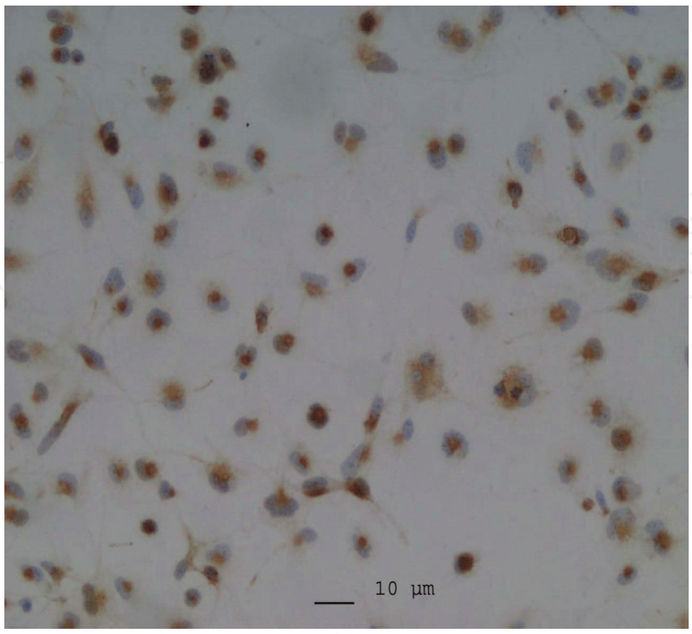

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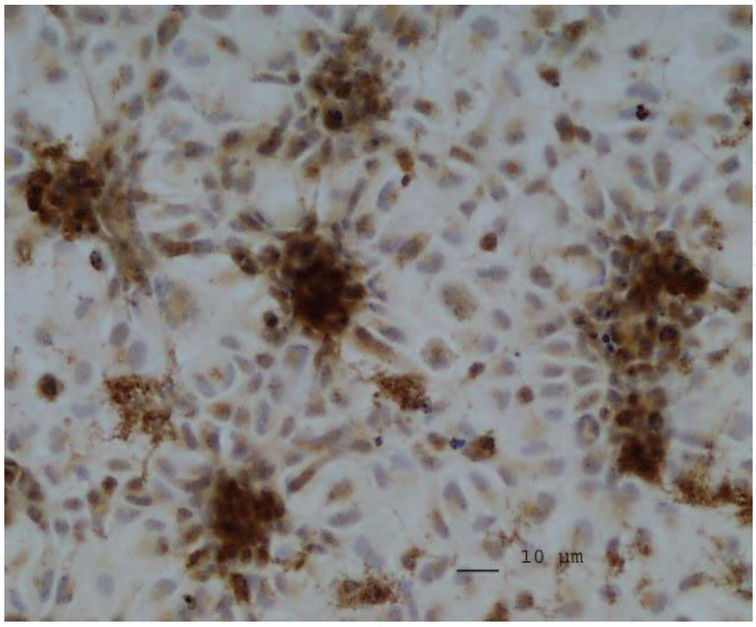

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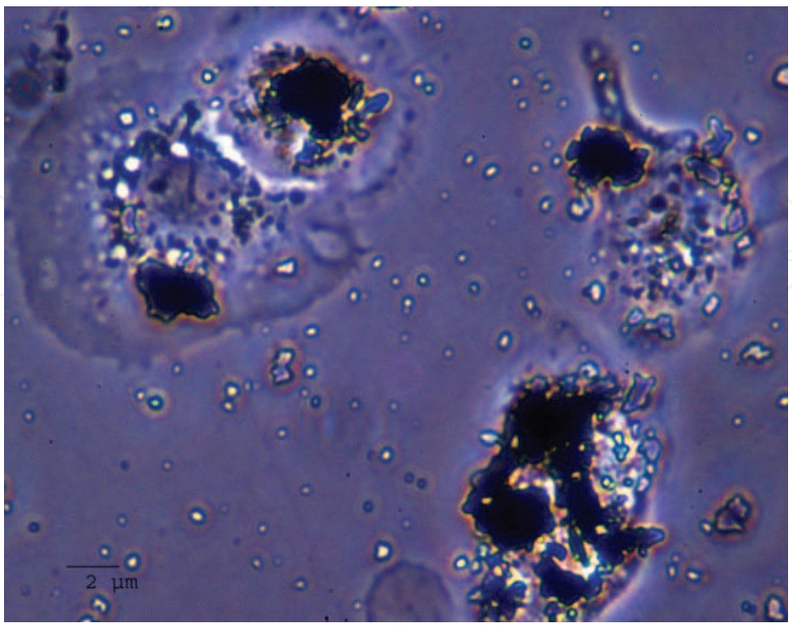

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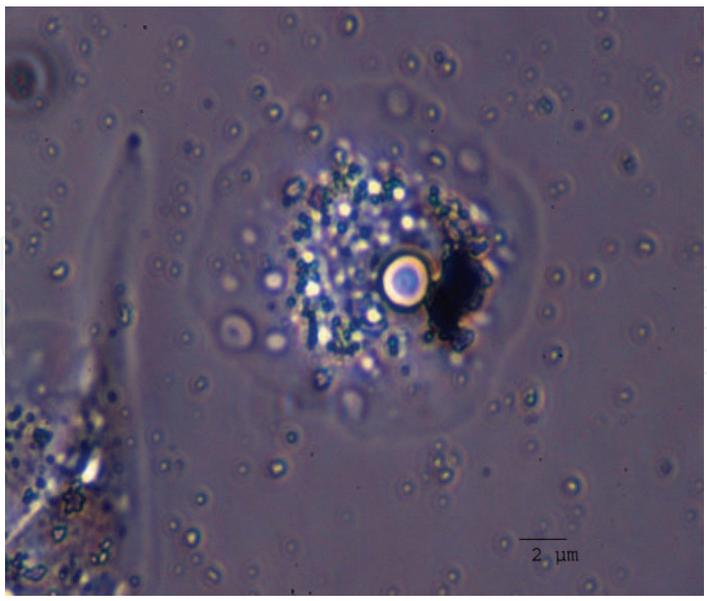

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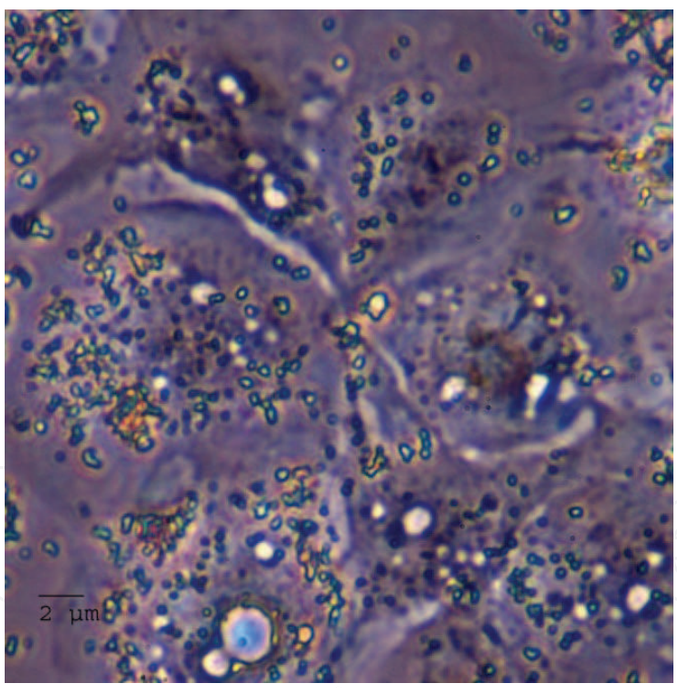

f)

Fig. 1. Light microscopic photographs of PMA-stimulated THP-1 cells after **immunohistochemical staining by CD68 antibodies (a-c) resp. at co-incubation with particles (d-f):** (a): 3 million THP-1 cells treated by 50 nmol PMA for 72 h, magnification 4x. (b): 1 million cells treated by 50 nmol PMA for 48 h, magnification 10x. (c): 5 million cells treated by 50 nmol for 72 h, magnification 10x. Cell aggregations are recognizable because of the high density. (d) + (e): THP-1 cells treated by PMA for 72 h phagocytosing titanium particles (for better overview at the rate of 1:10). After about 1 h already, a particle

accumulation in the cytoplasmic area could be recognized by light microscope. Besides the clearly visible large titanium particles (deep black), the smaller particles appear more transparent. Magnification 100x. (f): Ceramic particles of the kind CT1200SG in the cytoplasm of THP-1 cells treated in the same way. In comparison to the titanium particles, the smaller size of the ceramic particles is distinct. Under the light microscope, they are only distinguishable from the roundish intracellular vacuoles by their more oval shape.

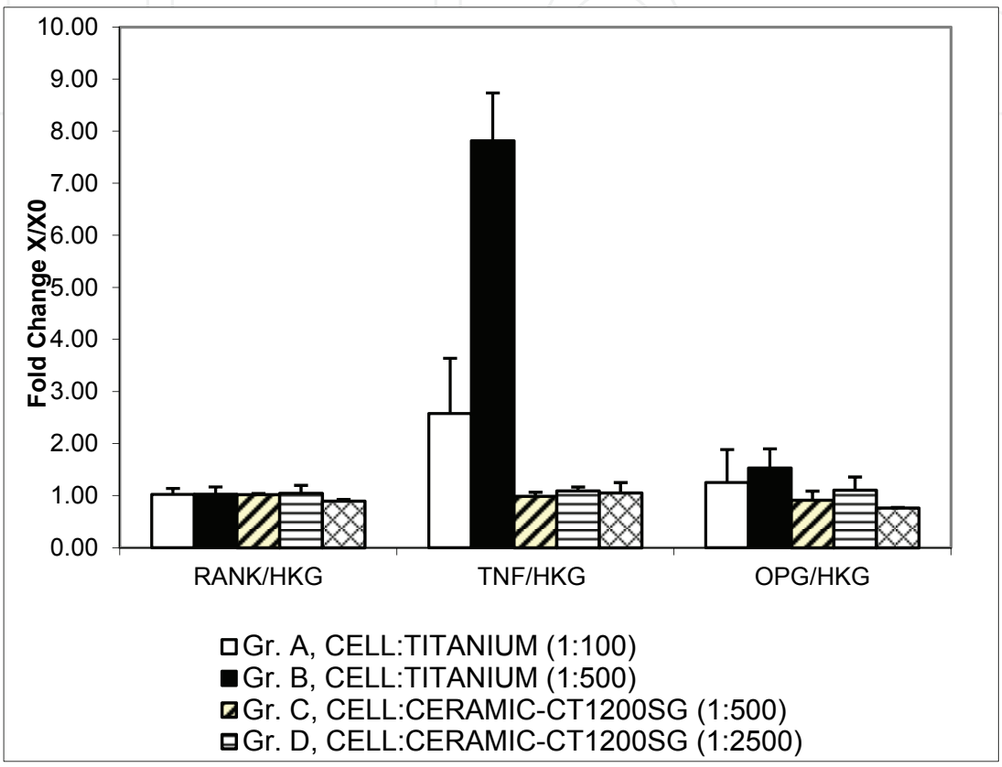

Fig. 2. Alteration of expression of RANK, TNF-α, and OPG caused by titanium and ceramic particles after an incubation time of 6 hours. Like before, the normalization took place by aid of the housekeeping-genes ß-actin and HPRT (here called HKG). A significant increase in expression could only be verified for TNF-α, which rose significantly in both titanium particle concentrations (group A and B, each $p<0.05$), while ceramic particles did not create a significant alteration of expression in any of the three genes. The group with smaller ceramic particles (group E) rather seemed to produce a decent but not significant suppression of RANK- and OPG-mRNA.

2.7 Possibilities and sense of prevention and intervention on particle-induced osteolysis

Currently, there exist several possibilities to prevent or to retard aseptic hip joint loosening whereas the different measures can start at different stages of anamnesis of patients with artificial hip joints.

In keeping with the philosophy of prevention, it could be targeted to avoid the necessity of hip implantation, for example by the reduction of adiposity as one of the most common causes for joint arthrosis, its early detection and conservative treatment.

If hip implantation is inevitable, its durability also depends on the surgeons experience and surgical technique. To avoid material abrasion or even fracture of the prosthesis, especially in case of ceramic prosthesis – described in chapter 2.1 – the exact positioning of the prosthesis components is particularly important.
To improve durability of prostheses, some decisive technical optimization were carried out referring to material properties as well as biocompatibility and durability. In the case of polyethylene, a smaller material abrasion has been reached by increasing the number of intermolecular binding (highly cross-linked UHMWPE), by high dosage gamma irradiation or by application of vitamin E for capturing the originated free radicals (Oral et al. 2007).
After the already undertaken further development of aluminium ceramics – e.g. by increasing purity level, strength and density – the research on this material continues to improve its tribological properties and especially its capacity (Masson et al. 2009). Using non-oxide ceramics, for instance silicon nitride or silicon carbide, Cappi et al. (2010) are aiming at applying ceramics for thin-walled implants (e.g. for resurfacing hip prostheses) which had not been possible previously because of the low mechanical strength of oxide ceramics.

2.8 Possible future problems of ceramics/ceramics sliding contact surfaces

The growing interest of orthopaedic surgeons in modern sliding contact surfaces like ceramics/ceramics is reflected by the more frequent clinical application to reduce wear debris and consequentially osteolysis in the young and active patient. Their wide range of use over the past decade, however, has led to complications, too, one being the developing of movement-related noises in hip-TEP patients. Most recent publications show that noises can occur in all sliding contact surfaces (Pokorny et al. 2010).

3. Conclusion

As ceramic bearing designs continue to improve with modified materials and manufacturing techniques, use will increase, especially in young and active patients and in concern to an earlier indication for total joint replacement and considering an eldery population. Clinical results for ceramic joint replacement , especially in young and active patients, show lower wear rates and a significant reduction of osteolysis. Furthermore our results support the thesis of bioinertness of ceramic components. New ceramic components are still under development, and the long-term results have to be evaluated over the next decades. Not every modern concept will likely stand the test of time, but some will be beneficial for patients undergoing total hip arthroplasty in the future.

4. Acknowledgements

The biomaterials research is supported by the German Research Foundation (DFG), Bonn, Germany (WE 3634/1-1).

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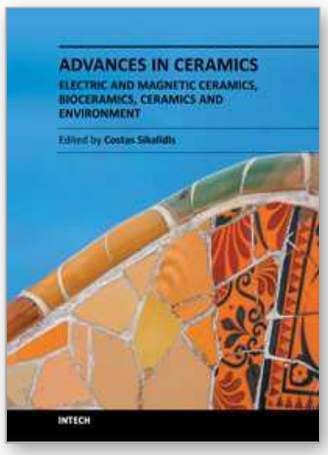

Advances in Ceramics - Electric and Magnetic Ceramics, Bioceramics, Ceramics and Environment

Edited by Prof. Costas Sikalidis

ISBN 978-953-307-350-7
Hard cover, 550 pages
Publisher InTech
Published online 06, September, 2011
Published in print edition September, 2011

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