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The bone-implant interface biology and potential targets for pharmacological interventions

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ABSTRACT

Total joint replacement, although considered an excellent surgical procedure, can be complicated by osteolysis induced by particles and subsequent aseptic loosening of the implant. The pathogenesis of implant-associated osteolysis includes inflammatory and osteolytic processes. An appreciation of the complex network that leads to these cellular and molecular responses will form a foundation on which to develop therapeutic interventions to combat inflammatory periprosthetic bone loss. In this paper, the authors will try to arrange the current basic knowledge of the bone - implant interface biology. The cascade of events that occur at the cellular and molecular level during osseointegration, osteolysis and aseptic loosening will be also provided. This knowledge would be very useful for researchers and orthopaedic surgeons, in order to intervene with pharmacological agents either locally or systematically and optimize the osseointegration of implants. Such biological and pharmacological interventions that have been currently tested will be finally reported.

KEY WORDS: joint arthroplasty; bone-implant pathology; osteolysis; aseptic loosening

Introduction

In joint replacement surgery the pre-requisite for clinical success is the achievement of good and fast bone-implant osseointegration. *Osseointegration* could be defined as the contact which intervenes, without interposition of non-bone tissue, between normal remodeled bone and an implant which can bear the distribution of load from the implant to and inside the bone tissue [1]. Furthermore, *bone ingrowth* could be defined as the formation of new

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bone tissue inside the porous surface of an implant [1]. The ideal osseointegration should provide early implant fixation with long-term stability of the prosthesis. The process of osseointegration reflects an anchorage mechanism whereby non-vital components can be reliably incorporated into living bone and which persist under all normal conditions of loading [2]. Thus, an implant is considered as osseointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact [3,4]. The long-term durability of joint prostheses is critically dependent on adequate peri-implant bone stock which can be compromised by wear-debris mediated osteolysis.

The contact area between the implant surface and the bone is called *bone - implant interface*. This is the field where the biology of osseointegration takes place. When prostheses are implanted directly to bone, the interface is the contact area between the implant and the host bone. If prostheses are fixed into the bone with the use of bone cement (poly-methyl-meth-acrylate, PMMA), there are two interfaces: One between the bone and the cement and the other between the cement and the implant surface.

The knowledge of the biologic pathways that lead to either osseointegration or osteolysis and aseptic loosening of an implant is the prerequisite for an investigator to understand the role of treatment modalities and pharmacological agents applied on experimental or clinical level and how these agents could enhance osseointegration or prevent osteolysis.

A. The pathway of osseointegration process

Bone healing at the interface area involves the activation of osteogenetic, vascular and immunological mechanisms that are quite similar to those occurring during bone healing [5]. Various cell types, cytokines and growth factors are involved and interact through the phases of osseointegration: inflammation, vascularization, bone formation and bone remodeling [6]. The initial host-bone response after the implantation of prosthesis is an inflammatory reaction elicited by (a) the surgical trauma during the insertion and impaction of the implant, (b) the tissue reaction to the foreign material, and (c) the thermal lesions to the bone with the death of osteocytes. Initially, a hematoma is formed at the bone-implant interface and plays a role as a scaffold for peri-implant bone healing [7]. The host response consists of: (a) platelet activation, (b) migration and activation of inflammatory cells into the hematoma, (c) vascularization, (d) mesenchymal cells and osteoblasts adhesion to the implant surface, (e) proliferation of the cells and protein synthesis, and (f) local factors and cytokines composition [7-11]. It is of great importance the role of growth factors released from the activated platelets. The growth factors are stored in the platelets in special secreting granules, the a-granules, and are excreted into the hematoma. These substances were synthesized by the platelet's precursor cell, the megakaryocyte, since the platelet itself does not contain a nucleus or the necessary elements for protein synthesis [12]. From the implant side, an oxidation of metallic surfaces has been also observed [13]. The osteogenic cells that are adhered on the implant surface very early (from day one) create a layer of non-collagenous proteins that regulate cell adhesion and minerals binding [14]. A few days after the implantation, osteoblasts begin to deposit collagen matrix either (a) onto the implant surface [11], or (b) into the afibrillar interfacial zone comparable to cement lines, which is reach in non-collagenous proteins such as osteopontin and bone sialoprotein [15]. Woven bone is then formed by early deposition of fresh calcified matrix to ensure tissue anchorage. Ultimately, the woven bone is substituted by lamellar bone, thus completing the biological fixation of the implant [16]. The peri-implant osteogenesis progresses either (a) from the host bone towards the implant surface (*distance osteogenesis*) or (b) from the implant towards to the healing bone (*contact osteogenesis* or *de novo bone formation*) [9]. During osseointegration the vascularization process is very essential as it influences cell differentiation and ossification [17]. Ultimately, bone remodeling occurs for reshaping or consolidation of bone at the implant site, providing a mechanism for

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TABLE 1. *Potential reasons for implant osseointegration failure and treatment strategies*

REASONS OF FAILURE	TREATMENT TARGETS
Wear debris	• Improvement of tribology and biomechanical properties in order to decrease the production of bone debris
Transfer of wear debris into the effective joint space	• Use of bone cement • implant surfaces coatings with materials (hydroxyapatite, trabecular metal) and rough surfaces manufactured with nanotechnology in order to stop the transfer of wear particles into the interface
Inflammatory (cellular and molecular) response to wear debris (particle-induced osteolysis)	• Pharmacological agents that induce bone formation or stop osteolysis • Molecular approaches to arrest osteoclast activity • Anti-inflammatory strategies
Poor peri-implant bone quality	• Pharmacological agents that increase bone density and quality

self-repair and adaptation to loading and stress.

Conclusively, osseointegration of implants in humans is a slow process and can last several months or few years [18,19]. Despite, the current knowledge of this process, a better understanding of the cascade of events that occur at the cellular and molecular level at the bone-implant interface is needed in order to intervene with pharmacological agents either locally or systematically and optimize the osseointegration of implants.

B. The pathway of aseptic loosening

The failure of joint implant is a disabling condition that affects patient's life and is very challenging for the orthopaedic surgeon. There are five major reasons for an implant failure: (1) an inadequate initial implant fixation, (2) the stress shielding phenomenon, (3) a systematic bone pathology such as osteoporosis, (4) infection and (5) the periprosthetic osteolysis.

At the latest, the generation of wear debris induces bone resorption and aseptic loosening of the implant. The generation of prosthetic implant wear is recognized as the major initiating event in development of periprosthetic osteolysis and aseptic loosening, the leading complication of this otherwise successful surgical procedure of joint arthroplasty [20]. (**Table 1**)

C. The biology of periprosthetic osteolysis

1. The cell biology of osteolysis

1a. Macrophages

In cases with osteolysis, the interfacial membrane is extensively infiltrated with macrophages [21]. and the presence of wear particles in these cells suggests active phagocytosis [22]. *In vitro,* cultured macrophage linear cells and cell lines can recapitulate this phagocytosis of wear debris [23-26]. This experimental phagocytosis is accompanied by the induction of pro-inflammatory mediators such as prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1β), and the pleiotropic cytokine Interleukin-6 (IL-6) [23,24,27-30] as well as proteases such as matrix metalloproteinases [31,32]. In these studies, the nature of the response of macrophages including the expression and secretion of the above mentioned mediators depends on numerous parameters such as the composition, [33-35] size, [26,36] shape,[37] volume, and surface area [35] of the wear debris. Furthermore, in animal models of osteolysis the role macrophages in response to particulate wear debris is also supported. Periprosthetic cells in canine osteolysis model produced elevated levels of proinflammatory mediators including PGE2 and IL-1 [38]. Periprosthetic cells from experimentally induced polyethylene loosening in rabbits tibiae

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produced elevated levels of PGE2 compared with cells taken from tissue around stable prostheses [39]. Smaller animals' models (mice and rats) of osteolysis using different materials such as particulate polymethacrylate (PMMA), ceramic powder, metal debris, polyethylene debris and cement particulate debris resulted also in macrophage response, production of pro-inflammatory cytokines and inflammatory reactions [29, 40-44].

1b. Osteoclasts

The pro-inflammatory response of macrophages to particulate debris leads to excessive generation, recruitment and activation of osteoclasts (OCs). Osteoclasts are multinucleated cells derived from circulating precursor cells (OCPs) of the monocyte/macrophage lineage and represent the only cell type capable of bone resorption [43]. Initially, OCPs are recruited from the blood into the periprosthetic space of patients with bone resorption and osteolysis, and they are differentiated to OCs. Observation of pseudomembrane macrophage lineage cells isolated from patients with osteolysis, display a greatly increased propensity to differentiate to OCs [44]. The increased OCP recruitment to periprosthetic tissue is mediated *via* activation of chemokine expression by the macrophages and fibroblasts. Chemokines are the principal mediators of haematopoetic cell recruitment to tissues and some of them, such as MCP-1, MIP-1-α and IL-8, are highly expressed in the periposthetic tissues of patients with osteolysis [45-50] MIP-1-a chemokine increases OCs motility and CCRI-1, a receptor for MIP-1-a is highly express in OCs and their precursors (OCPs) [51].

Wear particulate debris can generate functional OCs from OCPs with direct and indirect mechanisms. Directs mechanisms include: (a) the inhibition by titanium wear debris of the antiosteoclastogenic interferon gamma signaling in OCPs and (b) the inhibition by titanium debris and PMMA bone cement particles of IL-6 signaling which suppresses the OCPs differentiation [52]. Indirect mechanisms include: (a) the over-expression of bone pro-resorptive actions of cytokines such as TNF-α and IL-1 [53-55] and (b) the modulation of RANKL/OPG ratio [56]. Over-expression of TNF-α is sufficient to induce calvarial osteolysis even in the absence of added particles, emphasizing its proresorptive characteristics in mice [57]. The other most important indirect wear debris osteolysis mechanism involves the RANK/RANKL/OPG system. Osteoblasts and stromal cells express the protein Receptor Activator of nuclear Factor-kappaB Ligand (RANKL). RANKL is the key cytokine regulator of osteoclast generation and activation. RANKL binds to nuclear Factor-kappaB (NFkB or RANK) expressed on the surface of OCs and OCPs, [58] and is necessary for the differentiation of OCPs to mature and functional OCs in the presence of the survival factor MCSF. [59, 60] Osteoprotegerin (OPG) is a naturally occurring decoy receptor for RANKL functions to down-regulate-osteoclastogenesis by binding RANKL, thus preventing its interaction with RANK [61]. There are three reasons that support the theory that RANKL/OPG ratio is a critical parameter in the regulation of bone resorption and that elevated RANKL/OPG ratio is correlated with osteolysis: (a) First, there is literature that identifies elevated RANKL expression in the interfacial membranes from patients with osteolysis, with expression localized to the abundant macrophages, giant cells, and fibroblasts in these tissues [62-66]. Because macrophage lineage cells generally are thought not to express RANKL under normal conditions, expression of RANKL in such cells presumably reflects up-regulation by wear debris. (b) Second, RANKL blockade with OPG [67,68] or RANK:Fc (a RANKL antagonist consisting of the extracellular region of RANK fused to the Fc portion of human IgG1), or by using mice genetically deficient in RANK [69] prevented wear debris-induced osteolysis in the murine calvarial model. (c) Third, metallic and polyethylene wear debris can increase the RANKL/OPG ration in murine calvarial tissues, [70] and expression of RANKL by cultured osteoblasts and fibroblasts [71] Titanium-related fibroblasts, and also fibroblasts isolated from arthroplasty membranes of patients with osteolysis can support differentiation of OCPs to OCs [71, 72].

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TABLE 2. *The biology of osteolytic response*

Cell types recruited into the bone-implant interface	Phagocytes, macrophages, osteoclasts, fibroblasts, osteoblasts/stromal cells
Mechanisms of particle induced cellular activation	[1] Particle recognition by phagocytosis of small – sized particles [2] Cell surface interactions with the particles including: (a) non-specific physical induction of trans- membrane proteins, or (b) recognition of cell surface molecules by particles or proteins/factors that are adherent to the surface
Mechanisms of cellular reaction	Release large quantities of proinflammatory cytokines, growth factors, metalloproteinases, prostanoids, lysosomal enzymes, including the very critical TNF, IL-1α, IL-1β, IL-6, RANKL and PGE2

1c. Osteoblasts

There are *in vitro* data suggesting a potential role of osteoblasts (OBs) in the development of peri-implant osteolysis. However, there are no *in vivo* tests to confirm such a critical role. These *in vitro* studies, consider whether wear debris, in addition to promoting osteoclast activity, might also contribute to osteolysis through inhibition of osteoblast's function. According to these *in vitro* studies, different particle types can differentially affect OB activity and proliferation [73]. Polyethylene debris decrease OB matrix production [74]. Metallic particle such as titanium reduce OB viability by inducing apoptosis, [75] and also decrease expression of collagen type I and III by OBs [76-78]. Titanium particles can also down-regulate OBs differentiation from mesenchymal stem cells [79]. Finally, zirconium oxide particles induce mesenchymal stem cells apoptosis and indirectly inhibit OB formation and function [80]. In conclusion, if wear debris induce osteoclasts' function and simultaneously inhibit osteoblasts' function, then the coupling of resorption and formation that under normal conditions balance each other to allow bone remodeling and homeostasis would be totally blocked.

1d. Lymphocytes

The role of lymphocyte reactions in periprosthetic osteolysis is still unclear. The evolution of second generation metal on metal prostheses and the involvement of metal hypersensitivity reactions, led to the hypothesis that lymphocytic infiltrations into the bone-implant interface play a role to osteolysis [81,82]. T lymphocytes are key regulators of bone metabolism due to their ability to generate pro-osteoclastogenic (RANKL) and anti-osteoclastogenic (interferon-gamma) cytokines during activation [83-85]. However, involvement of T cells in periprosthetic osteolysis has been controversial. Some earlier studies measuring the cellularity of periprosthetic tissue from patients with osteolysis confirmed a great amount of activated T cells [86,87] while later studies found only non-activated or low amounts of T cells [88,89]. In animal studies, mice with lymphocyte deficiency or athymic mice did not show inflammatory response to either polyethylene particles or titanium particles injected into their knees [90,91]. However, in other animal studies, mice with lymphocyte deficiency retain their ability to form granulomas and develop osteolysis in response to wear debris [92-94].

2. The molecular biology of osteolysis

Understanding the molecular signaling pathways that regulate the expression of cytokines, chemokines and proteases seen in the bone-implant interface during osteolysis, is very important for focused *in vitro* and *in vivo* experiments to identify potential novel pharmacological agents that would block osteolysis or even enhance osseointegration.

The molecular responses to wear debris osteolysis include three major systems: (a) the mitogen-acti-

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vated protein kinases pathway (MAP), (b) the kinases and transcription factors interaction system, and (c) the complement cascade. These molecular pathways activation results in up-regulation of proinflammatory signaling and inhibition of the protective actions of antiosteoclastogenic cytokines (e.g. gamma-interferon). (**Table 2**)

The MAP kinase are seronin/threonin-specific protein kinases that respond to extracellular stimuli (mitogens, osmotic stress, heat shock and proinflammatory cytokines) and modulates cellular activities, such as proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis [95]. There are three major MAP kinase subgroups (p38, ERK, JNK) involved in macrophages responses to wear debris *in vitro* [24,52,96]. *In vitro* studies, showed that MAP kinases are critical transducers of the signals emanating from wear debris/particle-cell interaction to the nucleus. Inhibition of MAP kinases (a) reduced ability of wear debris to induce proinflammatory cytokine induction in cultured OCPs, [52] (b) reduced PMMA-mediated down-regulation of IL-6 signaling, [52] (c) protects against inflammatory bone destruction [97] and (d) blocks the wear debris mediated expression of SOCS3, a suppressor of antiosteoclastogenic cytokine signaling [52].

Particle-induced pathways lead also to activation of kinases and transcription factors that are essential for osteoclastogenesis. Among these are activation of the tyrosine kinase c-src, the nuclear factor kB cascade (NFkB), the NF-IL6, the AP-I as well as the mitogen-activated protein kinases system (MAP) as mentioned above [24,96,98-102]. The most notable implication is showed for the NFkB factor. Lack of this factor in experimental models results in inability to generate functional osteoclasts and protection against osteolysis [57,98,99]. *In vitro* inhibition of NFkB blocked wear debris induction of osteoclastogenesis and osteolysis in small animals [103,104].

The complement pathway plays also a role to osteolysis. Complement receptors located on the inflammatory cells' membrane (CR3) and scavenger receptors enhance titanium and PMMA particle uptake and opsonization by the monocytes, macrophages and phagocytes [24,105,106]. *In vitro*, administration of antibodies against CR3 reduced macrophage uptake of titanium and PMMA particles [24,106]. Although activation of all these molecular pathways might be secondary to other events, selective blockade of these downstream pathways with the administration of pharmacological agents seems to reduce particle transmitted effects [107,108].

The influence of pharmacological agents in the bone-implant interface

Many experimental studies have proved that various pharmacological agents are effective in enhancing osseointegration, preventing osteolysis or treating aseptic loosening. (**Table 3)** Clinical trials have also confirmed in many cases the *in vitro* and *in vivo* results.

A. Pharmacological agents that positively affect osseointegration

1. Antibiotics

Patients regularly take antibiotic chemoprophylaxis few or several days postoperatively after a joint arthroplasty and the knowledge of how such agents affect implant osseointegration would be very useful. *In vitro* and *in vivo* studies showed that doxocyclin inhibits osteoclastogenesis as well as PMMA or UHMWPE-induced osteolysis by inhibiting mature osteoclasts [109]. In another *in vitro* study, [104] erythromycin, a macrolide antibiotic, suppressed wear debris-induced osteoclastic bone resorption. Erythromycin significantly inhibited mRNA expression of NF-kappaB, cathepsin K (CPK), IL-1beta and TNFa, but not RANKS in the mice cells stimulated with wear debris.

2. Anti-inflammatory factors

Anti-inflammatory agents have proved effective when used for the treatment of osteolysis in animal models. Gene therapy with the anti-inflammatory cytokines IL-1Ra or viral IL-10 protects mice from the polyethylene debris induced osteolysis [55]. In animal models, the administration of TNF antagonists such as etanercept (a decoy receptor) and pentoxyfilline (an inhibitor of secretion), diminished the particle induced osteolysis [6-19,106]. IL-4 is also secreted by T-lymphocytes, as the above

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TABLE 3. *Pharmacological agents that affect bone-implant biology (osseointegration, new bone formation, implant biomechanical properties)*

Positive effect	Negative effect
Antibiotics (doxocycline, erythromycin)	Cyclosporine-A
Anti-inflammatory factors	Methotrexate
RANK/RANKL/OPG system	Cis-platinum
Statins	Warfarin
Calcitonin	Indomethacin
Bisphosphonates	
Strontium ranelate	
Parathyroid hormone / teriparatide	

mentioned IL-10, and is effective in antagonizing pro-inflammatory cytokine actions [110]. Finally, IFN-γ interferes with the RANK/RANKL signal transduction in osteoclasts and their precursors. It reduces degradation of tumor necrosis factor-receptor associated factor 6 (TRAF6), a RANK adaptor protein. This action results in failure to activate RANK downstream signals such as NF-kB and cJun/JNK pathways [110].

3. The RANK/RANKL/OPG system

The critical role of RANKL in inhibiting osteoclastogenesis makes this cytokine a very interesting pharmacological agent for the therapy of osteolysis. A dominant factor known to counteract the process of RANKL – induced osteoclastogenesis and osteoclastic bone resorption is the natural RANKL receptor antagonist protein osteoprotogerin (OPG). Many experimental studies [67,68,111,112] proved that OPG gene therapy effectively halted the debris-induced osteolysis, reduced local bone collagen loss and regained the implant stability in these murine models. In clinical level, the development of denosumab, [120] a fully human monoclonal antibody that acts by binding to and inhibiting RANKL could be a potential pharmacological agents that could lead to loss of osteoclasts at the bone- mplant interface area and thus, positively affect osseointegration. However, there are still no clinical studies proving this hypothesis.

4. Statins

Statins have been also considered as possible pharmacologic agents for osteolysis due to their role on blocking the mevalonate pathway. The recent discovery that statins act as bone anabolic factors suggests that these pharmacological agents can have a potential effect not only on the treatment of osteoporosis but also on implant osseointegration. Preliminary studies in animal models, [113-115] showed that simvastatin markedly promoted bone formation and net bone growth and decreased osteolysis in UHMWPE particle-induced osteolysis. *In vivo* animal studies with bone implantation models, [116,117] proved that simvastatin administered either orally or by injection enhanced peri-implant bone ingrowth or contributed significantly to implant osseointegration.

5. Calcitonin

Calcitonin as a commonly used antiosteoporosis drug in current clinical practice has also been experimentally confirmed to produce the effectiveness of promoting osseointegration at the interface between prosthesis and host bone and enhancing the long-term stability of the prosthesis [118-120]. However, bisphosphonates produce more pronounced effectiveness when compared to calcitonin [121] and this is the reason why calcitonin is not clinically tested as monotherapy for the prevention or reduction of the osteolysis phenomenon or the enhancement of implant osseointegration.

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6. Bisphosphonates

Bisphosphonates have been considered as therapeutic pharmacological agents for osteolysis. This is based to their role on the osteoclastic apoptosis by blocking the mevalonate pathway of isoprenoid biosynthesis [122]. Several bisphosphonates are intensively tested, especially alendronate, pamidronate and zolendronate, with either systemic (oral, iv) or local (localized drug delivery from implant coatings) administration in animal and clinical studies [122,123-127]. Most of these studies proved that bisphosphonates: (a) increase peri-implant BMD in cementless prostheses, (b) increase peri-implant BMD even in cemented prostheses when administered systemically, (c) reduce or prevent particle-induced osteolysis, (d) reduce or prevent peri-implant osteopenia induced by the stress-shielding phenomenon, (e) enhance osseointegration of cementless prostheses at the level of bone-implant interface, (f) increase implant mechanical stability, and (g) eventually affect positively the long-standing durability of the prostheses. However, there are still many questions to be answered: (a) there are still no studies comparing treatment with different bisphosphonates in order to know which bisphosphonate is the most effective, (b) there are no studies providing enough evidence that the positive effect of bisphosphonates treatment -noted in the early postoperative period -is maintained long-term, (c) there are no studies comparing the systemic with the local administration of bisphosphonates in terms of osseointegration enhancement, peri-implant BMD increase, osteolysis prevention as well as implant survival time.

7. Strontium Ranelate

Strontium ranelate is well known as an effective antiosteoporotic agent by its dual effect of anti-resorbing and bone-forming activity. There are several recent studies testing this pharmacological agent demonstrating that strontium ranelate has a peri-implant bone anabolic effect, [128,129] and enhances the bone biomaterial properties in the bone-implant interface and peri-implant bone area [130]. Conclusively, strontium ranelate is not only an antiosteoporotic agent with anabolic bone effect used in osteoporosis, but can also be used systemically or locally as a pharmacological agent that would have a positive effect at the bone-implant interface by increasing mechanical fixation of the implant and improving implant osseointegration. However, all above mentioned studies are *in vivo* animal experiments and further investigation with clinical studies by oral or local administration of strontium ranelate is needed.

8. Parathyroid Hormone (PTH) and Teriparatide

In animal models, systemic administration of teriparatide has enhanced implant osseointegration and increased implant biomechanical properties [131,132]. There are no clinical studies investigating the effects of PTH/teriparatide on the osseointegration of implants in orthopaedic surgery. In dental surgery, a recent open-label randomized controlled feasibility study [133] provided the first histological data on the osseointegration of titanium implants in individuals treated with teriparatide. Teriparatide treated group had significantly higher values for peri-implant new bone formation than placebo group.

B. Pharmacological agents negatively affecting osseointegration

Various pharmacological agents were found to impair implant osseointegration, including cyclosporine A, methotrexate and cis-platinum [134-136]. The administration of warfarin was found to significantly impair both the attachment strength and the ingrowth of bone uncoated porous implants made of cobalt-chromium-molybdenium alloy; however no such inhibitory effect was observed in hydroxyapatite-coated implants [137]. It is also suggested that peri-operative administration of the NSAID indomethacin causes an early and transient decrease in attachment strength, but this finding does not seem to significantly affect the long-term osseointegration of porous-coated implants [138].

Conflict of interest:

The authors declared no conflicts of interest.

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ΠΕΡΙΛΗΨΗ

Η ολική αρθροπλαστική, παρά το ότι θεωρείται μια εξαιρετική χειρουργική τεχνική, συνδέεται με την οστεόλυση, ως επιπλοκή των απελευθερούμενων σωματιδίων και της επερχόμενης άσηπτης χαλάρωσης της αντίστοιχης πρόθεσης. Η παθογένεια του συγκεκριμένου τύπου οστεόλυσης περιλαμβάνει φλεγμονώδεις και οστεολυτικές διαδικασίες. Η γνώση των μονοπατιών, που οδηγούν σε αυτές τις κυτταρικές και μοριακές αντιδράσεις, μπορεί να δημιουργήσει μία βάση πάνω στην οποία θα αναπτυχθούν θεραπευτικές παρεμβάσεις για την αντιμετώπιση της φλεγμονώδους περιπροθετικής οστικής απώλειας.

Με αυτό το άρθρο οι συγγραφείς θα προσπαθήσουν να παραθέσουν την παρούσα βασική γνώση της βιολογίας της σχέσης οστού-πρόθεσης. Επίσης θα παρουσιαστεί η αλυσίδα των γεγονότων που προκύπτουν σε κυτταρικό και μοριακό επίπεδο κατά την οστεοενσωμάτωση, την οστεόλυση και την άσηπτη χαλάρωση. Η γνώση αυτή αποτελεί χρήσιμο εργαλείο για ερευνητές και ορθοπεδικούς χειρουργούς, ώστε να παρεμβαίνουν με φαρμακευτικούς παράγοντες είτε τοπικά, είτε συστηματικά, βελτιστοποιώντας την οστεοενσωμάτωση των προθέσεων. Τέλος, θα αναφερθούν οι φαρμακευτικές και βιολογικές παρεμβάσεις, που έχουν πρόσφατα δοκιμαστεί.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: αρθροπλαστική, οστεοενσωμάτωση, οστεόλυση, άσηπτη χαλάρωση