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PERIPROSTHETIC BONE METABOLISM

Surgery

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ABSTRACT

The prosthesis replaces the articular surfaces and creates a biological and mechanical interaction with the bone. In order to optimize the bone-prosthesis ratio, over the years the surgical technique, the fixation of the bone prosthesis (cementation or biological fixation), the design, the geometry of the prosthetic components, the biomaterials have been improved. The prosthetic articulation acquires a "new normality" and there is a link with the "disease of the prosthetic joint". The nosographic profile, the pathogenetic mechanisms, the clinic and the medical-surgical therapy are becoming increasingly clear. The control over the years of a prosthetic implant consists therefore in the monitoring of the bone metabolism.

KEYWORDS

prosthesis, bone metabolism, osteolysis

INTRODUCTION

Articular prosthetic surgery in the last decades has completely occupied the surgical scene either in traumatic pathology or in the election of large joints. Osteoarthritis (OA) represents the epilogue of a disease with multifactorial etiology, whose prognosis is variable because there is no definitive definition of OA, because the X-ray interpretation of OA is problematic and because the prognosis varies depending on the area (1,2).

OA is a multifactorial etiopathogenesis disease, which over the years has identified as a fundamental pathogenetic factor the phlogistic component with respect to the degenerative one, both cause of tissue degradation. In severe OA, joint prostheses guarantee high standards of functional recovery and therefore "waiting" surgery (osteotomies) has been progressively abandoned. The prosthesis replaces the articular surfaces and creates a biological and mechanical interaction with the bone. In order to optimize the bone-prosthesis ratio, the surgical technique has been improved: the methods of fixing the prosthesis to the bone, the design and the geometry of the prosthetic components and the biomaterials. The prosthetic joint acquires a "new normality" (3). The control over the years of a prosthetic implant consists therefore in the surveillance of the bone metabolism, a prerequisite for a long duration.

Joint replacement

The introduction of cement, self-curing resin based on polymethyl methacrylate (PMMA), have given a great boost to prosthetic surgery since the 1960s (4). In the late '70s, PMMA was considered as responsible for the "cement disease". For this reason the biological fixation of the prosthesis had started, without cement, giving the bone the task of fixing the components (5). The cementless prostheses were made with a geometry capable of adapting to the bone morphology, to adhere to it as much as possible, to achieve primary mechanical stability on the cortical bone, giving osteogenesis to the cancellous bone and transmission of solicitations (6). The "minimally invasive" surgical approach, that is the least traumatic, allows to less interfere with the bone segments and with the soft parts (7). The rough surfaces of implants (madreporic, porous, fibrous, plasmaspray, etc.) and coatings of osteoinductive materials (titanium, hydroxyapatite, etc.) favor the proliferation of trabecular bone. The non-cemented fixation correlates with the biological age of the patient; the presence of osteometabolic damage (rheumatoid arthritis, steroid therapy, etc.), is linked with cemented fixation of the two components or of a single femoral component (hybrid implants). The prosthesis creates a new articulation and must respect three principles: the mechanical stability and the fixation of the components, the transmission of the tensions as close as possible to the physiology of the considered anatomical district and the chemical, physical and mechanical characteristics of the implant, compatible with the biomechanics district. The mechanical stimulus is transduced in biological effect in a positive way, generating a coexistence in time without pain. The new joint then induces an interface reaction (bone-biomaterial) to repair the surgical trauma with the formation of young bone tissue that replaces, fill the bone-implant cavity. The main factors are several: quality and quantity of bone tissue, reciprocal movement of surfaces, distance and regularity of the surfaces, characteristics of the system, extent of the load.

The joint reaction depends instead on the geometric relationships of the components and on the balance of the soft parts, with adaptation of the newly formed bone to the mechanical stress induced by the implant. "Organ response" refers to the reaction of the entire joint to the prosthesis, conditioned by the balance of the soft parts (muscles, tendons, capsule and ligaments), geo-symmetrical relationships and above all the distribution of loads. The removal of only pathological tissues (cartilage, osteophytes, articular surfaces, geodes) allows to save the physiological trajectorial lines of transmission of the loads of the two articular slopes, which are oriented according to the lines of force (spot-weld) and the cortical sleeve acquires a new tropism (8).

Bone-prosthesis interaction and Periprosthetic remodeling

The survival of an implant is a consequence of the bone-prosthesis interation process that correlates with the characteristics of the prosthesis, the anchoring of the prosthetic components and the "organ" response of the joint. The characteristics of the prosthesis, mechanical, physical and biotollerability must be inserted in an anatomical-biomechanical context, "disturbing" the implant site as little as possible, reducing the by-pass and stress-shielding of the stresses. The anchoring of the prosthesis is the major problem of prosthetics. In fixation with PMMA, initial necrosis of the interface follows the endostal bone repair influenced by various factors such as, for example, the introduction of cement. The biological anchor requires optimal bone-prosthesis adhesion and primary mechanical stability; the rough surfaces (madreporic, plasmaspray, etc.) of the prostheses favor a lively endosteal osteogenesis neoproduction which ensures the biological anchorage (9). In the process of bone-integration there are three phases: inflammation, repair and remodelling. Inflammation is the first reactive phenomenon in the bone-implant interspace where inflammatory cells, debris, blood and mesenchymal cells are present which differ in a macrophagic, fibroblastic or osteoblastic sense in relation to a complex of conditioning factors and quality of functional stimuli (9).

The osteoblastic differentiation, second phase, determines the formation of first osteoid tissue, therefore bone of the primitive type (with interwoven fibers) of lamellar type. Only in part occurs a process of migration of bone cells from the endosteum and from the bone bed to the implant (osteoconduction). At the end of the process the osteointegration is complete, such as to fill every minimum interstitium between the two surfaces that have been faced.

The third phase of the reshaping process of the newly formed bone consists in the acquisition of the "mechanical competence" of the neo-bone capable of amortising, harmonizing and transmitting the stresses induced in it. An initial instability evokes excessive stresses (axial, torsional and tectonic) with the formation of fibrous tissue at the interface. This tissue may remain such or may undergo secondary ossification if stability is subsequently achieved (secondary stability) (10).

Iuxtarticular bone in Osteoarthritis and Periprosthetic bone

The metabolism of the periprosthetic bone must be considered in a pathophysiological continuum, which starts from the OA and the related bone pathology, through the intervention and the immediate post-operative, up to the integration of the bone-prosthesis. The dynamic and active variable in the prosthetic articulation is the bone, reactive to any mechanical stress induced by the prosthesis, changing over time and subjected to the positive or negative influence of numerous mechanical and biological factors (1). There are some key moments of periprosthetic bone metabolism, considering: a) preoperative juxtarticular bone disease in OA; b) surgical bone damage; c) post-operative stress shielding; d) organ adaptation of the implant site articulation; e) daily bone-remodeling of the prosthetic joint: f) the pathology of the prosthetic joint.

The iuxarticular bone disease in the OA is now the subject of diagnostic investigation. The OA, a multifactorial disease, has increasingly included the phlogistic component over the years; together with the main target cartilage of the disease (22), the subchondral bone is involved, whose modifications represent a key event in the arthritic process, in the starting and progression of OA, being the cartilage in communication through channels with the subchondral region (11).

At every moment of the progression of the OA the protagonists of the inflammation are present. Synovial fluid may show an increase in mononuclear cells and Ig and Complement, while the synovial membrane demonstrates the hyperplasia of synovial lining cells with infiltrates of inflammatory cells in the subepithelial tissue, to recall early rheumatoid arthritis (12). Although the cartilage is free of blood vessels and is therefore excluded from immunological surveillance, there is an important immunological reactivity in the context of chronic inflammation, in which the catabolic moment of articular cartilage becomes predominant for the activation of the intra-articular cytokinic network (13). With reference to OA therapy, Clodronate has shown not only to reduce bone turnover, and therefore osteoclastic reabsorption, but also to act on the inflammatory process, by inhibiting the production and release of various pro-inflammatory mediators that would feed the subchondral osteometabolic damage in OA, especially in the more advanced stages. This bone damage recognizes the same pathogenetic mechanisms and the same chemical mediators of chondropathy. It is possible to recognize the moment of sclerotic reactivity, defined as an elementary mechanical compensation to the compartmental mechanobiological deficit; pain is characterized as nociceptive, mechanical, remitting with rest, with good response to analgesic and orthotic treatment; and the osteometabolic damage, of flogistic participation of the bone to the disease where the pain is transformed by intensity, location, type, duration and functional correlation. The increase in episodes of joint inflammation aggravates the osteometabolic damage, which the MRI documents as 'bone edema', while the pain becomes both the load and the rest (14). Bone edema, that is a pathological condition of inflammation imbibition clearly evident in MRI, in its various forms generally defined as bone marrow lesions (BMLs), of lacunar aspect or extended to the whole articular segment involved (14). The suffering of the subchondral and epiphyseal spongiosa becomes almost a prognostic marker of OA, sometimes preceding cartilage damage. The joint with his baggage of serious cartilage wear comes to the prosthesis with the juxta-articular osteometabolic damage.

The bone marrow lesions identifies an initial condition of sub-conditional and epiphyseal bone-loss with a negative influence in the general osseointegration process (15). At the time of the implant at the spongiosa bone site of the preoperative metabolic damage, at the moment the implant is asked to exercise its function of supporting and transmitting the stresses induced by the presence of the prosthetic components. (6). The metabolic status of subchondral bone is therefore an important factor for primary fixation of the prosthesis.

The surgical damage in the preparation for the housing of a prosthetic component preliminarily provides the resection of the pathological articular surfaces with the removal of the degenerated cartilage. The surgical moment exposes the subchondral cancellous bone with its characteristics of mineral density, and in general of mechanical resistance, with its rate of possible osteometabolic pain. It is therefore possible to visualize these characteristics in areas of porous and areas of pathological thickening of the spongiosa itself.

Postoperative stress shielding is a phenomenon that affects all prostheses. Before the process of 'integration' there is a phase of reduction of Bone Mineral Density (BMD); this is a constant datum and must be interpreted as a result of the surgical damage, of the presence of young bone and of a stress shielding related to the presence of the prosthesis. Dexa allows to evaluate the periprosthetic biological response; however, it requires a particular statistical accuracy, a prerequisite for the reliability and repetitiveness of the method. Kiratli et al (16) at 1 year of follow-up report a loss between 25% and 32%. Hughes et al. (17) report losses of BMD between 17% and 34% for Cr-Co stems and between 7% and 15% for Ti alloy stems. Nishi et al (18) also report oscillating data between 10% and 20%. Molfetta et al. (19) instead found in a longitudinal study in prostheses of Ti alloy a very low BMD loss on average around 1.4% (20), mainly related to the female sex, due to the greater incidence of osteoporosis. In general, the age, the metabolic state of the pre-implant bone, the design and the size of the stem condition the densitometric response (35). The biomechanical interpretation of changes in loss of BMD referred to the 7 areas of Gruen (19) makes it possible to identify the proximal sector of the femur (area 1-7) as the one with the highest turnover due to the presence of rich spongiosa; the intermediate sector (area 2-6) as the area with the least loss, being the stabilization area of the plant, subjected to greater stress; the distal sector (area 3-5), a function of centralizing and the sector distal to the stem (area 4) without significant modifications (19).

The bone-prosthesis gap with the presence of cellular elements, blood, bone fragments, etc. The microambiante in which the inflammation processes act, which then prelude to the reparative interface osteogenesis (bone growth). In context, osteoclasts and osteoblasts are activated and interact with cytokines (BMP, TGF-β, IL-1, IL-6, M-CSF, VEGF), giving rise to the resorption-periprosthetic neoapposition process (ARF, Activation -resorption -Formation). In this context osteoclasts and osteoblasts are activated and interacted through cytokines (BMPs, TGF-n). In analogy to the integration of a bone graft, the interface bone-growth benefits from mechanical stimuli controlled by intensity and duration by mechanoreceptors (integrins) capable of influencing cell proliferation (20). The mechanical stimulus induced by the prosthesis translates into biological stimulus, activating the proteosynthesis by the osteocytes, after the application of intermittent compressive forces to the bone, the membrane phospholipases of the osteocytes seem to play a role (5).

The Basic Multicellular Units (B.M.U.), functional bone units, are activated in the bone-prosthesis interaction process, forming trabecular bone tissue. Neoangiogenesis is associated with the migration of undifferentiated mesenchymal elements, which differ in the osteogenetic sense according to the stages of direct intramembranous ossification. When this sequence of events is disturbed, for example by a poor primary stability of the prosthesis, the bone-ingrowth turns into fibrous-ingrowth. According to a strictly biological interpretation, primary stabilization occurs according to "bone healing", a genetically programmed process that involves the recruitment and activation of particular genes in a way directly correlated to the level of biomechanical stability of the implant (13). These determine the synthesis of key macromolecules of the organic and inorganic preoxose matrix. Osteointegration ends with the process of trabecular ossification (8), directed by BMP (Bone morpfogenetic proteins), in particular BMP2 (21). Titanium, used for the prosthesis lining, does not inhibit the activity of BMP. However, osseointegration does not occur on the entire surface of the implant, with alternating areas of osteogenesis and areas of fibrogenesis.

Cook et all. they observed the phenomenon in 82% of the stems and in 43% of the cups, but on limited areas not higher than 5% of the prosthetic surface (22); Galante et al. have verified the extent of bone growth limited to 29% of the extension of the cups and about 45% of the surface of the stem (9). The daily bone remodeling of the prosthetic joint is the expression of a correct bone-prosthesis relationship and this

creates a condition of "new normalcy" of the joint (23). The bone accepts the host and adapts to the continuous variation of defects in defect or excess (10).

If the bone-prosthesis interaction over time becomes pathological, a loss of the bond and of the stability ratio is created. The macromovements at the interface induce the decrease in bone-ingrowth, a radiolucency, expression of a mobilization of the prosthetic component and therefore over time the progressive appearance of pain, expression of a pathological prosthetic joint.

The pathology of the prosthetic joint consists of loosening, ie the yielding of the link between bone and prosthesis at the interface for mechanical factors and biological factors. Among the former are the excessive consumption of joint interfaces, macromovements, traumas, malposition of the components, defects of cemented fixation, periprosthetic fractures, etc.; the latter include inflammatory processes in general which generally result from the disease of wear debris disease (24). On histological examination of the synovial membrane the polyethylene particles are small in the macrophages, the largest particles in the giant cells, while in the metallosis the debris appears as brown or black granules in the macrophages and in the giant cells.

Aseptic Loosening of prosthesis

Osteolysis is of an osteometabolic, multifactorial nature and is expressed by the biological and mechanical failure of the bone-prosthesis integration bond. Over the years this process has been differently defined, starting with Charnely who considered it to be septic in nature, with an unknown bacterium, given the presence of macrophages around the implant (4). An initial biomechanical interpretation of this phenomenon was then given (25) and at the end of the 1970s particulate debris in the periprosthetic area was highlighted (26,27) and studies of the pseudosynovial periprosthetic tissue began, thus clarifying the pathogenetic mechanism of the bone- reabsorbtion type , with the presence of macrophages and fibroblasts in the first line (28). Osteolysis is a negative metabolic process that appears over time but has a meiopragia already in the preoperative, ie in the quality and quantity of bone, in any pre-existing diseases, etc. Surgery also plays an important role in terms of trauma, technical invasiveness, process sterility, and the way components are positioned (29). In the physiopathological complexity of the osteolytic phenomenon there is therefore a TRIAD of factors that generates it: debris, micromovements and cell population, with a secondary immunological process.

Metal ion debris (chrome, cobalt, nickel, vanadium, titanium) derive from metal-metal interfaces for an electrochemical corrosion and fretting process. Both macrophages and haptens, which are bound to endogenous proteins, are activated, take on antigenic characteristics and induce immune responses of type IV (delayed hypersensitivity) involving T lymphocytes CD4+ (Th1-type lymphocytes) (30).

Non-phagocyte debris, larger than 15-30 millimicron (like those of PMMA), are phagocytosed by macrophages that form multinucleated giant foreign body cells, with phenotypic osteoclastic and with a reduced immune response, thanks to an interaction between the RANK molecule expressed by macrophages and the RANKL molecule expressed by fibroblasts (31).

Polyethilene and cement debris interact, however, essentially with the monocyte-macrophage system, with fibroblasts and with osteoblasts (small particle disease), able to "attack" and "weaken" the bone-prosthesis bond with osteoclastic reabsorption massive. The periprosthetic pseudosynovial fluid is transported to the interface, exerting the negative metabolic action, filling the periprosthetic areas with less resistance, called "effective joint space" as the set of periprosthetic areas variously extended, reached by the joint fluid and , as a result, from debris particles (32,33).

The phagocytizable polyethylene debris is 0.1-1 millimicron (type I wear), the macrophages, after having swallowed the particles, are "revealed" unable to digest them. The consequence of this "impossible digestion" is the chain expansion of the inflammatory reaction, through progressive chemotaxis and activation of other cells attracted by macrophage cytokines (TNF-alpha, IL-1, IL-6, PGE, PDGF, FGF, VEGF) and from the superoxides. Macrophages, activated by debris through surface receptors such as CD11b, CD14, Toll-like Receptors, promote osteoclast differentiation starting from the monocyte-macrophage line, secrete MMP which degrade the matrix, release proosteolitic cytokines and differentiate into osteoclasts, contact with the debris, through the interaction system RANK - RANKL (31).

The bioreactivity of the debris is greater for the small-sized particles phagocytosed by the macrophages and by the giant cells of the synovial membrane, responsible for the osteolysis, whether indirect or direct. The direct osteolysis, described by Athanasu et al., expresses the lithic activity by the macrophages which, with osteoclastosimilar properties, directly provoke bone resorption without the presence of osteoclasts (34). In indirect osteolysis, the cytokines (IL-1 beta, TNF-alpha, IL-6 and PGE2) released in the microenvironment directly activate the precursors of osteoclasts, or interact with the receptor-mediated system (RANKL / RANK). Among the essential mediators for the promotion of osteoclastogenesis we should mention the macrophage-colony stimulating factor (M-CSF) the receptor activator for RANKL / RANK able to stimulate a macrophage colony. The formation of osteoclasts occurs in the presence of binding factors (such as NF-kB) that interact with the receptor activator (RANK) forming an osteoclastic precursor. In this receptorial game, Osteoprotegerine is a soluble protein that competes against RANKL by expressing an anti-osteolytic activity (35).

In the aseptic loosening, bacterial endotoxins should be considered, especially titanium for biomaterials. Revisions for aseptic loosening showed subclinical levels of gram negative and positive bacterial colonies capable of producing endotoxins, respectively a lipopolysaccharide and peptoglycans. The first source are the implants themselves, which may contain a quantity of endotoxin adhering to their surface, adhering to the wear particles. The second source of endotoxin derives from infection foci (eg teeth) with high affinity towards the wear particles. The third source, perhaps the most important of endotoxin, is the bacterial biofilm found in many low-cut implants. Whatever the source, microorganisms release the lipopolysaccharides which, by coating the wear particles, release cytokines and activate the osteoclasts (30). An important role is played by fibroblasts, a connection between osteoclast-mediated and osteoclast-independent resorption processes. In fact, they produce PGE2 and IL-6, "pro-inflammatory and pro-osteoclastogenic" mediators, which favor the formation of giant macrophage cells. All the cellular elements involved in osteolysis, ie osteoblasts, osteoclasts and lymphocytic cells "speak to each other" through the "RANKL-RANK-OPG (osteoprotegerine)" system, under the stimulation of debris from the periprosthetic environment. Metal-metal couplings have shown slower wear, but have not solved the problems of metal ions and related osteolysis in addition to their systemic release in relation to a hypothetical carcinogenic capacity. Cross-linked polyethylene has demonstrated in the laboratory certain improvements in wear, without however certainty of the stability of the material in the production phase. The delta ceramic has improved the strength and hardness of the material, thus allowing it to be used with larger diameter heads which are the source of less wear (30).

Osteoimmunology in prosthetics

Finally, there is a genetic susceptibility towards the development of osteolysis, so variations in the DNA sequence determine different "behaviors" of the genes. It ranges from genetic polymorphisms in position 238 in the promoter of the TNF-alpha gene with a greater predisposition to osteolysis, to subjects endowed with HLA-DR2 genotype that manifest less effective immune responses towards the mechanisms of macrophage-mediated lymphocyte activation triggered by debris (low responders) (36).

This immunohistochemical phenomenology is associated with a mechanical macrofenomenology whereby the micromovements at the bone-implant interface together with the diffusion of the joint fluid in the pathological areas, generate a so-called "prosthetic synovitis" (or implant bursitis). These two associated phenomena then generate multiple osteolytic areas with a tendency to merge and lead to a secondary mobilization of the components. Micromovement determines the diffusion of joint fluid produced by the pseudo-ovarian membrane by transporting mediators and degradation products capable of transforming the fibrous ingrowth into a synovial membrane-like structure (SLIM, synovial like interface membrane), capable of directly degrading the matrix, through the secretion of lithic enzymes (metalloproteinases of the MMP-1 type matrix, cathepsin K, favored by the acidic environment and also produced by osteoclasts). Furthermore, the presence of acid pH inside the interface membrane

leads to the decalcification of hydroxyapatite and to the demineralization of the periprosthetic bone. The same pressure stress of the joint fluid interacts with the behavior of the monocyte-macrophage line present in the interface membrane, inducing the production of "reabsorption" cytokines such as IL-6 and TNF-alpha. Pressure stress, if elevated, leads directly to the death of the osteocyte. These mechanisms underlie the phenomenon of induced non-osteoclast periprosthetic osteolysis. The study of new biomaterials with increased resistance has created a greater resistance to wear, postponing the onset of osteolysis, but faced with new complications related to their use (54). There is therefore a role of the immune system of joint prostheses. Metal debris stimulates osteoblasts and osteoclasts to produce chemokines such as CC17 and CC22 (CCL17 / TARC = thyroid and activation-regulated chemokine, CCL22 / MDC = macrophage -derived chemokine) and also stimulate the production of T cells in the T lymphocytes. CCR4 (chemokine receptor CC17 and CC22). T-helper lymphocytes are localized at the periprosthetic interface, by local increase in concentration of CCL17 and CCL22, and express IL-17 and RANKL, contributing to the phenomena of osteoclastic activation (51). Moreover, metallic debris, both in ionic form and in particulate form, can form complexes with local proteins that are presented to T cells by cells expressing the highest class II histocompatibility complex (MHC II); a "T-activated" lymphocyte population is created, creating a situation similar to the delayed type IV hypersensitivity defined with the generic name of "metal allergy". Also the other types of debris (polyethylene, cement, etc) for wear can be presented to the T lymphocytes from macrophages and osteoblasts by MHC II, creating a mutual activation chain that, through the cytokines, involves both cytotoxic T lymphocytes and B lymphocytes, which are activated in plasma cells (37).

Following interaction with the cytokines and their receptors, they reduce the anabolic phenomena and decrease the synthesis of collagen and the components of the matrix, secrete, PGE2 and NO (particularly if mature osteoblast stage), release M-CSF and expose to the surface the RANKL molecule. This phenomenon can occur even in the presence of low quantities of debris, the consequence is the activation of the macrophage line and the differentiation-activation of osteoclasts, through the interaction with the intracellular system of MAP kinases (c-Jun, Erks, JNK, p38) can address the macrophage towards osteocyte differentiation and the production of reabsorption holes independently of the RANKL-RANK system; TNF-alpha and IL-1, in fact, in the presence of M-CSF, are sufficient to activate these cells. Preosteoblasts and MSCs residing in the periprosthetic microenvironment, in contact with debris (polyethylene, ceramic, titanium, 1.5-4 temporary size of M-CSF with its macrophage c-Fms receptor and RANKL with RANK. Moreover, debris particles can also induce caspase-dependent apoptosis in the same pre-osteoblasts-MSC: this further contributes to the reduction of the osteo-training processes around the implant (33).

Pharmacological therapy of periprosthetic remodeling

Bisphosphonates (BF) play an important role in bone metabolism in prosthetic implants. The progenitor of these drugs, etidronate, in the '70s-80s, was used in prosthetic surgery in the prevention and treatment of pararticular heterotopic ossifications. At the beginning of the 3rd millennium their employment had an acceleration due to an ever richer literature. Hilding et al. in 2000 they ascertained with the stereoradiometry in the knee prostheses that the Clodronate reduced the aseptic dissection percentage of the tibial component, which was evaluated with the stereoradiometry (38). This data was confirmed with a follow-up of more than 6 years, placing Clodronate at the center of the pharmacological devices (39). Numerous studies have taken place over the past twenty years, all agreeing that the systematic postoperative use of bisphosphonates and clodronate in particular contributes in a statistically significant way to counteract the periprosthetic bone-loss, inducing, however, an increase in Bone Mineral Density (BMD).

In view of the fact that osteolysis is the result of a clastic activation of macrophages and a greater production of osteoclasts, in addition to osteoblastic inhibition (40), the use of BF has established itself with the aim of preventing the periprosthetic bone-loss (osteolysis and stress-shielding) minimizing the failure and the revision rate (41). Prieto Alambra et al emphasized the protective effect of BF on both hip and knee prosthetic implant in patients with OA (42). The data was confirmed by Tilleman et al in patients with rheumatoid arthritis, also showing an increased risk of deep infections (43). Analysis of US registries on a retrospective population of approximately 13,000 prosthetic patients showed a low risk of revision in patients treated with BF for over 6 months (44). Prieto Alambra et al. Reach the same result. in 2015 on a cohort of about 96,000 patients operated, taken from the Danish prosthesis registry: significant reduction of the risk of revision of the implant prostheses in those who took BF for over 6 months (45).

Meta-analyzes represent the source of more valid and predictive information; Lin et al in a meta-analysis related to 14 trials have confirmed the beneficial effect of second generation BFs mainly to the post-surgical periprosthetic bone loss, which lasts up to 72 months after stopping therapy (46).

Pharmacological therapy in particular improves immediate stability without any inhibition on periprosthetic osteogenesis in patients with osteolysis, BF increases BMD around the stem and cup respectively by 2.4% and 7.1% respectively, indicating the use of BF not only in stimulating periprosthetic osteogenesis, preventing wear debris disease, and curing it when it is in place (47). Clodronate, in particular, finds an indication for its anti-resorbent and modulating properties of periprosthetic bone metabolism, but also for its anti-inflammatory properties towards macrophages in particular and painkillers (48).

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