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Osteointegration of Implants and Risk Factors of Disorders (Literature review)

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Abstract

Biological fixation of the hip joint endoprosthesis today plays an important role in cementless total hip arthroplasty. The duration of stable fixation of endoprosthesis components largely depends on the osseointegration of bone tissue into the implant.

Objective: To determine the features of osseointegration around the implant and to identify the risk factors which affect this process.

Methods: More than 40 works from electronic databases PubMed, Medline, as well as abstracts, articles and other sources of scientific and medical information were analyzed.

Results: Mechanisms and stages of osseointegration, factors affecting peri-implantation osteogenesis and osseointegration at arthroplasty. Osteointegration goes through the following stages: inflammation, migration and differentiation of osteogenic cells, formation of bone tissue, in which the surface of the implant is surrounded by an osteoid and a mineralized matrix; bone tissue remodeling. Factors affecting peri-implantation osteogenesis and osseointegration in arthroplasty are also outlined. The following risk factors negatively influencing the process of osseointegration are highlighted: decrease in the amount or activity of osteoblasts, increase in the density of osteoclasts, imbalance between local and systemic factors affecting the formation and remodeling of the bone, violation of vascularization as a key factor affecting the differentiation of osteogenic cells.

Conclusion: The implant surface plays a great importance in the process of osseointegration: its composition, technological characteristics, hydrophilicity or hydrophobicity in the biological environment, tropicity to cells and possibility to perform the expression of the products of genes forming a macromolecular environment between the implant and the bone, followed by mineralization and characteristic structure.

Keywords: Osteointegration; Biomaterial; Endoprosthetics

Introduction

Among various states that need total hip arthroplasty, about 90% of cases are osteoarthrosis, and others are: avascular necrosis of the femoral head, femoral neck fracture or traumatic joint injury, inflammatory arthropathy [1]. Year after year, implants are inhanced, among other means, with the use of new biomaterials. In general, biomaterials are widely applied in orthopedics and traumatology. These are frames and carbon materials, bioactive glass, natural and synthetic polymers and composites developed on their basis [2-5]. Among biomaterials, we can mention metal materials and their alloys, titanium with different coatings, of which implants and devices for intramedullary and external fixation are made.

Setting implants in the bone tissue contributes to creation of a new condition, the interaction of the living tissue with non-alive material. Thereby osteointegration plays an important role, which is described by PI Brönemark [6], who was investigating blood circulation in the bones of rabbits, in which titanium implant was set. Concluding the experiment, he noted that the implants are tightly connected with the bone. The author called this discovery "osteointegration", that is the formation of direct connection between implant and bone tissue without interposition of soft tissues. The first observations of osteointegration of titanium implant allowed for the conception of several levels - clinical, anatomical, histological and ultrastructural [7,8]. Osteointegration and its components were described in more detail by T Albrektsson & C Johansson [8], modern specialists studying this process under conditions of implantation of different biomaterials, who explore and expand the conception of its mechanisms [9].

Aim

Review is to determine the features of osteointegration with the implant and to identify risk factors that affect this process.

Mechanisms of osteointegration are based on such phenomena as osteoconduction or osteoinduction, i.e. constituents of successful implant interaction with surrounding tissues. Osteoconduction is the attachment of cells that migrate from the blood clot, bone marrow, endosteum and periosteum to the implant surface with the subsequent differentiation of cambial cells into osteogenic ones, their biosynthesis of macromolecular matrix, its calcification and bone formation [8]. Basing on the process that takes place at an early stage, depending on migration, cell adhesion, their proliferation and differentiation, it is possible to predict the success of osseointegration.

The core of osteogenic induction is to stimulate low-differentiated mesenchymal cells to differentiate into osteoblasts. Osteoinduction can be primary or secondary, i.e either the implanted material has inductive properties, or the induction is likely due to the absorption of biologically active substances from the interstitial fluid on the modified surface of the implant, followed by stimulation of adhesion, proliferation and differentiation of osteoblast precursor cells. Osteoinductors include transplants from bone tissue, demineralized bone tissues, implants saturated with biologically active substances (growth factors, etc.)

Regeneration of Bones around the Implant

Stages of osseointegration

On the border "implant - bone" there occur processes typical to reparative osteogenesis in the following stages: inflammation, proliferation and cell differentiation, formation of bone tissue de novo where new, remodeling [10-12]. There emerges contact and distance osteogenesis, processes that were first described in 1980 on the basis of studies of osseointegration of titanium implant [13]. In conditions of contact osteogenesis, new bone tissue is formed in the direction from the surface of the implant to the injured bone. The minimum distance between the bone and the implant is up to 1mm, the space between them is filled with a blood clot, from which erythrocytes, platelets and inflammation cells (polymorphic granulocytes and monocytes) migrate to the surface of the implant.

Precursors of osteogenic cells on the surface of the implant increase cytokines and growth factors, contribute to the further differentiation of cells. On the implant surface all conditions necessary for the adhesion of osteogenic cells are created for their differentiation into osteoblasts with the expression of macromolecular matrix, for the formation of osteoid and reticles of bone trabeculae, between which blood vessels and osteoblast cells-predecessors are located [14,10]. The newly formed bone is connected to the matrix. Distance osteogenesis is the formation of bone tissue in the direction from the surface of the injured matrix bone to the implant; osteogenic cells migrate on the bone surface from the bone marrow and blood clot and form new bone tissue that grows into the surface of the implant. Biological mechanisms are identical with contact osteogenesis. The final result of both osteogenesis types is similar: the implant is surrounded by the newly formed bone tissue associated with the bone matrix [9].

We analyze in more detail the stage of inflammation, which occurs in the case of contact and distance osteogenesis and is aimed at increasing the pool of osteogenic cells. The implantation of biomaterial in the bone is accompanied by a cascade of disorders in the local area, namely: hemorrhage, anoxia and apoptosis of cells [6]. There take place thermic and mechanical damage of the bone (bone tissue, periosteum and endosteum) and bone marrow. In the same time this stage is very important for further development of proliferation and differentiation of osteogenic cells into osteoblasts. Some authors clearly identify the stages of events in the time interval after the implant placement [15]. Within nanoseconds, the surface of the implant is surrounded by a molecular layer of water, and in the period from 30 seconds to several hours on the implant surface fibrin and other protein components settle; the implant is covered with a layer of matrix proteins, which first come from the blood and interstitial fluid at the place of damage, and then are emitted by cells, located in the implantation zone.

Cells interact with the surface of the material through the protein layer that initiates cell migration and adhesion. In fact, during the first day after surgery, platelets secrete on the implant surface among fibrin fibers numerous growth factors, namely: platelet, insulin-like factors (IGF-1, IGF-2), fibroblast growth (FGF-α, FGF-β), bone morphogenetic proteins, vasoactive factors - serotonin and histamine, that promote the migration of multipotent mesenchymal cells, their proliferation and differentiation, as well as the contact with the surface of the established implant. However, along with common mechanisms, the expression of chemokines and integrins differs on the surfaces of different materials. In particular, during the first 24 hours after the implantation of titanium implants with oxide coating to the cortical bone of rats, a significant density of cells with high expression of chemokines, CXCR4 receptors, β1 and β2 integrins and α-v compared to implants with mechanically treated surfaces. Around them there is recorded rising in the cells expression of pro-inflammatory cytokines, the necrosis factor tumors-α and interleukin-1β [16].

The authors came to the conclusion that after a surgical trauma depending on the implant surface, inflammatory responses are modulated, cellular diferons and their adhesive qualities are formed. The largest number of neutrophils was detected in 24-48 hours [15], and according to other authors - in the interval of 3-4 days and till the end of the first week [12], along with macrophages amount of lymphocytes (T, β-cells) and killers (K, NK cells) grew. This process is regulated by locally synthesized growth factors (autocrine and paracrine) and cytokines [12]. The differentiation of multipotent cells into osteoblasts depends on oxygenation, supply of nutrients, angiogenesis, and expression of regulatory factors. In the early

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terms after implantation, the expression of genes in cells on the surface of titanium implants with a microshort surface (AT-I) and nanostructured (AT-II) was studied [17]. Differences in bone comportment are not revealed, but the authors established significant differences in expression levels of regulatory genes.

On day 2, cells are expressed by 392 genes, and on the 4th, by 649. Functionally the corresponding categories of genes associated with mineralization, differentiation of osteoblasts, bone development, and biomineralization of tissues were increased on the surface of titanium AT-I (day 4 versus day 2), comparing with AT-II. The number of genes that were associated with the category of inflammation-immune response, was higher for AT-I than AT-II. It is proved that trabecular titanium also modulates expression genes encoding collagen proteins of the extracellular matrix - collagen type 1α1 (COL1A1) and 3α1 (COL3A1) [18]. However, it must be taken into account that transcriptomic analysis of the whole genome shows complex molecular pathways that can play an unpredictable role in osteointegration [19, 20]. The presence of osteoblasts launches a cascade of transformations in the cycle of osseointegration and bone formation de novo [9]. Formation of bone tissue de novo. On the 16th day an osteoid and a mineralized matrix are formed around the implant [15]. Osteoblasts synthesize organic matrix of bone, collagen type I, non-collagen proteins, fibronectin, thrombospondin, osteonectin, osteopontin, bone sialic protein. Among the latter, an important role in the mineralization of the matrix is played by osteopontin and bone sialoproteins.

On the 28th day, mineralized bone tissue appears on the surface of the implant, depending on its condition and microenvironment. Peri-implant bone remodeling. The resulting bone tissue that contacts with the implant, after being induced to stress and mechanical strain is reconstructed, i.e. remodeled [10]. Signs of remodeling are the presence of osteoclasts in the bone marrow between bone trabeculae adjacent to the implant, osteoblasts and osteoid, blood vessels and lymphatic vessels. Newly formed osteons are located in parallel to the implant surface and perpendicular to its long axis. Bone remodeling can spread up to 1 mm from the surface of the implant. It is proved that osteointegration processes in compact and spongy bone tissue differ in molecular profiles of gene expression [21]. Normally, in trabecular bone high expression of osteogenesis markers (alkaline phosphatase and osteocalcin) and bone resorption (Tartarate-resistant acid phosphatase and cathepsin K) are observed, which indicates increased metabolism. In the cortical bone, increased expression of pro-inflammatory cytokines (necrosis factor tumors-α, interleukin-1β) and osteocalcin [16,22] is noted.

When using titanium implants with an oxide surface in cells, that attach to them in the area of the trabecular bone, on the third day higher levels of expression of Interleukin-1β, and in the cortical layer - alkaline phosphatase and osteocalcin are revealed. That is, different bone sites show definite constitutive expression of genes- markers of inflammation and remodeling. The authors believe that there are biological differences between compact and spongy bone tissue both in normal stationary state, and in response to the introduction of biomaterials. Factors affecting peri-implantation osteogenesis and osseointegration. Molecular and cellular mechanisms that regulate the unique tissue reaction leading to osseointegration are not completely revealed. The fate of the implant in the bone depends on various factors, affecting its osseointegration and duration [12,23,24] anatomy of the implant – conformity in shape, cavity size, in which the material is implanted), state of the adjacent tissues, biocompatibility or biointeraction of the material, adequacy (compliance of the mechanical and physic-chemical characteristics of the implant with the properties of adjacent tissues or replaced structures), a-traumatism (minimal damage to adjacent tissues during insertion and functioning of the implant), functionality (the most complete and painless reconstruction of functions of substituted natural tissues), mechanical stability (parts and components of the endoprosthesis can function for longer period without corrosion, abrasive and other types of wear and tear, without intoxication with the products of the latter, microcirculation).

Factors that violate periimplanting osteogenesis include the decrease or activity of osteoblasts, increased density of osteoclasts, imbalance between local and system factors, influencing the formation and remodeling bone, violation of vascularization as a key factor of differentiation of osteogenic cells [10]. For successful osteointegration the structure of material surface is of great value, since osteoconductive qualities are highly dependent on its physical and chemical characteristics, relief, hydrophilicity or hydrophobicity [25-29]. The behavior of cells on the hydrophilic surface differs significantly from hydrophobic. On the hydrophilic surface a faster coagulation of the blood and fibrin attachment occurs [28], the fiber of which forms on the implant a matrix for further migration of cells and their differentiation [9]. Hydrophilic qualities of implants promote the stimulation of an early osteoblast migration and bone formation. Gene expression of cells is enhanced on the hydrophilic surface of the implants [29]. It was revealed that the structure of the surface is important for cells adhesion. To the rough surface of the cell the appendages attach better than to the smooth one, which raises the indicators of contact “bone - implant”. The porosity of the surface or material is also of great value. Of course, the bearing effect on the part of the skeleton in which the biomaterial is implanted is important.

In the bearing parts of the skeleton restructuring bones activity is more agile. Factors that disrupt osteointegration include some pharmacological products, such as cyclosporine, methotrexate, cisplatin, warfarin and low molecular weight heparins, non-steroidal anti-inflammatory drugs (NSAIDs), especially high-performance COX-2 inhibitors [10,30]. Cyclosporine has anti-anabolic effect on osteoblasts and suppresses T-lymphocytes, which play a critical role in

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remodeling of bone tissue, which leads to the development of osteopenia [31]. Negative effect on osseointegration is produced by glucocorticoids in conditions of chronic use, which is proved in an experiment on animals [32]. They reduce bone formation and increase its resorption. However, it's expedient to conduct randomized clinical trials to confirm the effect of glucocorticoids on bone formation around implants in humans. The negative effect of NSAIDs on osseointegration has been proved, its mechanism is associated with violation of the transformation of arachidonic acid into prostaglandin, which is needed for bone regeneration, osteoclasts activity, bone formation and angiogenesis.

All NSAIDs inhibit COX-2, which is involved in the differentiation of osteoblasts. In experimental conditions, violation was found in rats osteointegration of titanium implants in sponge and compact bone tissue after exposure to meloxicam and diclofenac sodium [31,33-35]. Negative impact on osseointegration is produced by radiation therapy [36]. Radiation therapy has negative impact on osseointegration [36]. A significant role is played by the patient's condition, because osteoporosis, rheumatoid arthritis, kidney failure reduce osseointegration. Smoking is also one of the negative factors of osseointegration. Some mechanisms of osseointegration disorders in patients with chronic alcoholism have been studied. Alcohol affects the nervous system, the gastrointestinal tract, the immune and cardiovascular system, the liver, acts as a risk factor for osteoporosis, slows the bone regeneration [31,37]. In experiments on rabbits and rats it was revealed that alcoholic diet decreases mineral density of bone tissue and direct contact between titanium implant and bone [38,37].

It is proved that vitamin D deficiency has negative effects on the formation of the contact "bone-implant" [39]. In the model of rats after ovariectomy and a diet with a low level of vitamin D, a failure of implant's contact with the cortical bone was noted. However, in case of sufficient income of vitamin D with food a close contact of the bone with the implant was recorded. Basing on genetic research, auxiliary mechanism to support osseointegration in a context of vitamin D deficiency it can be system circadian rhythms [19]. Positive effect on the osseointegration is observed at the use of bisphosphonates. Their anti-resorption action contributes to the prevention of bone loss due to the reduction of its local remodeling around the implant [40]. Statins which might be used either locally or systemically, stimulate osteogenesis and increase bone density around the implants [32]. The positive role of melatonin is determined by osteointegration, introduced locally (3mg) [41].

Conclusion

Osseointegration is a complex process associated with the formation of bone tissue around the implant. It consists of osteoconduction, osteoinduction, which can occur secondary. Osteointegration flows according to classical scheme of reparative osteogenesis and passes characteristic stages - inflammation, proliferation and cell differentiation, de novo bone formation with its subsequent remodeling. Osteointegration was investigated at histological, cellular and molecular levels. A new approach to this problem contains the genetic level, a study of genes expressed in the process of osseointegration. Human genome complex has individual properties, which can affect the final result. Till now a number of factors of exogenous and endogenous origin that affect osseointegration is being studied. Among them, technical and medical ones are defined. Of course, the surface of the implant is important: its composition, technological, hydrophilic or hydrophobic characteristics in the biological environment, tropism to cells and the possibility of performing their basic function - expression of genes products that form a macromolecular matrix between the implant and the bone, followed by mineralization and the formation of a characteristic structure.

Conflict of Interest

The authors declares no conflict of interest.

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