Role of the Tissue-Engineered Structure’s Proteome at Compensation of Bone Defects by Synthetic Osteoplastic Materials

As the authors furnish proofs of active participation of osteoplastic materials implanted in the bone defect in initiation of bone tissue regeneration and support – neo-osteogenesis processing. The material placed in the bone defect, provided that it is affine to non-collagen proteins of blood and tissue fluid, sorbs the latter ones forming a functional complex – tissue-engineered structure’s proteome, which launches the cascade: attraction of pluripotential stromal cells, their retention, proliferation, osteogenic differentiation, expression of bone tissue-specific proteins, the extracellular matrix capable of mineralization. This concept is confirmed by some of our observations.

Besides, studying non-collagen bone tissue proteins (NBP) – minor fraction of the extracellular bone matrix, bas helped us to determine that about 20 of them have a biological effect of local growth factors (LGF).

They dose-dependently impact proliferative activity of progenitors of osteogenic, blood-forming and immune cells, their differentiation and expression by differentiated cells of tissue-specific proteins [2, 3]. Induction of a composition of several NBP with LGF properties has a more energetic influence on reparative osteogenesis due to cooperativity of their effect. We have also registered different affinity of NBP with a different physiological effect to three basic bone tissue ingredients: hydroxapatite, β-tricalcium phosphate and collagen of type I, which contributes to deposition of proteins with a regulatory function. A composition with physical, chemical and biological properties identical to NBP was obtained from the blood serum at application of the same sequence of the preparative protein chemistry techniques.

Then, the composition of non-collagen bone tissue proteins consisting of 10-12 fractions with a molecular weight within the range of the isoelectric point from 5 to 9, migrating under the impact of electrophoresis in the area of α- and ο2-globulins, in the culture of embryonic fibroblasts dose-dependently impacts their physiological activity; at low concentrations it stimulates proliferation (DNA synthesis, increase of the number of viable cells), at high concentrations it stimulates osteoinductive differentiation and expression of differentiated cells (NBP synthesis, alkaline phosphatase activity, formation of calcific nodules) – Fig. 2-3.

In this case, bone NBP ensuing chemotaxis and adhesion of osteogenesis progenitor cells, supporting skeletal bone neomorphosis and taking part in mineralization, can be detected in circulating blood. At compensation of bone defects at medium and acute periodontitis with application of the osteoplastic material’s presence of osteopin (OPN) – bone phosphosialoprotein exercising connection between the mineral bone tissue phase and its collagen matrix, as well as adhesion of osteogenic cells on it, and cytokines of the tumor necrosis factor – osteoactivity...
protegrin (ORG) and its soluble ligand (sRANKL) responsible for the dynamic balance in the resorption-osteogenesis system (skeletal homeostasis), were detected in crevicular fluids – tissue fluid homolog – by means of the enzyme multiplexed immunoassay (example in Pic. 5), which confirms the referential data [5, 6]. The morphological dynamics of bone formation in the place of STES implantation for compensation of the bone defect in the experiment is one more proof in favor of the above concept (pic. 6c – on the third day after implantation we registered formation of an inflammatory cell shaft around the implant with an approximately equal share of inflammatory cells (degrading and native lymphocytes), monocytes-macrophages (source of cytokines coming into the tissue fluid) and fibroblast-like cells (undifferentiated progenitors of osteogenic cells). On the border of the implant and bone tissue of the recipient bed there appear osteoclasts, which by the 7th day (b) contributes to STES resorption (defragmentation), between the units of which there appears granulated tissue. The granulations contain osteoblasts, which ensure appearance of the first bone rods – provisional bone tissue by the 14th day (c). Vascularisation of the newly formed tissue, metabolic processes and biomechanics of the regenerate set conditions for its tissue-specific remodeling with formation of mature spongyous bone by the 75th day (d).

Thus, for implementation of the above neo-osteogenesis scheme in the place of osteoplastic material implantation there exist all the necessary and sufficient conditions. Osteoinduction of the material, as well as chemotaxis, adhesion and proliferation of osteogenic progenitor cells are enabled by the complex of non-collagen proteins affine to mineral and organic ingredients of the implant. This complex – the tissue-engineered structure's proteome – is formed by means of diffusion in the implanted material from the circulatory bed, post-surgery hematoma, produced by the cells of the inflammatory shaft surrounding the implant and released from the resorbed bone tissue of the recipient bed. This complex consists of NBP with the following functions: 1) attractants of PPSC, 2) affine to integrins of these cells, 3) signaling molecules modeling their physiological activity – depending on the dosage stimulating proliferation or differentiation of these cells. The cooperative effect of the components of this complex initiates a pleiotropic cascade of cell processes, which results in formation of a newly formed bone tissue. The speed of the STES proteome formation depends on the composition and properties of the implanted material. It is evident that the composition of hetero-phase material of the implant. This complex – the tissue-engineered structure's proteome – is formed by means of diffusion in the implanted material from the circulatory bed, post-surgery hematoma, produced by the cells of the inflammatory shaft surrounding the implant and released from the resorbed bone tissue of the recipient bed. This complex consists of NBP with the following functions: 1) attractants of PPSC, 2) affine to integrins of these cells, 3) signaling molecules modeling their physiological activity – depending on the dosage stimulating proliferation or differentiation of these cells. The cooperative effect of the components of this complex initiates a pleiotropic cascade of cell processes, which results in formation of a newly formed bone tissue. The speed of the STES proteome formation depends on the composition and properties of the implanted material. It is evident that the composition of hetero-phase calcium orthophosphates and silicates of type 1 is optimal. To the best of our knowledge, silicates and sulfates used at production of osteoplastic materials are not tested for affinity to NBP. On the contrary, fibril- lous heteropolysaccharides – hyalurates, alginates, chitosan, etc. – due to their physical and chemical properties can have properties of a biochromatographic system forming the
Evaluation of dental implant therapy – implant loss

By Olivier Carcuac, UAE

The concept of osseointegration was first introduced by P.I. Brånemark and his co-workers in Sweden (1969; 1977). On a global perspective, acceptance of the clinical application followed the Toronto conference held in 1982. Implant-retained prostheses have since become a popular treatment modality, aiming to fulfill functional and aesthetic needs. Today, the use of dental implants in the rehabilitation of fully and partially edentulous patients is a safe, well-documented and commonly applied method (e.g. Jung et al., 2012, Pytulsion et al., 2012).

About 15 million dental implants are installed annually worldwide and it is estimated that about 4.5 million patients receive dental implants every year. Clinical research evaluating dental implant therapy has mostly been limited to descriptive observational studies. Evaluations were performed following different time intervals and focused on implant survival rate, marginal bone loss, and included, to a lesser extent, biological and technical complications. Outcomes were mostly presented on the implant rather than the patient level. Furthermore, study samples were usually small and consisted of selected patient groups, treated by trained specialists. Thus, existing clinical documentation represents, for the most part, evaluation of efficacy, (i.e. the probability of an intervention being beneficial to patients under ideal conditions), while evaluations of effectiveness (the care provided to the general population under conditions found in practice) are essentially lacking.

Due to traditional attitudes within the field, approaches to research, including study design, have changed little over time. Although a small number of controlled studies have been performed, critical issues were rarely considered. In addition, study populations were usually too small to analyse possible differences between patient groups, categories of clinicians or dental implant systems. In clinical, additional prospective studies should be registered at designated websites prior to recruitment in order to guarantee validity and quality of the research. Today, only few dental journals require such documentation.


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Integration of the implant with hard and soft tissues. In line with this prerequisite for success, the second field of interest for implant research is the occurrence of biological complications (Tonetti and Palmer, 2012). By definition, such complications include issues related to the soft and hard tissues surrounding the implant.

**Implant loss**

The most dramatic biological complication, which occurs when both soft and hard tissue integration has failed, is the complete loss of the implant. From a research point of view, implant loss is an easy outcome to study and is rarely disputed. Thus, no specific case definition is required. In fact, loss of dental implants is the most commonly reported outcome in the literature (Needleman et al., 2012). As mentioned earlier, implant loss has usually been presented as a percentage of implants installed. This in itself is not incorrect but somewhat misleading. Thus, it was argued that, in addition to implant-related figures, the proportion of affected patients should be presented (Berglundh et al., 2002; Berglundh and Giannobile, 2015). During this time, osseointegration should occur, and, thereafter, prosthetic devices replacing the missing tooth/teeth may be connected. Implant loss occurring prior to loading is considered as early implant loss. In other words, such implants have failed to achieve osseointegration during the healing phase and need to be removed. In this context, it should be realized that some authors considered implants lost during the first 6 (Vervaeke et al., 2015) or 12 months (Jent et al., 2014; Friberg and Jent, 2015) of function as early lost implants.

Evidence in regard to early implant loss originates from studies describing efficacy rather than effectiveness of treatment. In selected patient groups treated at specialist clinics, the rate of early implant loss is generally low. Figures of about 1% of implants being lost prior to prosthetic loading have been described (Boccuzzo et al., 2010; Friberg and Jent, 2015). In contrast, findings from studies including larger patient cohorts described higher proportions (about 5%) (Cecchinato et al., 2004). The proportion of affected patients was usually higher than the proportion of implants lost. Alsaadi et al. (2007) reported early implant loss for 5.6% of all implants, while 8.9% of all patients were affected. Similarly, Vervaeke et al. (2015) reported on an early implant loss of 0.8% affecting 2.9% of all patients.

The apparent variation in terms of proportion of early implant loss is intriguing and may be explained by factors related to patient selection and to experience of the clinician. A systematic review on implant complications observed that the extent of the restorative therapy was of significance (Berglundh et al., 2002). While less than 1% of implants failed to integrate in situations of single-tooth replacement, the rate of early implant loss in overdenture (full jaw) cases was almost three times as high. Patient- and clinician-related factors associated with early implant loss were studied by Alsaadi et al. (2007). The authors reported that smoking, habits implants, implant length, implant diameter and implant location were all significantly associated with early implant loss. Implant installation in fresh extraction sockets (immediate implantation) has also been shown to lead to an increased rate of early implant loss. Analyses on the consequences of early implant loss are however lacking. Ultimately, it is the consequence of a complication that is of the highest interest to the patient. Early implant loss might entail additional surgical interventions or alterations of the treatment strategy.

**Late implant loss**

Implant loss occurring after loading has been defined as late implant loss. Similar to what has been reported for early implant loss, the rate of late implant loss is described as low, predominantly in studies originating from well-controlled clinical settings. Friberg & Jent (2015) observed lost implants of 0.7% of implants following the first year in function. Larger patient cohorts have been described to present with rates of late implant loss of around 2% or above (Alsaadi et al., 2008; Jent et al., 2014). Proportions of affected patients were not always reported but were higher when compared to implant-related data. Figures ranging from 2.1% (Vervaeke et al., 2015) to 16.0% (Alsaadi et al., 2008) were observed. In a recent study, Derks et al. (2015) evaluated effectiveness of dental implant therapy including the occurrence of implant loss. In this nation wide project, patient records and radiographs from 2,785 patients were obtained from about 800 clinicians. Information on patients, treatment procedures, and outcomes related to the implant-supported restorative therapy was extracted from the files. 596 of the 2,785 subjects attended a clinical examination 9 years after therapy. Early implant loss was assessed in patient files, while late implant loss was recorded at the clinical examination. While total implant loss (early and late) was noted for 5.0% of all installed implants, the proportion of affected patients was higher. In total, 7.6% of all individuals, i.e., 1 out of 13, lost one or more implants.
Factors associated with implant loss

In the nation-wide project conducted by Derks et al. (2015), results of different regression analyses revealed that several of the patient-, and implant-related factors were associated with implant loss. It was demonstrated that implants installed in patients with a history of periodontitis, as reported in patient records, showed significantly higher odds ratio (3.5) for early implant loss when compared to implants placed in subjects without a history of periodontitis. Smoking was associated with a higher risk for early implant loss, demonstrated by an odds ratio of 2.5 for implants placed in smokers. Implant-related factors were also identified, as short implants (<10 mm) were more likely to be lost prior to prosthetic connection (odds ratio 5.8) when compared to longer implants. In addition, certain implant brands were associated with a higher risk for implant loss: Straumann implants show the lowest rates of early implant loss when compared to Nobel Biocare, Astra Tech and the other implants represented in this observational study (including Biomet 3i, CrestecOTh, Xive, Fraital, Lifecore, Implamed and API).

References


Editorial note:
The full list of references is available from the publisher.