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

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Abstract

The authors furnish proofs of active participation of osteoplastic materials implanted in the bone defect in initiation of bone tissue regeneration and support – neo-osteoogenesis 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 pluripotent 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, has 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 immunocompetent 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 3 to 9, migrating under the impact of electrophoresis in the range of the isoelectric point with a molecular weight within 30-40 kDa, allows for recovery of proteins determining structural and functional properties of bone tissue-specific proteins, the extracellular matrix capable of mineralization. This opens prospects for favorable outcomes of osteoplasty in patients with a reduced regenerative potential.

The technologies of implantation of osteoplastic materials representing derivatives of the allo and xeno bone have been more and more widely used in traumatology and orthopaedy for compensation of bone defects. There is also a tendency of an increase in the share of synthetic tissue-engineered structures (STES) at such interventions. There is a widespread opinion that the role of the material implanted in the bone defect is reduced to formation of an inert matrix, a frame, “building timbers” for osteogenic processing at application of the same serum proteins for bone regeneration and support – neo-osteoogenesis processing. The purpose of this study is to prove active participation of osteoplastic materials in initiation of bone tissue regeneration and support – neo-osteoogenesis processing. Based on the references and our own data we have offered [1] a concept shown in the diagram (Fig.1). 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 pluripotent 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.

In this case, bone NBP ensuring chemotaxis and adhesion of osteogenesis progenitor cells, supporting skeletal homeostasis 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 osteopontin (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; at low concentrations it stimulates proliferation (DNA synthesis, increase of the number of viable cells), at high concentrations it stimulates osteoblast differentiation and expression of differentiated cells (NBP synthesis, alkaline phosphatase activity, formation of calcific nodules) – Fig.2-3.

Thus, 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 3 to 9, migrating under the impact of electrophoresis in the area of α1- and α2-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 osteoblast differentiation and expression of differentiated cells (NBP synthesis, alkaline phosphatase activity, formation of calcific nodules) – Fig.2-3.

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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 – he means of the enzyme multi-

plied 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 com-

pensation of the bone defect in the experiment is one more proof in favor of the above con-

cept (pic. 6c – on the third day after implantation we regis-

tered formation of an inflammatory cell shaft around the implant with an approximately equal share of inflammatory cells (degrading and native lymphocytes), monocytes-mac-

rophages (source of cytokines coming into the tissue fluid) and fibroblast-like cells (uniform-

erated 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 tis-


sue. 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, meta-

bolic processes and biome-

chanics of the regenerate set conditions for its tissue-specific remodeling with formation of mature spongous bone by the 75th day (d).

Thus, for implementation of the above neo-osteogenesis scheme in the place of osteo-

plastic material implantation there exist all the necessary and sufficient conditions. Os-

teoinduction of the material, as well as chemotaxis, adhesion and proliferation of osteogenic progenitor cells are enabled by the complex of non-colla-

gen 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 hematomas, produced by the cells of the infl-

amatory shaft surrounding the implant and released from the resorbed bone tissue of the recipient bed. This complex consists of NBP with the follow-

ing functions: 1) attractants of PPSC, 2) affine to integrins of these cells, 3) signaling mol-

ecules modeling their physi-

ological activity – depending on the dosage stimulating prolifer-

ation 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 de-

pends on the composition and properties of the implanted material. It is evident that the composition of hetero-phase calcium orthophosphates and collagen of type I is optimal.

To the best of our knowledge, silicates and sulfates used at production of osteoplastic ma-

terials are not tested for affinity to NBP. On the contrary, fibri-

lous heteropolysaccharides – hyalurates, alginates, chitosan, etc. – due to their physical and chemical properties can have properties of a biochromato-

graphic system forming the
Evaluation of dental implant therapy – implant loss

By Olivier Carcuac, UAE

The concept of osseointegration was first introduced by P.I. Bruneau and his co-workers in Sweden (1986; 1977). On a global perspective, acceptance of the clinical application followed the Toronto conference held in 1982. Implant-retained prostheses have since become an essential part of 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, Pjurtsson 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 designs, 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 addition, clinical 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.

Long-term success of dental implant therapy depends on the initial and long-term implementation of individualised and evidence-based treatment.

The Diploma in Implant Dentistry, conducted by RCSEd, is an assessment of core knowledge and competence in the field of Implant Dentistry. The examination is designed to provide an assessment at the level expected of a general practitioner with a particular interest in Implant Dentistry. This includes aspects of minor augmentation, but not detailed examination of more advanced procedures, such as major bone grafting, sinus grafting or full arch prosthodontics rehabilitation.

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tegration 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 (Berghlund et al., 2002; Berglundh and Giannobile, 2015).

**Early implant loss**

Traditionally adopted treatment strategies include a healing period of 3 to 6 months following implant installation (Bleinemark et al., 1977). 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 (Vervekke et al., 2015) or 12 months (Jent et al., 2014; Friberg and Jenö, 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 (Rocuzzo et al., 2010; Friberg and Jenö, 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) and Friberg and Jenö (2015) reported early implant loss for 5.6% of all implants, while 8.9% of all patients were affected. Similarly, Vervekke 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 (Berghlund 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 osteoporosis, Crohn’s disease, smoking habits, implant length, implant diameter and implant location were all significantly associated with early implant loss. Implant installation in fresh extraction sockets (immediate installation) 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, primarily in studies originating from well-controlled clinical settings. Friberg & Jenö (2015) observed a loss 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; Jenö 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% (Vervekke et al., 2015) to 16.0% (Alsaadi et al., 2008) were observed. In a recently study, Deeks 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 im-
When compared to shorter implants, there is 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, CrestcoI, Xive, Friadent, Lifecore, Implanmed and API).

Factors associated with implant loss

In the nation-wide project conducted by Derks et al (2015), results of different regression analyses revealed that several patient-related factors were associated with implant loss. Implants installed in the posterior region of the mandible were also shown to be at higher risk for late loss (Alsadai et al., 2008).

Implant-related factors were associated with late implant loss. Implant-related factors may also differ. Few studies have evaluated risk indicators of late implant loss. History of periodontitis (Bocuzzo et al., 2010) and radiotherapy (Alsadai et al., 2008) have been identified as patient-related risk indicators. Implants installed in the posterior region of the mandible were also shown to be at higher risk for late loss (Alsadai et al., 2008).

References


ICOI 2015: World of oral implantology comes to Berlin

The International Congress of Implantologists (ICOI) is not only the world’s largest dental implant organisation, but also the world’s largest provider of continuing dental implant education. For more than three decades, the ICOI has drawn dental professionals to various places around the globe each year. In 2015, the congress is taking place in Berlin from 15 to 17 October and will address contemporary concepts and philosophies in implantology.

On 15 October, scientific presentations as part of the Young Implantologists programme and several free sponsored pre-congress workshops will be held, followed by the welcome reception. On 16 and 17 October, 16 international main podium speakers will offer clinicians an understanding of current implant treatments and their applications. Topics include treatment planning and the use of 3-D imaging, implant site development, hard- and soft-tissue regeneration, simple to complex surgical and prosthetic procedures, and management of complications. The gala dinner will be held on the evening of 16 October.

More than 1,000 dental professionals, including general dentists, specialists, laboratory technicians, students and industry representatives, from all over the world are expected to attend.

For the meeting in Berlin, the ICOI joined forces with two German partner societies for the first time, namely the German Association of Dental Implantology and the European Association of Dental Implantologists.

Berlin is a unique city with many historical sites and creative hot spots. It is the largest city in Germany and the country’s capital. Since the fall of the Berlin Wall in 1989, Berlin has become one of the world’s most popular cities, a metropo- lis where culture, the economy, science, and politics meet. With around 3.4 million residents from about 180 nations, it is also one of the largest cultural melting pots in Europe.

The congress venue is the Maritim Hotel, situated in the city’s embassy district in the picturesque Tiergarten close to the Brandenburg Gate, the historic symbol of Berlin’s reunification.

The ICOI, which was founded in 1972, is an association of various dental professions, including general dentists, oral and maxillofacial surgeons, periodontists, prosthodontists, endodontists, and laboratory technicians. The organisation currently has over 15,000 members.