Current and future options of regeneration methods and reconstructive surgery of the facial skeleton

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Musculoskeletal defects attributable to trauma or infection or as a result of oncologic surgery present a common challenge in reconstructive maxillofacial surgery. The autologous vascularized bone graft still represents the gold standard for salvaging these situations. Preoperative virtual planning offers great potential and provides assistance in reconstructive surgery. Nevertheless, the applicability of autologous bone transfer might be limited within the medically compromised patient or because of the complexity of the defect and the required size of the graft to be harvested. The development of alternative methods are urgently needed in the field of regenerative medicine to enable the regeneration of the original tissue. Since the first demonstration of de novo bone formation by regenerative strategies and the application of bone growth factors some decades ago, further progress has been achieved by tissue engineering, gene transfer, and stem cell application concepts. This review summarizes recent approaches and current developments in regenerative medicine. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:315-323)

The first free vascularized fibular flap was performed by Taylor et al.[1] in 1975. Some years later, this technique was successfully transferred to the facial skeleton mainly for mandibular reconstruction.[2] To date, this flap is used as the gold standard for any extend of mandibular replacement.[3] The use of a reconstruction plate is also well established, but sometimes disadvantages are apparent over time, especially in anatomically difficult situations like the chin region or after radiation therapy, which is often combined with a large amount of bony loss.

NEW TECHNOLOGIES IN RECONSTRUCTIVE BONE SURGERY

Recently, various virtual planning tools have been developed to support microvascular bone replacement surgery. Computer-aided design and computer-aided manufacturing (CAD/CAM) are the key technologies.[4] Two possibilities have emerged from CAD/CAM. The indirect method supplies a stereolithographic (STL) anatomic model that can be used to prebend osteosynthesis plates before operation.[5] The main disadvantages of this method are intraoperative fitting irregularities of the preoperatively preformed plate because of anatomic variations between the in vivo situation and alterations of the STL-model as a result of artifacts. The direct method is based on a virtual 3-dimensional (3-D) planning tool. The resection part of the mandible is transferred to the lower leg. Cutting guides are offered to delineate osteotomy lines. This simplifies the exact position and attachment of the bone segments to each other in order to mimic the original mandibular shape especially in the chin region.

However, these computer-aided technologies do not provide successful operative treatment for all patients. Degenerative and oncologic disorders with treatment-related bone defects are becoming a growing medical and socioeconomic challenge. The incidence of degenerative musculoskeletal diseases is continuously increasing because of the aging population. This burden illustrates the need to develop new therapeutic treatment strategies beyond the standards of transfer of autologous bone grafts and microvascular anastomosis.

As a result of minor functional and aesthetic outcome of patients, microvascular flaps have displaced pedicled flaps. However, in patients with poor vascular conditions, microvascular anastomosis is difficult to handle. Therefore, a new method was developed some years ago. A prefabricated vascularized region of bone such as from the iliac crest was inserted into a mandibular defect by using, for example, the latissimus dorsi

Statement of Clinical Relevance

We reviewed recent standards in reconstructive surgery and tissue engineering. We focused on achievements in maxillofacial surgery enhancing autologous bone grafts and free vascularized flaps. We discussed gene transfer and also stem cell therapy by the aims of reconstructive surgery.

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muscle as its pedicle for an autonomous blood supply. After vascularization of the 2 flaps at the donor site, the muscular flap was cut without loss of the inserted bone.[6] The latter method is described as an exceptional rescue technique for transferring bone, especially in combination with a skin island without providing microvascular surgery.

The complete replacement or regeneration of bony structures or any form of stimulation of bone formation are key strategies in the field of reconstructive surgery, particularly to restore the function and contours of the facial skeleton. To this end, the autologous bone graft is still the gold standard in the treatment of exended or critical-sized skeletal defects that would not heal by local wound healing processes.[7] Nevertheless the use of autologous tissue is associated with harvesting defects and with increased morbidity and stress for the patient. Therefore, it might not offer the optimal treatment of choice.

In 2004, a pioneering clinical trial found that tissue engineering (TE)[8] of a full-size vascularized heterotopic bone graft in a custom-built shape (in this case, a mandible) was possible in humans.[9] This method further used the patient as his own personal bioreactor as the new replacement jaw was grown inside his latissimus dorsi muscle, away from the radiated defect, over a period of 7 weeks, to allow vascularization of the cell- and bone-inductive protein-loaded jaw scaffold (endocultivation). The scaffold was designed by CAD from 3-D patient data to enable a perfect fit and subsequently was transplanted into the recipient site to repair the original mandible defect. This technique avoided the creation of a secondary bone defect. However, such endocultivation strategies are still experimental and require the necessary extensive infrastructure. Furthermore, these trials require, as do all clinical trials, good clinical practice guidelines, including the informed consent of patients and enduring quality assurance.[10] Patient selection is also important, because any new technique will have to compete against the gold standard to allow for overall improvement of the treatment regimen. Vascular diseases or pretreatments such as radiation or chemotherapy are the main risks for bone regeneration. Bone substitute materials (BSM) are currently used in various surgical disciplines, such as in maxillofacial surgery or orthopedics, for a vast spectrum of bone defects. However, such material can only guarantee the formation of bone of often minor quality and limited to a certain size. The improvement and acceleration of bone healing and osseointegration of alloplastic implants is therefore still a major challenge in reconstructive surgery. Hence, research into alternatives such as growth factors (GF) or gene therapy (GT) has gained increasing interest in the last few years.

Growth factors

In 1965, Urist reported that protein extracts from bone could induce cartilage and bone formation. He described this de novo bone formation by heterotopic implanted demineralized bone matrix for the first time.[11] Osteoinductive matrix proteins were isolated and assigned to the group of "bone morphogenetic protein" as a subgroup of the transforming growth factor β (TGF-β) family.[12]

In the following years, other growth factors (GFs) were identified. The common characteristics of the latter are their significant acceleration of bone growth by the differentiation of bone building cells and stimulation of the healing effect of the surrounding tissue.[13] The structure of the factors reveals polypeptides of 6-45 kD) that are involved in cell proliferation, differentiation, and the morphogenesis of tissues and organs during embryogenesis, growth, and also in adulthood.[14] Osteoinductive effects have been detected for various GFs by their stimulation of osteo- and chondrogenic cells[15] in several studies. Of particular importance are bone morphogenetic protein (BMP), TGF, fibroblast growth factor (FGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF),[16] and epidermal growth factor (EGF).[17]

The amount of bone formation and resorption depends on the concentration of GFs.[18] Their available active concentration in bone varies because of the localization of the damage, the physiologic conditions, and, not least, the age of the patient. Concentrations of IGF-I and TGF-β decline with increasing age in cortical bone.[19]

The half-life of GF in serum ranges only for a few minutes to hours,[20] its regulation being carried out at several molecular levels through proteasomal degeneration.[21] Carrier systems with slower release kinetics of BMP molecules can maintain longer lasting drug levels.[22] Thus, rhBMP-2 associated with a collagen sponge can sustain a release of the active protein with a half-life of 3-5 days.[23]

The significant effects of BMP in the musculoskeletal system consist of tissue differentiation during embryongenesis and during the differentiation of precursor cells such as mesenchymal stem cells into chondroblasts and osteoblasts.[24]

BMP-2, in comparison with other growth and differentiation factors, has been found to have a greater potential for promoting bone healing and has a positive effect on fracture healing.[25] The interaction of rhBMP-2 promotes the differentiation of osteoblasts and the maturation and mineralization of the extracellular matrix and thus has an effect on the early stages of bone growth.[16] The increase in fracture stability is achieved