Opšti pregledi/
General reviews

CURRENT "GOLD STANDARD" AND FUTURE PROCEDURES IN MANDIBULAR RECONSTRUCTION

SADAŠNJI "ZLATNI STANDARD" I BUDUĆNOST REKONSTRUKCIJE DONJE VILICE

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Abstract

The surgical techniques for mandibular reconstruction has evolved tremendously in the 20th century. Numerous advances in microsurgical technique, plating technology and instrumentation devices, as well as development of new, clinically useful alloplastic materials have made consistent and reliable mandibular re-establishment possible. Sophistication of techniques is still improving in order to perform a reliable high fidelity mandibular re-establishment that would enable previous state of function and restore bony continuity as well as facial shape. Huge efforts are also being made in tissue engineered mandibular grafts creation that would have long-term compatibility with body tissues and would be more clinically acceptable for bone tissue regeneration. Surgeons aim to ensure that the replacement could be individually molded to fit the defect perfectly, thus improving the chances of adequate postoperative function and a satisfactory aesthetic result.

INTRODUCTION

The jaw bone or mandible consists of three conjoint anatomical parts: body, angle and ramus:
  ● ramus is vertically placed and carries the condylar process and the coronoid process.
  ● condylar process abuts the mandibular fossa and forms the temporomandibular joint.
  ● coronoid process is insertion point for the temporalis muscle, one of the muscles of mastication.
  ● angle inferiorly connects vertical ramus to the body.
  ● body is transverse, connected to the ramus at one side and to the mentum on the other side [1].

For mandible defines the profile and appearance of the lower third of the face, it is both functionally and cosmetically important. Mandible contributes to facial contour, proper occlusion, mastication, airway support, deglutition and speech.

Techniques for mandibular reconstruction were developed in the 20th century and today there are multitude methods for restoration of mandibular defects. There are three categories of insets, based on the materials that are used:
  -   autogenous bone (avascular bone grafts, pedicled bone flaps and vascularized osteomyocutaneous flaps)
  -   alloplastic materials solely
  -   alloplastic trays with bone chips.

Etiology of mandibular defect

Partial loss of the jaw bone due to the trauma, infection or the removal of a tumour results in esthetic deformity, psychological impairment and functional disability. The goals of mandible reconstruction are: reestablishment of mandible continuity, achievement of an osseous-alveolar base and replacement of soft tissue defects. Restoration of a full thickness mandibular defect requires discontinuity of the mandible to be restored with a graft of sufficient length to restore facial symmetry. Satisfactory cosmetic effect is fully achieved if lower border of the mandible is correctly shaped to restore the patient's appearance. Whereas the intra-oral contours may be restored by onlay bone grafting, guides to the shape of the lower border are fewer particularly when the bone defect crosses the midline [2], requiring computer-aided designing/computer-aided manufacturing rapid prototyping technology. In general, mandibular loss due to benign processes results in preservation of soft tissue and is more likely to heal. In contrast, mandibulectomy for carcinoma more frequently results in large bone and neighboring soft-tissues, muscles and nerve defects [3].

Lateral mandibular defects generally require reconstruction to the less extent compared to the antrior mandibular defects which result in severe functional and cosmetic deformities. These deformities are characterized by deficiency of

intraoral lining, bone, muscle, external coverage and neurologic function, and complicated by scar contracture. These patients are often severely disfigured, with compromised nutritional status whose quality of life is tremendously compromised Special attention and preoperative planning should be undertaken in patients who have additional health problems. Nowadays, the diverse reconstructive procedures are used for immediate restoration of composite mandibular defects. Attempts to individualize reconstructive modality are strongly suggested if the patient is to derive maximum benefit.

Preoperative planning and workup

Algorithm of preoperative planning and designing should include etiology, time elapse from the cause of the defect, the latitude of bony and soft tissues' defect and a thorough evaluation of the patient's anatomy. It is recommended to measure and mark the patient prior to surgery to provide an excellent guideline for technical precision.

Presentation is variable and patient dependent, although cephalometric and photographic measurements may assist with localizing and quantifying the deficiency, including the length and width of the bony and soft-tissues loss. Careful planning before the operation increases the likelihood of a good outcome. Communication with the patient is critical, particularly with respects to the patient's facial contour and the result he or she can expect. Ascertaining patients' expectations by any means possible is important. In addition, amend unrealistic expectations that are beyond accomplishment. Patient consent must be ensured through proper information and reconstructive method selection.

Contraindications

Contraindications include present infection, teeth problems, thinning mandible bone stock, bleeding disorders, unrealistic expectations, use of isotretinoin within previous 6 months, a history of radiation, or a number of other health problems contraindicating an elective procedure.

Imaging Studies

Apparently, the process of planning for surgery is highlighted by the physical examination of the face and its contours. Cephalometrics and anthropometric facial and dental measurements should be made, and midline markings should be photographed. Imaging studies and digitised data can also be used in the assessment as they could significantly improve facial appearance and occlusal rehabilitation [2].
● Preoperative photographs from various angles could be easily taken and comprise a first step in decision on reconstruction modality.
● Cephalometric radiography (anterior and lateral projections), can be used in patient assessment. The anteroposterior (AP) cephalogram can be used to evaluate the frontal plane and to compare right- and left-sided structures. Aditionally, submental vertex views can be used to evaluate the transverse plane and the morphology of the body of the mandible [4].
● CT scans and MRI are becoming standard in assessing different maxillofacial abnormalities, including bony and soft-tissue defects.

● Imaging techniques available today enable creation of computer 3-D biomodels to determine the treatment planning, the need for soft or hard tissue reconstruction and/or augmentation, the study of the biomechanical performance of mandibular reconstruction, and even the template for the custom creation of facial implants [5].

The deficiencies that require implantations usually are either vertical or lateral. Two basic approaches exist for implantation. The extraoral approach is advantageous because it allows easier approach and more accurate placement of the implant. The intraoral approach is liked because no visible scar is created but bears the risk of higher rate of infection.

In general, the implant should be accurately placed in healthy tissue away from areas of irradiation or excessive scar formation. This accuracy of placement can be attained if preoperatively determined landmarks, measurements, and 3-dimensional imaging is obtained. The implant should be in firm contact with the tissues, and compression of the implant pores should be avoided.

It is advised to apply antibiotics before and after surgery. After the implant is properly placed into position, it should be screwed, wired, or sutured, and compressive dressings should be used to minimize dead space and avoid hematoma formation. The success of the procedure depends on many factors, including the implant's strength and biocompatibility, proper handling, the surgeon's operative experience and manual skill, as well as postoperative reaction due to well care.

Reconstruction modalities

Segmental mandible resection often leads to composite defects of bone, oral cavity lining, tongue and supporting structures, and occasionally external skin. When planning the reconstruction, the various components of the defect must be considered individually [6]. The use of osteocutaneous free flaps provides a source of composite tissue, including bone, muscle, fascia and skin. Usually one well-planned flap will be adequate to reconstruct most defects.

Bone reconstruction should replace the missing segment of mandible while maintaining proper alignment of the remaining native mandible in order to minimize problems with trismus and malocclusion. Replacement of intraoral soft tissue should be designed to maximize mobility of tongue and buccal mucosa, restore an adequate buccal sulcus for dental rehabilitation and correct soft tissue contour deformities. If external skin needs to be replaced, a second flap is often necessary. External skin replacement detracts from the aesthetic quality of the reconstruction due to the inherent color and texture mismatch between the flap and facial skin. The treatment of these abnormalities requires the use of all applicable diagnostic aids [7, 8]. It also requires extensive presurgical planning to fully understand the 3-dimensional extent of the patient's defect and potential for correction.

The best functional and aesthetic results occur with immediate mandible reconstruction. Delayed reconstruction results in scarring and fibrosis of the remaining bone and soft tissue, making the proper placement of the reconstructed bone rather difficult or even impossible.

The most common indication for oromandibular reconstruction remains ablative surgery for advanced neoplastic processes of the oral cavity and oropharynx. Reconstruction of these complex three-dimensional composite bony and soft-tissue defects is paramount for rehabilitation of shape, form and function. Early reconstructive procedures comprised nonvascularized bone grafts that were plagued by a high incidence of postoperative complications, implant rejection and poor long-term outcomes. This improved significantly with the invention of microvascular reconstruction [8, 9].

Bone grafting

Free bone grafting for mandibular reconstruction was initially reported by Bardenheuer in 1881, but numerous techniques were developed in the 20th century [10]. Early attempts were focused on the nonvascularized bone grafts, particularly the illiac crest with external fixation of bone grafts in delayed mandible reconstruction (during World War I). Internal wire fixation of grafts and the use of antibiotics that was performed during World War II made it more successful. The later period was characterized with the use of osseous allografts and alloplastic materials (metallic trays). The use of metallic trays allowed the good restoration of mandibular continuity, but poor long-term results for frequent cases of infection, fracture or rejection. Metal reconstruction plates were developed in 1980's and used with nonvascularized bone grafts in mandibular reconstruction, but the functional results were unsatisfactory and the failure rate was as high as 30%.

Particulate bone grafts were used to restore mandibular continuity by Converse in 1954. The advent of pedicled osteomyocutaneous flaps by Conley in 1971 allowed the transfer of well-vascularized tissue into the damag ed area. In the 1980's, utilization of vascularized free tissue grafts increased the success rate of reconstruction with free flaps up to 90%. Less resorption was noted compared to nonvascularized bone grafts, but functional results were still poor due to the bad quality of the transferred bone.

Osteogenetic distraction

Osteogenetic distraction is a biologic process of new bone inset formation between two separated bone segments and thus used to restore the continuity in certain cases. The gap is gradually filled by incremental traction. A callus forms between the separated bone segments and as long as the traction proceeds, callus tissues are stretched inducing the new bone formation.

Osteogenetic distraction is an alternative treatment method for mandibular bone lengthening in conditions such as mandibular hypoplasia or post-traumatic defects of the mandible where gradual bone distraction is required, and for use where a segmental loss of bone is a result of a severe trauma or a tumor resection.

The external mandibular distractor is a device that can be utilized to perform bone transport procedures such as bone grafts and free flaps. The system can be adapted to achieve a wide range of clinical results for 3-dimensional distraction, transport distraction, or single-vector distraction of the mandible [11]. Osteogenetic distraction has some risks such as infection, loosening of the distractor, paraesthesia, and excessive skin damage caused by the pins leading to facial scar as the inevitable consequence [12, 13]. If it is necessary to restore the mandibular height, a vertical distraction osteogenesis should be performed to unable optimal implant positioning for ideal prosthetic rehabilitation [14].

Avascular bone grafts

Nonvascularized autogenous bone grafts can be used for reconstruction of small to medium size mandibular defects. These can be harvested from the patients calvarium, rib, ilium, tibia, fibula, scapula, humerus, radius, and metatarsus and provide viable and immunocompatible osteoblastic cells [15, 16].

The amount of bone formed during the first four weeks of bone graft healing is directly proportional to the amount of osteoblasts transferred. The newly formed bone during this phase tends to be poorly organized, but it ultimately determines the size of the resulting bone. The second phase begins about two weeks after implantation and it continues indefinitely. It involves revascularization, remodeling, and reorganization of the newly formed bone. This process is mediated by bone morphogenetic proteins which are most abundantly present in cortical bone.

Cancellous bone grafts contain the highest percentage of viable osteoblasts as they consist of medullary bone and bone marrow. They become revascularized rapidly after transplantation, and could be used in cases with small defects as the phase two healing process is encouraged by surrounding periosteum and bone [17]. On the contrary, cortical grafts consisting of lamellar bone struts contains mainly osteoclasts that rarely survive transplantation due to the time delay required for revascularization. Corticocancellous grafts contain both osteoblastic cells as well as strength necessary for bridging mandibular discontinuity, but an alloplastic tray support is required because of the lack of rigidity [18, 19].

Vascularized pedicled bone transfer

In 1980' was developed the use of pectoralis mayor and latissimus dorsi pedicled myocutaneous flaps that were transfered with the segment of underlying fifth rib. During these years, the trapezius with scapula osteomyocutaneous flap was also introduced with success rate as high as 87%. Pedicled bone transfers are used infrequently nowadays because of difficulties to harvest those flaps, a limited arc of the rotation, tenous blood supply of the bone portion and insufficient thickness of bone that limits dental rehabilitation. In spite of those disadvantages they may be useful in some situations [20, 21].

Microvascular osteocutaneous free flaps

Pedicled myocutaneous flaps is highlighted as one of the most important reconstructive methods as compared to all other available methods nowadays. When reconstruction with microsurgical free flaps ushered in use they were tagged as the "golden standard" [22, 23, 24], and still represents the state-of-the-art for restoration of the anatomic arch, oral functions, and facial esthetics. Those flaps can sustain the load and stresses of mastication.

The choice of tissue graft depends on the adequate length, width and heigth of the gap for reconstruction and should be well vascularized with a pedicle of proper length [25]. The bone portion of the flap should be similar in contour to the patients' native mandible, should be easily curved into the most similar shape, without vascular compromise, having skin paddle thin, pliable and sensate [26]. Autologous bone grafting techniques involve the use of tissues that need to be extracted from healthy sites that leads to significant and inevitable donor-site morbidity leading to a two-site defect instead of a one-site defect [27]. Nevertheless, donor-site morbidity of these osteocutaneous flaps has received less attention than the reconstructive advantages. The incidence and kinds of morbidities are donor-site dependent with complications that are "minor"(scars, hematoma, temporary sensory loss in the mental nerve distribution, acute pain), or "major" (fractures, permanent sensory loss, chronic pain, infection).

Anyway, their incoporation at the site of mandibular defect remains the most reliable method in achieving single-stage, immediate reconstruction of the mandible and thus still represent the gold standard of care untill the new methods utilizing vascularized tissue engineered mandibular grafts are developed [23]. Although there are different indications for the use of non-vascularized bone grafts (NVBG) and vascularized bone grafts (VBG) in mandible reconstruction, the estimation of those techniques could be done by comparing bony union, and overall implant success. Evaluation of a relatively large cohort of patients that undergone either NVBG or VBG indicated successful bony reunion in 69% NVBG patients compared to 96% of VBG (p<0.001), and also higher rates of overall implant success in VBG than NVBG (99% compared to 82%, p<0.001). Our experience with NVBG and VBG in mandible reconstruction indicated similar results. We assessed primary success in mandible reconstruction in 50% NVBG compared to 88.2% VBG patients and finally in 67.2% NVBG compared to 96.6% VBG patients, respectively [8].

The most commonly used free flaps for mandibular reconstruction with microvascular anastomosis are:

● Bare bone graft vascularized with circumflex iliac artery [28]
● Radial forearm osteocutaneous flap [29, 30]
● Latissimus dorsi with attached rib flap [31]
● Scapular bone with trapezius osteomyocutaneous flap [32, 33]
● Fibula osteocutaneous flap [34, 35]

The titanium mini-plates and screws are routinely used for vascularized bone grafts fixation and contouring as they are easy to use, could be easily molded and perform exact fixation of each osteotomy site so that the graft can be easily shaped.

Vascularized osteocutaneous radial flap is commonly used in reconstruction of composite bony and soft tissue defects of the lower third of the face because of the outstand¬ing quality of its cutaneous component (30, 36, 37). We performed reconstruction of mandible defects caused by war wounding with vascularized osteocutaneous radial flaps and assesed primary success in 87.5% and total success in 100% cases [36].

Microvascular osteocutaneous scapular flaps is suitable for reconstruction of mandible followed by massive loss of adjacent skin and mucous membrane due to its vascular supply, bulkiness, suitability and mobility of cu¬taneous component of the flap [38, 39]

The fibula is an ideal bone for mandibular reconstruction and most commonly used. In cases where the fibula is not available or only a small piece of bone is required, other options are considered [40]. The very proximal fibula is likewise not removed in order to avoid injury to the peroneal nerve which courses over the neck of the fibula. The peroneal artery and its venae course the inner aspect of the fibula bone in the deep posterior compartment. The artery provides vessels nourishing the bone and supporting its blood flow. In practice, the muscles are repaired to maintain length after bone harvest and do not usually cause any significant donor muscular disturbance.

The fibula is thus ideal for microvascular free tissue transfer as it provides 20 to 30 cm of bone for harvest, has consistent shape throuought the length, and its segmental blood supply permits multiple osteotomies. The flap can be used to span an angle to angle defect. It is also convenient for osseointegrated dental implantation as it wide and high enough to provide it. Using fibular grafts for the reconstruction of posttraumatic mandible defects obtained excellent results in our clinical study, concerning the functional recovery and mandibular strength [41, 42].

Early postoperative complications decreased even in the setting of postoperative radiation, and expectations for successful oral rehabilitation, including placement of osteointegrated implants, rose markedly. Implants can be placed either immediately or delayed. Immediate placement of implants may compromise bone viability, lengthen the operative procedure, or result in implant malposition [43]. In addition, restoration of near-normal facial appearance became a new standard of care. The long-term excellent functional (mastication, maintenance of bone volume, speech) and aesthetic outcomes (facial appearance) of this technique have recently been reported [2].

One of the problems with bone grafts is a certain degree of resorption. There may be a longer recovery time with bone grafts and an increased risk of bone infection as well as excessive calcifications. The donor site, if using autogenous bone, is also an issue which can be subject to a secondary site infection or other complications.

Cadaveric bone grafts come from cadavers (from deceased donors) and are used the same way as your own. The chance of rejection is slightly higher but very rare. The way a cadaveric bone graft is incorporated is the same as above but without, of course, the donor site risks and complications.

Each of these typically accepts endosseous implants is improving functional outcomes. The use of mandibular reconstruction plates and coverage with a soft-tissue flap remains a reconstructive option for selected patients. The latest refinements in technique include temporary intraoperative external fixation, the use of periosteal free flaps, distraction osteogenesis, and development of biodegradable biomimetic scaffolds for mandibular defects.

Alternative approaches to grafting

The choice of grafting method is controversial in maxillofacial surgery. Three methods have been advocated - autogenous corticocancellous block bone as a free graft or as a vascularised bone flap, or corticoncancellous bone chips may be packed in alloplastic trays. Free grafts are used more for bone enhancement as onlay grafts than for restoration of full thickness defects. Vascularised bone flaps have the disadvantage that there is no bone or part of a bone which is the same shape as the mandible, whereas an alloplastic tray can be custom made [44, 45, 46, 47]. Good success rates are claimed for both methods. The success of osseointegrated titanium implants is well documented with 5-year success rates in the order of 98% in the edentulous mandible [45]. The success of implantation into mandibles with grafted bone is about 75% [46].

Blunted mandibular angles may create a softer oval appearance of the lower face, which may be undesirable, especially in persons who naturally had a strong, chiseled jaw prior to impairment of mandible shape due to trauma or tumor extirpation, or if they desire a more masculine appearance. Reasons for seeking augmentation of the mandibular angle include congenitally small mandible or micrognathia reconstruction, reconstruction secondary to trauma or resection, and, recently more commonly, cosmetic augmentation of a normal anatomic variant.

Alloplastic materials

Mandibular reconstruction plates and screws are the most widely used alloplastic devices for mandibular reconstruction. The most common metals used in the fabrication of these plates are stainless steel, vitallium and titanium. Vitallium is an alloy of cobalt, chromium, and molybdenum. This type of plate initially seemed to be ideal, however the low malleability can make application difficult. Stainless steel and titanium reconstruction plates were developed in an attempt to find a mandibular reconstructive option that was fast, single-staged and reliable while maintaining oral function and form. Reconstruction plates are usually shaped before the mandibular resection and placed afterwards. These plates were have been used with various rates of success. Pedicled and free flaps may be combined with plate reconstruction for soft tissue supplementation and to minimize the possibility of postoperative complications.

Other alloplastic materials that could be used are: dimethylsiloxane polytetrafluoroethylene, polyethylene, polyester, acrylics and calcium phosphate ceramics. Hydroxyapatite and other calcium materials are known to interact with and can even incorporate into living bone tissue. Both porous and dense ceramic forms can be used for implantation. However, these materials are brittle and lack much strength, although they do not resorb. Their biocompatibility is excellent, and they appear to bond to bone by natural cementing mechanisms. This material is osteoconductive and allows for tissue ingrowth without the formation of a fibrous capsule, vascularization and deposition of bone. However, it is not osteoinductive. Block forms have been used as interpositional grafts in mandibular reconstruction. Nonceramic forms also exist and come as a powder that is mixed in the operating room to fill bony defects. The disadvantage is that due to their lack of strength and potential for fracture, they should not be used in load-bearing areas. This may limit their use in mandibular reconstruction. Recently, it was shown in experimental studies that calcium phosphate ceramics can be used as a biodegradable, easily shaped scaffold together with mesenchymal stem cells (bone marrow stromal stem cells) and osteoinductive substances for tissue engineering mandibular grafting.

Ample evidence exists that the composition of the alloplastic material transplanted clearly affects biocompatibility. One of the major obstacles that have plagued the reconstruction of the mandible has been the adverse reaction seen with the use of alloplastic, non-biologic materials. These inert and passive materials, by themselves, do not respond to normal biochemical or mechanical biologic signals which are present in situ within the facial skeleton. The patient, because of the biological inertness of these materials, must adapt to the material that has been used. This is usually associated with a compromised functional outcome. However, the surgical technique and location of placement clearly have a critical role in long-term clinical success. The quality of tissue (eg, vascularity, the thickness of the tissue covering the implant) into which the implant is to be placed must be critically inspected. Patients who previously have had radiation to the area may have decreased vascularity, which impedes the body's ability to mount an inflammatory response to microbial invasion should the implant become inoculated or infected [48].

There are no suitable reconstructive treatments with alloplastic materials available for major load-bearing-mandible defects, because bone is a living, dynamic system with specific biological and mechanical properties that are not found in artificial materials. Bone uniquely combines elasticity and stiffness and is always capable of adapting itself to changing circumstances. This adaptability is primarily due to the combined action of living bone forming and bone resorbing cells that need proper oxygen and food supply by vascular network.

The development of a hybrid technology assesed by a combination of biotechnology (for the development and characterisation of bone-cell culture systems) and materials technology (for the development of three-dimensional biodegradable polymeric matrices that facilitate bone cell growth and have similar mechanical properties to either load-bearing or non-load-bearing bone). This hybrid technology will allow the production of a laboratory-made tissue-engineered living-bone equivalent that will exhibit mechanical, chemical and biological properties similar to those of normal human bone tissue, and is therefore expected to reduce the shortcomings of all current, artificial, bone-replacement materials.

Prefabricated free flaps with tissue engineered bone

It has been more than twenty years that techniques of autologous bone reconstitution with bone marrow stromal cells together with the prefabrication flap procedures were described, leading to the possibility to obtain autologous bone growth ectopically in a myofascial/myocutaneous flap. The integration of tissue engineered bone graft of the desired shape in a soft tissue (i.e. m. latissimus dorsi) could make it possible to generate prefabricated vascularized free flaps

combining a variety of tissue components that aim to meet the special requirements of a particular tridimensional defect (50, 51, 52).

Biomimetic tissue engineered mandibular grafts

Tissue engineering include the principles of biomimetics for the restoration, repair, replacement and assembly of functional tissues and organs. Biomimetics is an interdisciplinary field that incorporates and combines information from the study of biological structures and their function with physics, mathematics, chemistry and engineering in the development of principles that are used for the generation of novel biocompatible synthetic materials for restoration of tissues and organs. This newly emerging field has lately developed much more sophisticated methods that may enable an alternative approach to supplement the existing treatment strategies in mandibular reconstruction, thus avoiding painful and unnecessary treatments.

Creation of tissue engineered mandibular graft yields a perfectly-fitting custom device and simultaneously avoid the donor-site morbidity. It employs selection, expansion and modulation of osteoprogenitor cells in combination with a conductive or inductive 3-D designed and manufactured biodegradable scaffolds to support and guide regeneration together with judicious selection of osteotropic growth factors that act synergistically with and promote the bone-forming capability of cell/scaffold constructs [53]. The goal is for the cells to attach to the scaffold, multiply, differentiate (i.e., transform from a nonspecific or primitive state into cells exhibiting the bone-specific functions), and organize into normal, healthy bone as the scaffold degrades. The signaling molecules can be adhered to the scaffold or incorporated directly into the scaffold material.

Mesenchymal stem cells or human bone marrow stromal stem cells are defined as pluripotent progenitor cells with the ability to generate cartilage, bone, muscle, tendon, ligament and fat. These primitive progenitors exist postnatally and exhibit stem cell characteristics, namely low incidence and extensive renewal potential. Scaffold-implanted mesenchymal stem cells form bone grafts by the following processes:

● Induction: Activation of host osteoblasts and differentiation of primitive mesenchymal cells into chondroblasts and osteoblasts.

● Inflammation: Graft is invaded by immunogenic polymorphonyclear cells and its cellular elements are degraded. Neurovascularization and mesenchymal proliferation follow. Small avascular autografts can become vascularized within 4-5 days.

● Soft tissue callous formation: The cellular matrix of the invading granulation tissue becomes more dense and the vascularity increases. Osteoclasts continue to remove dead bone, while chondroblasts deposit a new matrix of chondroid on the old bone; this begins to calcify. In cortical bone there is a preferential removal of necrotic Haversian systems rather than lamellae leading to an increased porosity of the graft.

● Hard callus formation: Osteoclasts continue to remove dead bone and also begin degrading calcified cartilage, while osteoblasts lay down membranous bone to replace it.

● Remodeling: Graft is remodeled into lamellar bone and a medullar canal is established.

Future perspectives in creating living-tissue-engineered bone-substitute materials that can replace load-bearing and non-load-bearing bone is an advanced CAD/CAM (computer-aided-design/computer-aided-manufacturing) bioreactor system capable of growing large-scale, customized bone together with soft tissue substitutes that could be implanted back into the patient [2].

A scaffold for mandibular reconstruction should provide interactive and/ or functional biologic cues or signals to guide incremental matrix production by either implanted cells [54]. The architectural design of the scaffold/matrix should be instrumental in influencing biological activity (cell infiltration, attachment, differentiation and function) and mechanical integrity (ability to withstand or distribute mechanical forces). It also serves as a barrier for infiltration of surrounding tissues that may impede the regenerative process. In experimental studies on porcine, canine, caprine and nonhuman primates' mandible segmental defects, the size and shape of the composite reflects each surgically created bone lesion. The purpose of these studies was to evaluate the feasibility of those cell/bioceramic constructs: porous scaffold carriers made of poly(lactide-co-glycolide) copolymer, beta-tricalcium phosphate or coralline hydroxyapatite seeded with only a small amount of bone marrow mesenchymal cells. One of the current challenges in scaffold design is to promote proper vascularization in the implant to prevent cell death and promote host integration.

Bone morphogenetic proteins (BMPs) are powerful regulators of cartilage and bone differentiation in embryonic development and in postnatal life and are soluble mediators of tissue morphogenesis and regeneration. BMPs induce their activity throughout a serine-threonine kinase transmembrane dimeric receptor binding complex. There are two kinds of receptors: type I and II. Receptor phosphorylation activates a cascade of intracellular signals that are transduced through SMAD-dependent and SMAD-independent ERK-MAPK pathway. There is a cross-talk between these two pathways. Osteoblasts secrete anti-BMPs (e.g. inhibitory SMADs) to provide self-regulatory control (negative autoregulatory loop).

A striking and discriminatory feature of BMPs is their ability to induce de novo bone formation in extraskeletal sites, recapitulating embryonic development. Osteoinduction in experimental models of tissue engineered mandible was purchased with the use of recombinant human morphogenetic proteins (rhBMP) that improve osteoblastic phenotype [54]. Instead of administering growth factors directly, it is also possible to use genes that encode those molecules. Recently, some investigators constructed a BMP-2-expressing adenoviral vector with high efficiency and succeeded gene transfer by electroporation with a BMP-2-expressing plasmid vector. These bone regeneration inductive substances may be useful in clinic [55].

Human bone marrow osteoprogenitors can be isolated and enriched using selective markers, such as STRO-1, from a CD34+ fraction and these cells can be readily expanded. The combination of in vitro formed graft of culture-expanded bone marrow cells with rhBMP-2 in a collagen sponge, regenerated in vivo the missing segment of mandibular bone

completely, achieved bony-union and penetration of blood vessels [55]. The new bone formation was observed 4 weeks post-operation, and bony-union was detected 12-32 weeks after implantation, detected by radiographic and histological examination. The implant will be active in immune surveillance and function. More importantly, the engineered bone with bone marrow mesenchymal cells/beta-tricalcium phosphate achieved a satisfactory biomechanical property in terms of bending load strength, bending displacement, bending stress and Young's modulus that means it is durable to withstand the stress.

During the healing process (growth of cell/scaffold construct) a structural support in the form of an allopllastic tray (titanium reticulum or titanium plate) reinforcement is required, because of the lack of rigidity of this type of graft. It shows the potentiality of using this method for the restoration of mandibular defect in clinic [56]. It could be an effective method of regenerating large bone defects in elderly patients. Some problems remain to be addressed before clinical trials can proceed, such as the procedure for harvesting bone marrow cells or the serum to be used in culture; however it is strongly suggested to be a promising new technique for bone regeneration in large bone defects. The implantation of either rhBMP-2 only or cells derived from bone marrow itself might be useful in regeneration of small bone defects, especially in younger patients [57].

Creation of a bio-absorbable/bio-degradable matrix with porous architecture can provide a well perfused scaffold onto which larger subunits can be prelaminated. An important research aim is the generation of more clinically acceptable temporary osteoconductive trellis that provide adequate support and a suitable microenvironment for cells to regenerate bone tissue and could be molded into the shape of the defect. Long-term durability of the engineered bone block should be assessed after its transfer for mandible reconstruction and osseointegrated implant insertion [58]. Bioprinting is a recent technology in tissue engineering used for the design of porous constructs through layer-by-layer deposition of cell-laden material. This technology would benefit new biomaterials that can fulfill specific requirements for the fabrication of well-defined three-dimensional (3D) constructs, such as the preservation of cell viability and adequate mechanical properties [60].

However, it is difficult to culture a large volume of cells within these scaffolds. It is necessery to provide a microcarrier cell-culture system that would support attachment, spreading, growth, and differentiation of cells. Also, the long-term compatibility of those scaffolds with body tissues and their chemical similarity to the natural mineral of bone in this applications must be well-established. Clinically useful analogues can be generated by appropriating and mimicking structures from many different organisms such as marine invertebrates (mineralised skeletons of corals, sea urchins and sponges) or monocotyledon plants (fibre bonded collagen network of bamboo culm) that could provide suitable space filling natural structures. Composite scaffolds could be designed and fabricated out of different materials, such as hydroxyapatite – silk, that could imitate trabecular structure of mandible [57]. Certain research efforts are directed towards making nanofibers, small fibers (between 10 and 1000 nanometers) made from a variety of biodegradable nat-

ural and synthetic compounds, and to grow stem cells on nanofiber scaffolds that provide both physical and chemical cues that mimick bone and soft tissues nativa extracellular matrix [58, 59].

Ushering the new era of tissue engineering, there is momentous interest in having an off-the-shelf supply of donor cells. These cells would be expanded ex vivo and immortalized. Fetal or neonatal cells are extremely useful for this purpose since they are naturally non-immunogenic and are a rich source for stem cells; this approach, however, is an extremely controversial ethical issue. Another approach will be "ex vivo gene therapy" consisting of isolation of relevant determined stem cells or committed progenitors from mature adults or from animals, expansion of them ex vivo, transfection of them and selection of transfected cells ex vivo, and then reintroduction of the cells in vivo. Genetic engineering, however, has numerous hurdles to overcome to make this approach feasible, reliable, practical, safe, and generally accepted. Recently, research efforts introduced fat tissue as an ideal source of stem cells [61]. Growing them in an adequate environment containing bone-tissue inducing factors render perfect base for the tissue engineered implant for replacement of diseased or lost mandible.

Perhaps the biggest challenge for all of tissue engineering (including mandible) is how to insure angiogenesis in a timely fashion within the cell/scaffold hybrid; cells without a blood supply will die, and mass infection will occur. The adequate ingrowth of blood vessels into porous scaffold with incorporated stromal cells is to be provided [62].

This new approach to tissue engineering a mandibular missing part would be advantageous because of its patient site-specific anatomical configuration as well as its potential ability to adapt to the loading forces placed on it during function. The future of this field of endeavor is formidable and, with further research, experience, and interdisciplinary collaboration, bioengineered tissue constructs will become a reality [63].

CONCLUSION

The high end of maxillofacial surgeon is to be familiar with an assortment of alternative reconstructive patterns, thus being able to choose the best one for each patient. Nevertheless, tissue engineered grafts are thriving and presumably ushering into use, aiming to amend imperfections of current methods. Hopefully, currently established state-of-the-art procedures will soon be replaced by new, advanced reconstruction modalities.

Apstrakt:

Hirurške metode rekonstrukcije donje vilice razvijale su se dramatičnom brzinom u 20-om veku. Rekonstrukcija mandibule poboljšana je zahvaljujući napretku mikrohirurških tehnika, razvoju tehnologije i instrumenata za ugradnju pločica, kao i primeni novih, klinički upotrebljivih aloplastičnih materijala. Dalje usavršavanje tehnika nastavlja se da bi se obezbedili što prihvatljiviji rezultati rekonstrukcije donje vilice: uspostavljanje normalne funkcije, poboljšanje estetskih rezultata. Ogromni napori se ulažu i u razvoj tkivnog inženjeringa radi stvaranja graftova koji bi bili imunološki kompatibilni i koji će biti klinički upotrebljivi za regeneraciju kosti. Cilj rekonstrukcije donje vilice je da se obezbedi da implantat bude individualno oblikovan tako da savršeno odgovara defektu i na taj način poveća mogućnost adekvatnog postoperativnog uspostavljanja funkcije i obezbedi zadovoljavajući estetski izgled.

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