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# Mandibular reconstruction – state of the art and perspectives

## Rekonstrukcija mandibule – dosadašnja dostignuća i perspektive

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**Key words:**
**oral surgical procedures; mandible; transplants; surgical flaps; bone and bones; muscles; microsurgery.**

**Ključne reči:**
**hirurgija, maksilofacijalna, procedure; mandibula; graftovi; režnjevi, hirurški; kost; mišići; mikro hirurgija.**

### Introduction

The human mandible is a horseshoe shaped bone, anatomically divided into a body, angle and ramus. It is the only both movable and unpaired facial bone. The mandible defines the profile and appearance of the lower third of the face. Thus it contributes to facial contour, proper occlusion, mastication, airway support, deglutition and speech [1].

Discontinuity of the mandible is caused by trauma, infection or the extirpation of a tumor and results in cosmetic deformity, psychological impairment and functional disability. The most common indication for mandibular reconstruction remains ablative surgery for advanced neoplastic processes. Reconstruction of complex three-dimensional composite bony and soft-tissue defects is a paramount for rehabilitation of vastly hindered form and function. In general, mandibular loss due to benign processes results in preservation of soft tissue. In contrast, mandibulectomy for carcinoma more frequently results in large bone and neighboring soft-tissues, muscles and nerve defects [2].

The goals of mandible reconstruction are: establishment of mandible continuity, establishment of an osseous-alveolar base, correction of adjacent soft tissue defects, and it has to provide sufficient durability and strength to allow resumption of daily activities. Restoration of a full thickness mandibular defect requires discontinuity of the mandible to be repaired with a graft of sufficient length to achieve symmetry and correct shape. Whereas the intraoral contours may be repaired by onlay bone grafting, guides to the shape of the lower border are few especially when the defect crosses the midline [3].

Techniques for mandibular reconstruction could be classified into four categories: autogenous bone (avascular bone grafts, pedicled bone flaps, free vascularized osteomyocutaneous flaps, prelaminated and prefabricated bone grafts), osteogenetic distraction, alloplastic materials (with or without bone), tissue engineered grafts.

Preoperative planning should include age, sex, smoking habits, alcohol consumption, comorbidities, etiology, dental status, time elapse from the cause of the defect, the localization and latitude of bony and soft tissues defect and a thorough evaluation of a patient's facial anatomy.

The planning for surgery is highlighted by the physical examination of the face and its contours. Facial and dental measurements should be made (cephalometrics and anthropometrics). Imaging studies and digital data can also be used in the assessment as they could significantly contribute to mandibular reconstruction and implant stabilized occlusal rehabilitation. The treatment of these abnormalities requires the use of all applicable diagnostic aids [4]. For those purposes these imaging techniques are widely used: panoramic orto-pantomography, cephalometric radiography (anterio-posterior cephalogram, submental vertex views). Multislice computerized tomography (CT) and magnetic resonance imaging (MRI) are also becoming popular in assessing maxillo-facial abnormalities (Figures 1). With imaging techniques available today, 3-D models can be created to determine the need for soft or hard tissue reconstruction and/or augmentation (at demand), rehearse the procedure, or even to serve as a template for the custom creation of facial implants [5].

Contraindications for elective procedure include infection, teeth problems, thinning mandible bone stock, bleeding disorders, unrealistic expectations, a history of radiation, or comorbidities.

### Reconstruction modalities

Bone reconstruction should replace the missing segment of mandible while maintaining the proper alignment of the remaining native mandible in order to minimize problems

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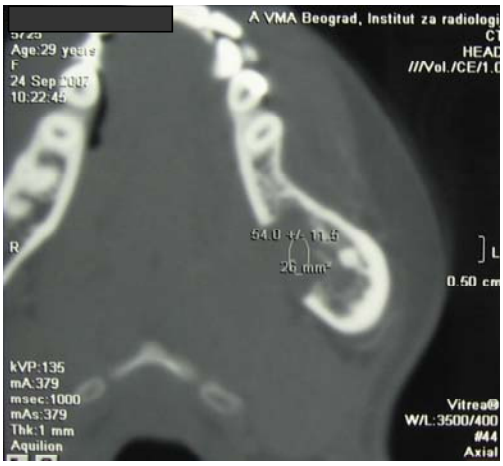
with mouth opening and malocclusion. The best functional and aesthetic results occur with immediate mandible reconstruction. Delayed reconstruction results in scarring and fibrosis of the remaining bone and soft tissue, making the proper placement of the reconstructed bone rather difficult or even impossible [6].

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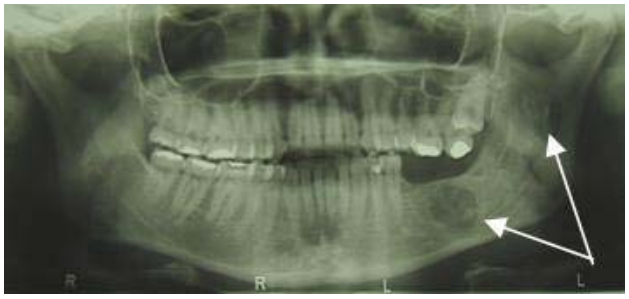


**b)**

**Fig. 1 – (a) Computerized tomography (CT) of mandible with the tumor, and (b) ortopantomography of the same patient**

Free bone grafting for mandibular reconstruction was initially reported by Bardenheuer in 1881, but numerous techniques were developed in the 20th century. 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% [7].

The advent of pedicled osteomyocutaneous flaps by Conley in 1971 allowed the transfer of well-vascularized tissue into the damaged area. In the 1980's, utilization of vascularized free tissue grafts increased the success rate of reconstruction with free flaps up to 90%. The choice of grafting method is patient-specific: corticoncancellous bone chips packed in alloplastic trays and free grafts used more for bone enhancement as onlay grafts than for restoration of full thickness defects. Vascularized 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 [8]. Good success rates are claimed for both methods.

**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 scull, rib, ilium, tibia, fibula, scapula, humerus, radius, and metatarsal bones which can provide viable and immunocompatible osteoblastic cells [9, 10].

Cancellous bone grafts contain the highest percentage of viable osteoblasts as they consist of spongiose bone and bone marrow (Figure 2). They become revascularized rapidly after transplantation, and could be used in cases with small defects. Corticocancellous grafts contain both osteoblastic cells as well as strength necessary for bridging mandibular discontinuity, but an aloplastic tray support is required because of the lack of rigidity.

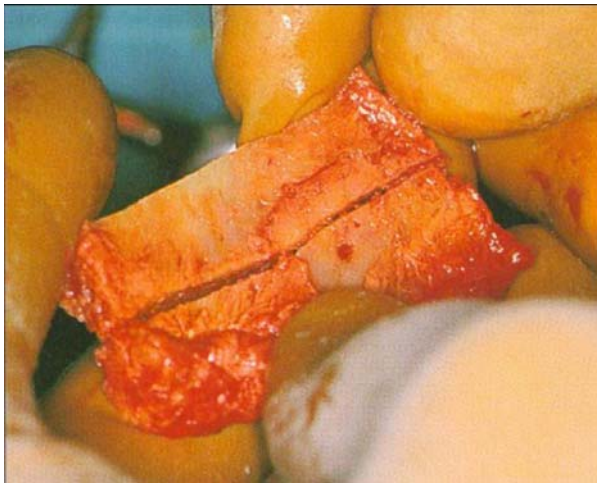


**Fig. 2 – Corticocancellous bone graft from iliac crest**

**Vascularized pedicled bone transfer**

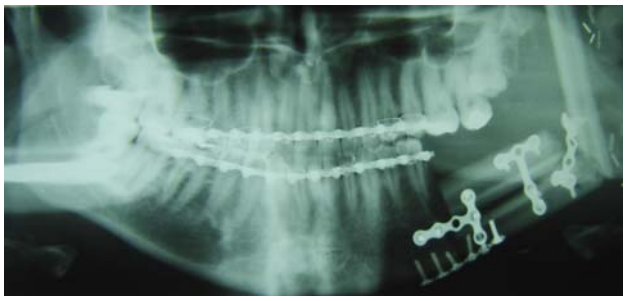
In 1980' was developed the use of *pectoralis* major and *latissimus dorsi* muscles as pedicled myocutaneous flaps that were transferred with the segment of underlying fifth rib. The trapezius with scapula osteomyocutaneous flap was also introduced. Pedicled bone transfers are used infrequently nowadays but they may be useful in some situations [11, 12].

**Microvascular osteocutaneous free flaps**

Nowadays, microvascular osteocutaneous free tissue transfer is the state-of-the-art for rebuilding of composite defects that can handle the stresses of mastication. The tissue should be of sufficient length, width and height for reconstruction of a proposed defect and should be well vascularized with a pedicle of adequate length [13, 14]. Autologous bone grafting techniques involve the use of tissues that need to be elevated from healthy sites that leads to significant donor-site morbidity and causes one-site defect to become a two-site defect [15, 16]. 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) [17].

Thus, it is still the most reliable method to achieve single-stage, immediate reconstruction of the mandible and therefore are still the gold standard untill the new methods utilizing vascularized tissue engineered mandibular grafts are developed (Figure 3).



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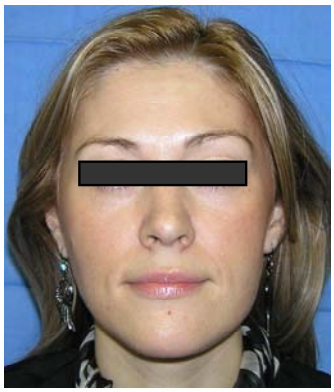

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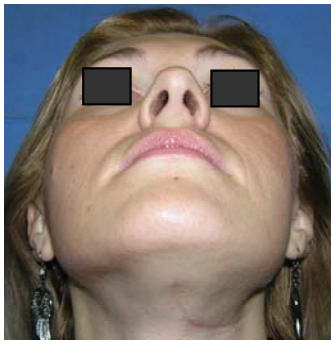


**c)**

**Fig. 3 – (a) Ortopantomography after reconstruction with fibular graft, and (b and c) postoperative appearance of the patient whose preoperative tomography is shown in Fig. 1**

However, transferred free flaps preserve biological values of the donor area that suit the recipient area. The restoration of the sensitivity, touch, pain, hot and cold senses as well as the preservation of sebaceous and sweat glands secretion in the skin part of the transferred flaps, were registered as well [18].

Although there are different indications for the use of non-vascularized bone grafts (NVBG) and vascularized bone grafts (VBG) in mandible reconstruction, the comparison between these techniques could be made concerning bony union, and overall graft success. Evaluation of a relatively large cohort of patients that had undergone either NVBG or VBG indicated successful bony reunion in VBG patients compared to of NVBG, and also higher rates of overall graft success in VBG than NVBG 3.

The most commonly used free flaps for mandibular reconstruction with microvascular anastomosis are: circumflex iliac artery osteocutaneous flap, radial forearm osteocutaneous flap, *latissimus dorsi-serratus*-rib flap, scapular osteocutaneous flap and fibula osteocutaneous flap [19–24].

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 outstanding quality of its cutaneous component [20] (Figure 4). We performed reconstruction of small mandibular and adjacent soft tissues defect caused by war wounding with vascularized osteocutaneous radial flaps and assessed primary success in 87.5% and total success in 100% cases [20] (Figure 5).

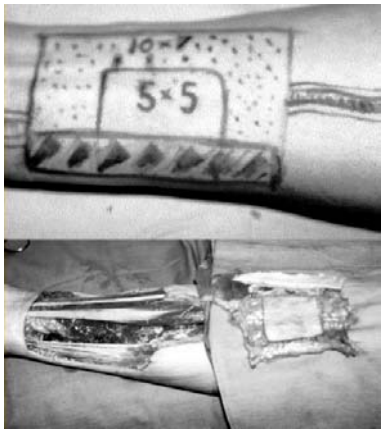
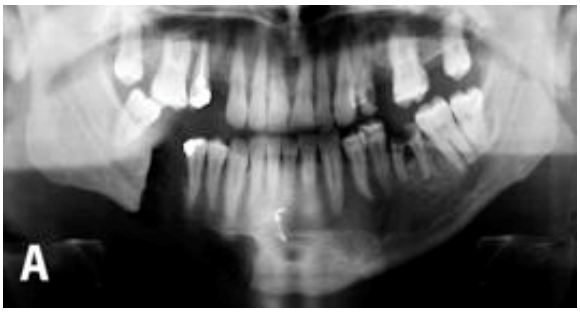



**Fig. 4 – Osteoseptocutaneous radial flap**



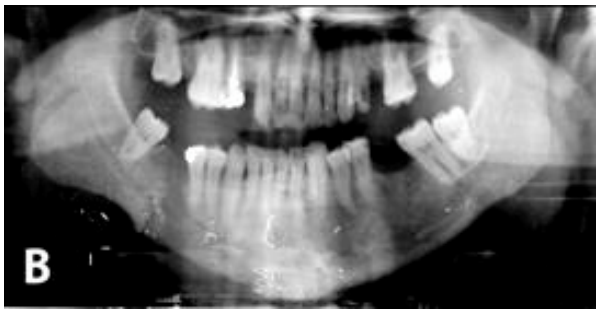




**Fig. 5 – (a) Preoperative, and (b) postoperative ortopantomography of mandible reconstructed with radial flap**

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 cutaneous component of the flap [25] (Figure 6).

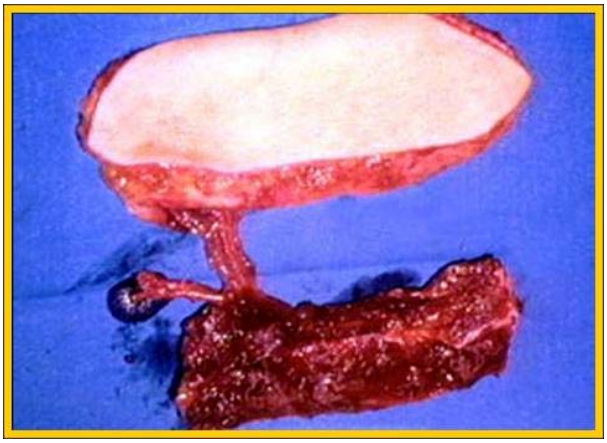


**Fig. 6 – Osteocutaneous scapular flap**

The fibula is an ideal bone for mandibular reconstruction and most commonly used [26, 27]. Thus, it is preferentially used for microvascular free tissue transfer as it provides 20–30 cm of bone for harvest, has consistent shape throughout the length, and its segmental blood supply permits multiple osteotomies (Figure 7). The flap can be used to span an

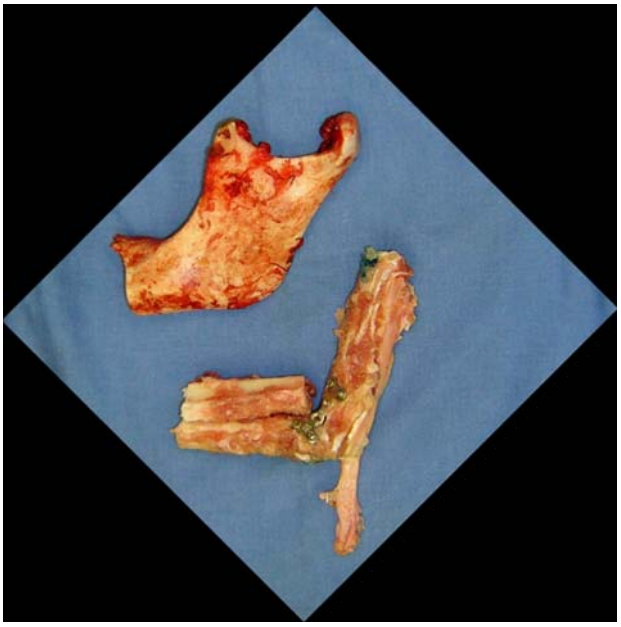


**Fig. 7 – Fibular graft is perfectly shaped to fit the missing part of the resected mandible**

angle to angle defect [28]. It is also convenient for osteointegrated dental implantation as it is wide and high enough to provide it. Using fibular grafts for the reconstruction of posttraumatic mandible defects gave excellent results in our clinical study, concerning the functional recovery and mandibular strength [29, 30]. If the bone height of the mandible after reconstruction is about half that of the dentulous mandible, the deficiency in bone height makes implant placement impractical. If it is necessary to restore mandibular height, vertical distraction osteogenesis of free vascularized fibula flaps and double-barred flap (Figure 8) are reliable techniques that optimize implant positioning for ideal prosthetic rehabilitation [31, 32].

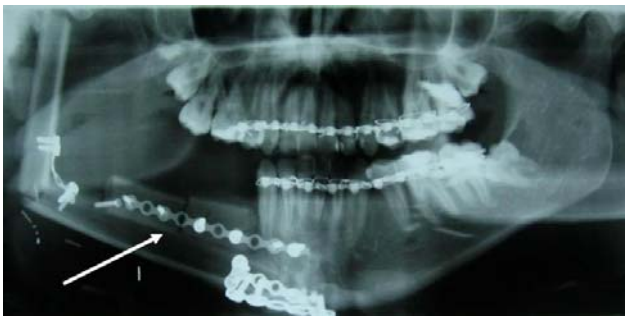


**Fig. 8 – Ortopantomography of the mandible reconstructed with the double-barred fibular flap**

**Functional reconstruction**

Nowadays, functional reconstruction of the mandible following resection or traumatic injury depends on the bony reconstruction that supports dental implants. Endosseous dental implants may improve functional restoration by ensuring the stable dentition essential for normal mastication and speech.

The minimum bone height required for implants is 10 mm. The bone graft must be wide enough to provide adequate bone around the implant. Urken et al. [32] noted that implants can be placed at the time of reconstruction with the second stage of prosthesis insertion four to six months later. Reasons for placing implants at the time of the reconstruction include reliable vascularity, wide access, ability to assess relationships for accurate placement, elimination of additional procedures, and earlier restoration of dental rehabilitation. The success of implantation into mandibles with grafted bone is about 75% [32].

**Prefabricated and prelaminated bone flaps**

Tissue prefabrication starts with transposition of a vascular pedicle into a body of donor tissue to enable creation of a vascularized graft out of an avascular graft. Prelamination procedure is a transfer of different tissues into an established vascular bed. It is a surgical technique for joining various tissues and establishing all-in-one flap. These two methods obtain vascularized bone grafts of desired size and shape needed for a particular defect reconstruction [33]. Ectopical ingrowth of bone graft in pectoral or dorsal muscle result in formation of a complex osteomyocutaneous flap and so it is suitable for rebuilding of a composite defect. Although prefabricated and prelaminated bone flaps do offer reconstructive advantages, they also have some disadvantages. Disadvantages of this procedure are clinical difficulty in handling (operation of least 2 stages is required for bone harvesting

and placement into muscle region, as well as the latter operation for reconstruction), and a failure rate exceeding 10%.

**Osteogenetic distraction**

Osteogenetic distraction is a biologic process of new bone formation between the surfaces of separated bone segments. 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. The goal of distraction is to increase the size of the lower jaw and surrounding tissues.

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 [34]. 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 result of the extraoral device [35, 36]. 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 [37].

**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. Stainless steel and titanium reconstruction plates were a mandibular reconstructive option that is 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 have been used with various rates of success. Pedicled and free flaps may be combined with plate reconstruction.

One of the major obstacles is the adverse reaction of alloplastic, non-biologic materials. These inert and passive materials, do not respond to normal biochemical or mechanical biologic signals which are present *in situ*.

There are no suitable reconstructive treatments with alloplastic materials available for major load-bearing-mandible defects [38]. This is because bone is a living, dynamic system with specific biological and mechanical properties that are not found in artificial materials.

The development of a hybrid technology assessed 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.

**Tissue engineered mandibular grafts**

The aim of tissue engineering (TE) is to restore tissue and organ functions with minimal host rejection. This arises from the need to develop an alternative method of treating patients suffering from tissue loss or organ failure. TE has been heralded as the new wave to revolutionise the healthcare-biotechnology industry. Within the last decade the newly emerging field of TE has developed to a level of sophistication that may offer an alternative approach to supplement the existing treatment strategies in mandibular reconstruction. TE include the principles of biomimetics for the restoration, repair, replacement and assembly of functional tissue and organs. Biomimetics combines informations from the study of biological structures and their function with physics, mathematics, chemistry and engineering in the generation of novel synthetic materials and organs.

There are many approaches to bone tissue engineering, but all of them involve one or more of the following key ingredients: harvested cells, recombinant signaling molecules, and three-dimensional (3D) matrices. One popular approach involves seeding highly porous biodegradable matrices (or scaffolds), in the shape of the desired bone, with cells and signaling molecules (e.g., protein growth factors), then culturing and implanting the scaffolds into the defect to induce and direct the growth of new bone.

Creation of tissue engineered mandibular graft yields a perfectly-fitting custom device and simultaneously avoid the donor-site morbidity. It is based on the 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 [39]. 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 (MSC) are defined as pluripotent progenitor cells with the ability to generate cartilage, bone, muscle, tendon, ligament and fat. They are commonly harvested from the bone marrow, but can also be found in other organs including the fetal lung, fetal liver and adult adipose tissue. Apart from aspiration of bone marrow, MSC could also be provided by liposuction. Ushering the new era of TE and regenerative medicine, there is a significant 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 of stem cells; this approach, however, is an extremely controversial ethical issue.

A scaffold for mandibular reconstruction should provide interactive and functional biologic cues or signals to guide incremental matrix production by either implanted cells [40]. 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). Creation of a bio-absorbable/bio-degradable matrix with controlled 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 a suitable microenvironment for cells to regenerate bone tissue, to be moldable into the shape of the defect, and enable osteointegrated implant insertion [41]. It is also necessary to provide the long-term compatibility of those scaffolds with body tissues and their chemical similarity to the natural mineral of bone in this application must be well-established. Certain research efforts are directed towards making nanofibers, small fibers (between 10 and 1 000 nanometers) made from a variety of biodegradable natural and synthetic compounds, and to grow stem cells on nanofiber scaffolds.

Scaffold-implanted mesenchymal stem cells form bone grafts mediated by inductive signaling molecules, proteins loosely referred to as growth factors: BMP, TGFβ, IGF, PDGF, FGF, VEGF, WNT, ET1, uPA, PSA, MDA-bf-1 and others. Growth factors are produced both locally by bone cells and systemically from other sites. They are not only important for growth, development, and day-to-day maintenance of bone tissues, but are mobilized during times of bone remodeling and injury. Their signaling network is essential for fine tuning of those processes.

Bone morphogenetic proteins (BMPs) are powerful regulators of bone differentiation in embryonic development and in postnatal life and are soluble mediators of tissue morphogenesis and regeneration. A striking and discriminatory feature of BMPs is their ability to induce *de novo* bone formation in extraskeletal sites. Today, over 15 members of the BMP family have been isolated and produced in the laboratory through recombinant DNA technology. Osteoinduction in experimental models of tissue engineered mandible was purchased with the use of recombinant human morphogenetic proteins (rhBMP) that improve osteoblastic phenotype [42]. Instead of administering growth factors directly, it is also possible to use genes, incorporated into adenoviral or plasmid vectors, that encode those molecules. During the healing process (growth of cell/scaffold construct) a structural support in the form of an allopllastic tray reinforcement is required, because of the lack of rigidity of this type of graft [43]. It could be an effective method of regenerating large bone defects in elderly patients, and 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 [43].

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 (i.e. mandible) together with soft tissue substitutes that could be implanted back into the patient.

Perhaps the biggest challenge is how to insure angiogenesis in a timely fashion within the cell/scaffold hybrid; the adequate ingrowth of blood vessels into scaffold with incorporated stromal cells is to be provided.

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 [44].

The future of this field of endeavor is formidable and, with further research, experience, and interdisciplinary collaboration, unprecedented bioengineered tissue constructs will become a reality.

## Conclusion

Although microvascular free flap grafting is the utmost in reconstruction of complex and large mandibular defects, it is important for the surgeon to be familiar with a wide range of reconstructive alternatives so that the best procedure for each patient can be chosen. Nevertheless, tissue engineered grafts are thriving and presumably ushering into use in future, aiming to amend imperfections of previous methods. Hopefully, todays state-of-the-art will soon become vintage art reconstruction methods.

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