

Mandibular ridge reconstruction: A review of contemporary methods

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Abstract

Reconstruction can be very problematic in the case of mandibular alveolar bone loss, which can also hinder the implant restorative treatment. The aim of the study was to present current views on reconstructing the alveolar part of mandibular bone, which allows the insertion of implants and then the placement of denture. Based on the available literature, the efficacy of various techniques of filling of mandibular bone losses was described and compared. Reconstruction with autogenous bone block graft had been used as a gold standard. Recently, other techniques have appeared that offer better functional and esthetics results. They include reconstruction with allogeneic bone block graft, osteotomy allowing immediate insertion of implants, bone distraction, guided bone regeneration using titanium mesh (Ti-mesh), new techniques using scaffolds (biphasic calcium phosphate, poly-lactide-co-glycolide/tricalcium phosphate, bioresorbable polycaprolactone), Sonic Weld Technique® (Tuttlingen, Germany) using resorbable membrane and pins with polymer lactide acid (PLA), and the tent technique. These abovementioned techniques allow solving the problem of insufficient amount of bone for prosthetic treatment.

Key words: allogeneic bone, titanium mesh, scaffold, resorbable pins, tent technique

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Introduction

Mandibular ridge atrophy often results in difficulties and compromises in prosthodontic treatment. It manifests itself in insufficient retention of the lower restorations or prosthetic base overload pain. The lack of restoration causes eating and speaking difficulties, but also adversely affects the appearance and mood of the patient.¹ The use of dental implants as prosthetic pillars for fixed dentures could be the solution to this problem. It is one of the most common, predictable, fully functional and esthetic methods to replace missing teeth.^{2,3} A sufficient amount of bone is necessary to ensure the long-term success of dental implants. According to the research, it is believed that minimum amount of bone required for implantation is 4 mm in width and 7 mm in the vertical dimension.⁴ When the mandibular ridge is decreased, especially because of periodontitis, inserting short implants is often insufficient. Shallow vestibule and small amount of the keratinized gingiva significantly reduces effective application of dental restorations. Another consequence of using short implants with a small vertical dimension of mandibular ridge is the increased distance between the implant and the occlusal plane that induces unfavorable biomechanical forces. Increasing the vertical and horizontal dimension of alveolar ridge enables us to achieve optimal conditions for teeth reconstruction, including function and esthetics.¹

The aim of the study was to present a review of the literature concerning the possibility of mandibular ridge defects reconstruction.

Methods used in mandibular ridge reconstructions include: bone blocks taken from extra- or intraoral site,^{5,6} allogenic material blocks,⁷⁻⁹ bone distraction,¹⁰ osteotomy,¹¹⁻¹³ controlled bone regeneration using resorbable or non-resorbable membrane^{14,15} or titanium mesh (Ti-mesh) and modern methods using biphasic calcium phosphate (BCP),¹⁶ polylactide glycolic tricalcium phosphate¹⁷ and polylactide media gelatin scaffolds (PLC),^{18,19} bioresorbable pins,²⁰ and "tent technique."²¹ To increase the amount of space for long implants, transposition of the inferior alveolar nerve can also be performed.²²⁻²⁴

Autologous bone

Autologous bone was considered the golden standard of jaw atrophy treatment because of its osteogenic, osteoinductive and osteoconductive properties. However, to get the bone material, it is necessary to conduct an additional procedure that could lead to numerous complications, including infection, bleeding, pain, edema, destruction of blood vessels or nerves, and high degree of resorption. The availability of autogenic bone is limited. Vascularized bone grafts may be used to reduce the risk of bone graft resorption, particularly in extensive reconstructions.

Vascularized grafts in comparison to nonvascularized ones have uninterrupted blood flow through microvascular

anastomosis. As a result, the bone is nourished, healing time can be reduced and complications such as infection or resorption occur less frequently than in nonvascularized grafts. This method can be particularly useful after a mandible resection. While harvesting the graft in one area and placing it in another, there are 2 places where intra- and post-operative complications may occur. The important properties that affect the post-performance effect is the presence of living osteocytes in the graft, which develop their functions by providing immediate circulation, allowing the graft to be stabilized regardless of bone block vascularization. Survival of the graft is not determined by its size or the extent of contact between the graft and the bone.²⁵ Vascularized graft survival rate equals 96%, whereas nonvascularized grafts have a survival rate of 69%. A particularly important advantage they have over nonvascularized grafts is with deficiencies bigger than 6 cm and when tissue recipient region has earlier been inflamed.

Places to harvest bone for mandible reconstruction are the fibula, iliac crest, scapula, and forearm radial bone. In the past, allografts were used from ribs and the metatarsus, but due to the numerous disadvantages, such as thinness and difficulty in matching shape, they have fallen into disuse.²⁶

Vascularized fibula flap

A vascularized fibula flap provides a good base for implants. The efficacy of this treatment was described by Kramer et al., who examined 51 implants in 16 patients.⁶¹ In this study, the authors reported that out of 51 implants inserted in 16 patients only one was rejected. Because of soft tissue inflammation, 2 implants remained undiscovered. Therefore, the effectiveness of treatment reached 96%.

Fibula graft involves the smallest risk of complications of all vascularized grafts.²⁷ The discrepancy between the amount of fibula material and the bone loss can be a great impediment in prosthetic reconstruction. The average height of mandible (including dentition) is 2–3 cm and the height of the fibula flap is 1–1.2 cm. Thus, dividing fibula for several parts by osteotomy may be the solution, allowing for esthetic and functional reconstruction. A 25 cm long transplant can be taken from the fibula without compromising its blood supply. The fibula is supplied with blood by the sagittal artery and vein common peroneal, both 15 cm long. Usually, the newly created jaw contour depends on the curvature of the plate formed preoperatively.²⁸ A stereolithography model allows for planning a preoperative treatment, designing suitable shape and cuts, shortening surgery and significantly increasing the accuracy and functionality of the transplant.²⁹

The possibility to conduct 2 operations (fibula resection and mandible reconstruction) at the same time is an important advantage.³⁰ The results of 10-year-long Hidalgo observations show that a fully functional and esthetic

effect was achieved in 70% of the patients, and the appropriate amount of bone was maintained in 92–93% of cases.²⁷ Postoperative complications in the donor site were minor; they included walking pain (24–28%) and small instability within the ankle. The problem of ankle instability and pain can be solved by leaving the distal part of fibula. As in any surgery, the donor and recipient may suffer from complications such as bleeding, hematoma, pleural, infection, and dehiscence. One possible complication in the recipient site may be an unsuccessful transplantation (5% patients). Among the predisposing factors to such complications are previously mentioned technical difficulties during the procedure (related to designing, collecting or matching graft and making vascular connections), external compression (too tight wound closure, hematoma, twisted artery), problems associated with recipient site (prior radiotherapy, postoperative sepsis), and other general diseases.²⁵

Attachment of neurosensory component increased reconstruction possibility. Lateral peroneal skin nerve was incorporated to the graft.³¹

Other vascularized grafts

Another place to harvest vascularized graft may be the iliac crest. This method allows collecting long (6–16 cm) and wide graft of appropriate thickness containing compact and spongy bone. The flap has a natural curvature, which can be used in jaw oval reconstruction. Peripheral iliac arteries are 5–7 cm long. Thus, significant amount of bone may be collected, contrary to that obtained from the fibula.³⁰

In the study by Maiorana et al., the collected and properly fitted graft was attached to the jaw bone using titanium plates and screws. Next, surgical anastomoses were built. The treatment required hospitalization for 14 days.³² Approximately 5 months after alveolar ridge reconstruction, patients were provided with implants. In 1 out of 4 patients, fracture of the hip bone graft after implantation happened. After proper dental implants osteointegration and healing of the wounds, the missing teeth were supplemented. After a half-year and a 3-year control, there were no complications or pathological changes – it proves new formed bone creates very good conditions for implants. Treatment was successful in 95.2%.³³

The bone curvature often makes it difficult to create anterior mandible shape, and grafts collected with surrounding mucosa and skin leads to difficulties in obtaining good esthetic results. Extensive preparation and a section of oblique and transverse muscles are required when collecting a graft, as this might create the risk of postoperative hernia (this complication can be prevented by a thorough closing of the abdominal wall). Another complication that may occur when collecting a large flap is cutting the skin thigh nerve and following numbness in this area. In older patients, treatment in this area often causes pain

and impaired walking in the early postoperative period. Because of these drawbacks, iliac crest graft is usually used as a second choice to collect bone flap when it is not possible to collect it from the fibula.³⁰

Another place to collect bone graft is the forearm, where the bone is nourished by the radial artery and the accompanying veins or superficial veins. The graft may be approx. 10–14 cm long. Its advantages include the presence of vascular pedicle, and appropriate length and diameter that enables creating graft. There is a risk of radius fracture, so the graft thickness should not exceed 30% diameter of the radial bone.³⁴ In addition, some difficulties may occur with restoring the proper shape of the bone; moreover, the height obtained after the surgery may appear as insufficient for implants.

Since 1982, scapular grafts, which included skin and bone, were used for jaw bone reconstruction. A graft from this area can be up to 14 cm long. Peripheral artery and vein are capable of nourishing large bone graft and mucous membrane. Also, there is an elastic connection between the bone and the mucous membrane. A significant disadvantage of a graft is its location that does not allow simultaneous resection of the mandible and collecting graft. When, after resection, extensive cavity and lack of soft tissue exist, an additional graft with fragment of latissimus dorsi musculus can be collected. Because of good blood supply, graft can be properly shaped. Vessels are 6–9 cm long. The quality of the scapular bone in the context of implantological and prosthetic treatment is usually worse than when the material is taken from fibula or iliac crest. After the procedure, mild pain may occur, but it does not restrict normal life activity.²⁶

Allogenic bone from tissue bank

Allogenic bone taken from tissue bank can be an alternative bone block to the autogenous one. All complications connected with the donor can be avoided.⁷ During the process of removing immunogenic properties, its biomechanical properties do not change.⁸ Stabilization of allogenic bone block is necessary for vascularization and bone remodeling.⁹

Allogenic transplants are taken from individuals of the same species. They exhibit osteoconductive and slight osteoinductive properties, which are often sufficient to initiate osteogenesis. An additional source of these factors can be platelet rich plasma (PRP). Platelet rich plasma accelerates the process of graft remodeling and increases the density of newly formed bone.⁸ In addition, this method enables the construction of a 3-dimensional bone model designed by computed tomography (CT). In the next step, allogenic material is shaped to exactly fill the bone defect. The block is sterilized and transferred to the patient's mouth. In one of the studies, a 5-month observation confirmed the quality of newly formed cortical and cancellous bone.⁷

In another study, fresh-frozen blocks of allogenic cortical-cancellous bone were used.⁹ Augmentation was performed using the onlay technique. After cutting and detaching the full-thickness vestibular graft, holes were drilled into the bone in order to improve grafts blood supply. Lingual graft was not detached. Allogenic material had been processed and matched *ex tempore*, and then fixed in the recipient site using titanium microscrews. Collagen membranes were used to seal xenogenic materials. Screws were removed after 16 weeks, and implantation procedure was performed. In a study group of 10 patients, the procedure was successful in 8 of them. Failure of treatment in 2 patients had occurred due to premature resorption of allogenic material and the development of local inflammatory process.⁹

Using a technique that utilizes freshly frozen allogenic bone requires a device for its storing and conditioning. When autogenous bone harvesting surgery is inadvisable, the allogenic bone allows for the reconstruction of defects. Grafts made preoperatively on a 3D model significantly shorten the procedure time and allow the precise shape of jaw bone defect to be obtained.

Bone distraction

This method is used in the treatment of numerous bone deformities; it was described by Ilizarov, who studied and systematized its biological basis.³⁵ According to the first principle, continuous distraction of the bone causes stress reaction upon stretching, rapid growth and regeneration. According to the second principle, the mechanical load and the need for blood affect the rate of growth and shape of the new-formed bone.³⁶ Bone blood supply during osteodistraction comes from the lingual periosteum, where the mucosa and periosteum remain attached at all times.³⁷ Distraction of alveolar ridge can be divided into vertical and horizontal. Increasing the vertical dimension of the decreased mandibular ridge enables subsequent implant or prosthetic treatment. Along with the reconstruction of the bone, soft tissues are reconstructed using the same mechanism.³⁵ The effect of extending bone length uses a mechanism of healing process by progressive stretching of 2 split bone segments.

After the proper osteotomy, process of bone lengthening is divided into 3 phases. First phase – inertia – lasts 24–72 h; it is a period between osteotomy, fixing osteodistractive device and onset of distraction. At this time, clot formation occurs between bone fragments, then it is transformed into granulation tissue and soft callus. Granulation tissue is replaced by fibrous tissue. After inertia, the distraction phase follows, when the daily extending span of distractive device that connects segments of bone progressively moves bone fragments. Increased stretching of soft callus induce enhancement of metabolic activity and bone formation. Bone growth equals 1–2 mm a day. Once

the desired amount of bone is obtained, the final stage follows – stabilization phase. At this point, mineralization and remodeling of newly formed bone occurs, which takes about 6–12 weeks.³⁶

In comparison to autogenous bone graft or alloplastic materials, bone created in the osteodistraction process shows the absence of postoperative resorption and fewer complications. Simultaneous reconstruction of soft tissues eliminates its deficiency. Another big advantage of this method is the short time needed to achieve the correct amount of alveolar bone.^{10,38}

The average increase of bone to be obtained is between 8.2 mm and 13 mm. In the study by Kumar et al. and Gerber-Leszczynyn et al., high quality bone for dental implants was obtained and restoration was introduced.^{35,36}

Complications that may occur during osteodistraction include the bad position of bone segment or its fracture, errors in new tissue formation and bone infections. During the entire osteodistraction process, the occurring complications may be related to the distractor device, distraction phase and phase of consolidation: early fracture (2%), late fracture (17%), bleeding or hematoma (4%), infection (6%), skin perforations (2%), mucosal dehiscence (8%), sensory disturbances (28%), hanging chin (13%), and failures associated with inserting dental implants (13%). The sensory disturbances may be caused by mental nerve irritation while establishing or removing the distractor.³⁷

Transposition of the inferior alveolar nerve

Carrying out the procedure of implanting suitable length implants may not be possible in case of significant mandibular ridge resorption or reduction of the distance between ridge and vault of inferior alveolar nerve canal.^{22,23} Transposition of the inferior alveolar nerve may allow inserting longer implants into the bone, which would provide better stabilization.²³ There are 2 methods of inferior alveolar nerve transposition. The first one includes mental foramen to bone fragment during osteotomy cuts, whereas the second method leaves it intact, when cuts are made distally from it. The size of the bone block depends on the number of implants to be inserted.²² Vertical cuts should be distanced about 3–4 mm from mental foramen. This distance reduces the risk of neurosensory disorders after surgery.²⁴ After detaching the bone fragment and gently removing it from the proximity of the nerve with a special rounded and polished hook, a bundle of vascular and nervous bunch was moved away and held down with a wide, elastic band for the time of implant placing.

Pulling nervous vascular bundle or using force on the nerve must be reduced to avoid the risk of damage, a wide contact, instead of single point pressure, should be used. During the procedure, the nerve should be humidified by saliva. After completing the treatment, the vascular

nervous bundle has to be placed in the initial position. Direct contact between the nerve and implant is inadvisable. A membrane, a bone block or newly formed bone may be used to separate them.²⁴

Not using a mental foramen violation causes less risk of nerve damage (33.3%) in comparison with the method including a mental foramen (77.8%)²³, and fewer post-operative complications.²² One of the major complications after surgery is lack of feeling in the lower lip, which, according to the study of Kan et al. concerned 7 out of 21 operated areas.²³ This neurosensory disturbance did not affect the patients' daily life. In a study by Nocini et al., numbness occurred postoperatively in patients, especially in mental nerve area, but anesthesia or paresthesia did not appear.²² Intraoperative complications that may occur include mandibular fracture, postoperative infection, and hemorrhage. When the blood supply to nerves is impaired – usually when the nerve is damaged – nerve necrosis in its distal part may occur. Another method is to create a channel in outer layer of mandibular compact bone, where the nerve can be transferred. In the study by Kan et al., implementation preceded by inferior alveolar nerve transposition ended osteointegration at 93.8%.²³ However, the increased distance between the alveolar part of the mandible and the occlusal plane causes many difficulties in esthetic supplementation. Horizontal forces of chewing, which impact dental implants, have a destructive influence on the surrounding bone.²¹

Osteotomy

The osteotomic technique is a one-step expansion of the alveolar ridge in buccal-lingual dimension and dental implants insertion. A huge advantage of this method is a significant reduction in the time of treatment from the beginning of the procedure to the final prosthetic supply (no bone augmentation is performed).¹¹

In a 5-year study by Engelke et al., the efficacy of this method amounted to 86.2%. The average marginal bone loss was 1.7 mm.¹² Researchers observed a lower level of infection than with guided tissue regeneration (GTR) techniques using membranes. According to this research, the minimum ridge width for the procedure with a reduced risk of complications such as perforation is 3.12 mm.¹³

After the muco-periosteal flap was detached, a segmented separation of vestibular cortical lamina was performed in order to move it to the position it had occupied before the extraction.¹³ Using a diamond disk or Piezosurgery® (Mectron, Genova, Italy), a vertical cut was made to mobilize the vestibular bone fragment.¹³ Vertical cuts were made 5 mm mesially and distally from the planned implantation. Using osteotomes, the base of the lamina was broken and placed buccally. During mobilization, the periosteum should not be interrupted. Implants were placed in the space between bone fragments without further preparation. Microscrews

provided bone and implant stability. It is possible to use a granulate form material to provide additional protection or polytetrafluoroethylene membrane (e-PTFE) or polylactide membranes. After 4–6 months, the microscrews were removed, the implants were revealed and healing abutments fixed. Prosthetic treatment begins around 3 weeks after the implants are revealed.¹³

The use of new technologies

Rapid prototyping

Immediate prototyping (rapid prototyping – RP) allows for the creation of structures and models by the use of a computer and computed tomography. Rapid prototyping can be divided into 2 groups: addition (build-up of material) and the material cutting from the block.

Two commonly used technologies of immediate production of individual models (prototypes) are 3D printing (3DP) and stereolithography. 3D printing is characterized by high precision, faster printing and lower production cost than stereolithography. This technology is applied to the virtual treatment planning, production of models used as a template to carry out cuts, or drilling the matrix for the retaining screw (if proper material or mesh scaffold is too fragile). It also makes it possible to prepare the mesh and scaffold for the reconstruction.^{26,39,40} Preoperative preparation of the appropriate model shortens the operating time, and thus the exposure of tissues to infection, long-term lack of nutrition and stretching.

The use of computer-aided design/computer-aided manufacturing (CAD/CAM) also allows us to obtain the desired shape of the scaffold or mesh, which is perfectly fitted to the bone loss. The shape is created using mirror algorithm of the opposite site, or by using hole-filling technology. In some cases, both algorithms are used to obtain the desired shape of the final product.⁴¹

Stereolithography is a very popular RP technology based on the conversion of monomer from a resin in a hard polymer after UV radiation. This technique is more precise and enables – as opposed to the alternative of cutting – the production of complex internal structures. The process is not widely used because of its high cost, long preparation time and limited size of the final object.

New technologies are also used to design bioresorbable scaffolds and titanium, polyglycolactide and tricalcium phosphate meshes to reconstruct a decreased mandibular ridge.

Titanium mesh reconstruction

Functional bone reconstruction is also allowed by guided bone regeneration (GBR) with mixed autogenous and xenogeneic bone and titanium mesh generated with the aid of CAD/CAM technology. Titanium mesh (Ti-mesh) with

a thickness of 0.2 mm is used for the reconstruction. This thickness creates enough space for the material, making it possible to obtain the desired, durable shape of the alveolar ridge, prevent soft tissue collapse, following the compression and displacement of the material.⁴² Some authors define the thickness of 0.2 mm as optimal – it has inherent rigidity to maintain graft and protect new forming bone, but is flexible enough to minimize the risk of mucosa dehiscence.⁴³ Due to the presence of pores, Ti-mesh does not block the blood flow from the bone and the mucous membrane.⁴² The most common post-surgery complication is soft tissue dehiscence, but the risk is much smaller in comparison to the use of a membrane. There is no inflammation at the exposed site due to the biocompatibility of titanium.^{44,32} On the surface of titanium, titanium oxide layer is formed passively, causing cell adhesion and colonization, as well as osteocytes differentiation on the surgical side. According to the research of Lizio et al., each 1 cm² of uncovered mesh reduces 16.3% of the planned bone growth. There is also a relationship between early exposure and planned volume of newly formed bone.⁴⁵ Proussaefs et al. noted that Ti-mesh exposure causes horizontal and vertical bone loss of 8–10%.⁴⁶ Before dental implants insertion, the mesh has to be removed. The shape of the mesh was designed and constructed prior to surgery (using RP).⁴⁶ Manual forming did not allow obtaining a perfect shape or smooth edges, and it also heightens the risk of soft tissue dehiscence. The mesh is stiff, so manual forming is difficult and time-consuming. The risk of dehiscence is increased by superficial muscles position and insufficient mucosa amount.⁴⁷

Different materials may be used to fill the bone loss. Autogenous material can be sourced extra- or intraorally. The most common extraoral sources for harvesting material are hip bone, fibula and scapula, and the most common intraoral sources are the angle of the mandible, mentum, and mandible branch.⁴⁸

The material obtained extraorally undergoes resorption to a significant extent, whereas the amount of material harvested intraorally is often insufficient. This limitation can be avoided by using xenogeneic materials, e.g., deproteinized inorganic bovine bone matrix (DBBM), which has osteoconductive properties. Mixture of powdered autologous material with DBBM has osteoconductive properties of the DBBM material and osteogenic and osteoconductive properties of the autogenous material.⁴⁹ In a study by Lizio et al., autologous bone powder and inorganic bovine bone was used in the proportion of 70:30. Simion et al. used this material in the proportion of 1:1.^{14,45}

Surgical technique

Autogenous bone material may be collected extra- and intraorally, both have advantages and disadvantages. If autogenous bone material is collected extraorally, there is another procedure to be conducted under general

anesthesia; however, if the bone material is collected intraorally, local anesthesia is sufficient. In the study conducted by Zaffe and D'Avenia, bone was pulverized and mixed with inorganic DBBM in the ratio of 70:30.⁴⁸ At the top of toothless mandibular ridge, a horizontal and then a vertical cut was made, releasing the full-thickness buccal-lingual flap. Then, the fibrous tissue was removed and perforations in the bone to a marrow space with a small surgical drill were made to increase bleeding and adaptation of bone material.

Titanium 3-dimensional mesh, which had been made before the procedure, was completely filled with augmentative material, placed in a prepared location and stabilized with titanium miniscrews.⁴⁸ Then, the periosteum of the buccal flap was cut to allow its coronal shift, and the wound was tightly stitched.⁵⁰

Postoperative antibiotics and pain therapy should be introduced. Patients should avoid harming postoperative area by adhering to a soft diet for 3 weeks and maintaining proper oral hygiene, rinsing the mouth with 0.2% chlorhexidine solution and applying a 0.2% chlorhexidine gel on the wound 2 times a day. Patients should not wear removable dentures for 4 weeks after the surgery.⁵⁰

Postoperative histological analysis

Just before implantation, a punch biopsy with an inner diameter of 2.6 mm was performed in the postoperative site.⁴⁷ The biopsies were placed in 10% formalin solution for a period longer than 48 h. After proper preparation, all specimens' mixture bone (36.47%), connective tissue (49.18%) and the material particles DBBM (14.35%) were observed. There was no indication of inflammation or resorption. In the case of early titanium mesh exposure, the proportion of the newly formed bone in the specimen was smaller.⁴⁷

Measurements of newly formed bone were also taken from pre- and postoperative CT.⁴⁷ One month after inserting dental implants, the level of newly formed bone was 8.6 mm, 6 months after it was 7.1 mm. According to this study, 6 months after augmentation, bone resorption equaled 15.11% and did not rise after the implant treatment.⁴⁷

Bioresorbable hydroxyapatite and poly-L-lactide mesh

The mesh formed from hydroxyapatite (HA)/poly-L-lactide (PLLA) is stronger than the pure PLLA mesh and influences faster bone formation; it is also bioresorbable and, therefore, does not require reoperation in order for it to be removed from the mucous membrane. The process of total resorption takes 3–5 years.⁵¹ The composite in 40% of its weight is composed of the sintered HA. The scaffold is designed on the basis of CT and is created in the process of stereolithography. In Matsuo et al.'s study

on the mandibular ridge reconstruction, a particulate cancellous bone and marrow (PCBM) of the iliac crest were used and then placed in the mesh with an addition of PRP.⁵² The filled mesh was placed in a prepared place with screws. A 0.8 mm thick HA/PLLA mesh (standard Ti-mesh thickness is 0.2 mm) provides rigid attachment comparable to titanium mesh. Important advantage in comparison with titanium mesh is no need to remove the mesh prior to the dental implants insertion. No X-ray contrast makes it difficult to track the effects of the procedure.⁵² According to Louis et al., the average size of new manufactured bone was 10–12 mm.⁵³ Histologically, bone formation and remodeling were observed within the macropores. Mineralized bone in macropores was combined with fragments of scaffold and BCP, where rows of osteoblasts were visible. In macropores, arteries and veins of various size can also be observed, which prove that the bone was alive.⁵⁴

Sonic Weld Technique® – resorbable membrane and pins with polymer lactide acid

The use of thermoplastic membranes and resorbable prefabricated pins made of polymer lactide acid (PLA) is a modern technique that increases the vertical and transverse dimension of the mandibular ridge. It can also be used to stabilize the membrane during sinus lifts surgery, GBR, bone defects reconstruction in proximity to dental implants (shell technique) or to stabilize the bone transplant.

Pins are inserted into the bone (using ultrasound) and placed in Havers channels, which provides them with a stable fixing. They act like a scaffold and support the bio-material and membrane covering it. The full time of pin resorption is more than 9 months.

Because the pins and the membrane are resorbable, there is no need for second surgery to remove them. The membrane can be shaped in 70°C water, allowing long and complicated 3DP or stereolithography procedures to be avoided. When the desired shape is obtained and the membrane is cooled below 70°C, it becomes rigid. Stiffness provides the space beneath it and ensures there is no pressure on new forming bone. The membrane is attached to pins that ensure its stability. The technique also allows changing the shape of pins and rounding the sharp edges using special ultrasonic tips, even after a diaphragm placement. If additional stabilization is needed, it is possible to use longer pins at the site of the reconstructed defect.

The advantages of the method are: short operation time, low invasiveness and no need for second surgery, low risk of xenogeneic material displacement. Perforation of the membrane allows good circulation from the periosteum. The limitations are the small possibility of the alveolar ridge width restoration and a limited amount of soft tissue to cover reconstruction.²⁰

Tent technique using titanium screws, allogenic bone and bioresorbable membrane

Tent technique allows the reconstruction of a large loss of the mandibular ridge. It is predictable and allows to achieve esthetic results without the use of autogenous bone. Additional studies are necessary to evaluate the long-term effects of this procedure.

The tent technique enables the alveolar ridge to be augmented in patients who have loss of vertical dimension exceeding 7 mm. To rebuild the ridge height, titanium screws with a 1.5 mm diameter were used.⁵⁵ They were inserted partially into the alveolar ridge, protruding 5–7 mm above the alveolar ridge to keep the soft tissue above the bone defect filled with allogeneic material mixed with the patient's blood. Allogenic material completely covered the titanium screws. Resorbable membrane was used in order to prevent allogenic material resorption and the expansion of soft tissue. Newly formed bone was examined and dental implants were inserted 4–5 months after augmentation. In cases where the edge of mandibular ridge shape required corrections, allogenic bone was applied during implant insertion.

In the study of Simion et al., an average increase of alveolar ridge increase reached 9.7 mm.¹⁴ The condition qualifying a patient for surgery was a vertical alveolar bone loss of more than 7 mm, and the width of the ridge bigger than 4 mm. In 2 patients, dehiscence occurred that resulted in the loss of allogenic bone. Osteointegration had occurred in all implants. An histological examination showed an average quantity of bone (around 43%) in the collected material. In all specimens, a correct pattern of cancellous bone was observed, as well as a good connection with bone trabecules.

Biphasic calcium phosphate scaffold

The structure of BCP is similar to the mineralized bone. It has suitable mechanical properties. Biphasic calcium phosphate has good porosity for vascularization and diffusion of nutrients, whereas chemical properties of its surface allow the adhesion of osteogenic cells and proliferation. Moreover, it is biocompatible and has osteoconductive and osteoinductive properties.

In the study of Mangano et al., scaffold was planned individually on the basis of CT and produced using CAD/CAM block containing 70% beta-tricalcium phosphate and 30% HA. Scaffold in shape of bone defect was obtained.^{16,56} In its center there is a hole for the stabilizing screw. Replica of the scaffold – made from polytetrafluoroethylene (PTFE) – is used as a template for drilling the bed needed to stabilize the screws (BCP scaffold is fragile and could be broken if not handled properly). Both the scaffold and its replica require sterilization prior to surgery. One of the main limitations to the use of BCP scaffold is the maximum size for the deficit – 12 mm high and 10 mm wide. It is dictated by the need for adequate

diffusion of oxygen and nutrients through the entire structure.⁵⁶ Osteoblasts require a high concentration of oxygen for the bone matrix production; the higher the permeability of the vascular scaffold, the higher the efficiency of a new bone formation.¹⁶

During the procedure, the muco-periosteal flap was detached under local anesthesia, a replica of PTFE was positioned, a precise bed for the stabilizing screw was drilled, and then the replica was removed.⁵⁶ Prior to the application of the appropriate BCP scaffold, a few small holes in the atrophic mandible bone to the medullary canal were drilled to provoke bleeding the presence of blood assure growth factors, platelet rich and poor plasma and fibrin – they induce healing process and tissue regeneration. After preparing the recipient site, the BCP scaffold was imposed in the correct position, fixed with screw and covered with a fibrin membrane.

The scaffold acts as a sponge absorbing the blood from the bone. The recombinant bone morphogenetic protein (RBMP) is used to increase scaffolds osteoinductive properties. BMP-2 belongs to the family of TGF- β that is present during the bone development and healing; it can be used for the new bone formation within the scaffold.⁵⁷ Lan Levengood et al. researched BCP scaffold and observed that the density of bone cells per mm² in the micropores (not related to macropores) of BCP scaffolds was significantly higher after 3, 12 and 24 weeks than in the control group, where the scaffold BCP did not contain additional BMPs.⁵⁴

The aim of the histological evaluation was to rate the quality bone that was formed by augmentation. Two biopsies were performed (in the place prepared for the implant) with a trephine 2 × 10 mm. The histological examination revealed the presence of dense, mature bone, leukemia, newly generated spaces, and trabecular bone surrounded by residual BCP molecules. The presence of new blood vessels in the bone marrow was observed.¹⁷

An important advantage of this method is a significant reduction in treatment time. The time required for accurate design and construction of the scaffold is certainly a disadvantage.

Poly-lactide-co-glycolide/tricalcium phosphate scaffold

Modern method, but still in the area of research in mandibular ridge reconstruction is poly-lactide-co-glycolide (PLGA) and tricalcium phosphate (TCP) scaffold. The mechanical properties of the scaffold are similar to the human cancellous bone.⁵⁸ The average diameter of macropore is 380 μ m (sufficient macropore volume to enable vascularization and regeneration of mature Haversian systems of bone), micropores 3–5 μ m and porosity of the scaffold 87.4%. If the porosity is too low, there may be too few quality connections between pores; also low susceptibility to tissue growth and increased degradation time may occur because insufficient amount of surface is in contact

with body fluids. The scaffold designed for a patient has a smooth outer surface and a porous inner surface. On the outer, smooth surface, the gingiva is circumferentially rested, also preventing its ingrowth, promoting bone growth within the scaffold.⁵⁸

In the study conducted by Ruhe et al., holes were drilled into the bone marrow before the insertion of dental implants.⁶⁰ This way the scaffold tightly adheres to the bone, and osteoblasts and progenitor cells are involved in bone formation. The progenitor cells of the matrix of human bone marrow mesenchymal stem (HBMSCs) are capable of adhesion and proliferation on the stage, which is why biocompatibility was confirmed. The disadvantages of the PLGA/TCP material are PLGA hydrophobicity, thereby inhibiting cell adhesion and regeneration of tissues after the implantation of the scaffold. The degree of degradation of the PLGA does not correspond to the degree of tissue regeneration. Poly-lactide-co-glycolide metabolic products have acidic character and toxic effect on tissue. They accumulate during scaffold degradation and cause aseptic inflammation. Compared to PLGA, TCP has a higher degree of degradation and its surface has hydrophilic properties. TCP degradation products are alkaline and they can neutralize and alleviate the toxic effects of metabolites PLGA. Tricalcium phosphate has poor mechanical properties, but in TCP particles, the deposition of PLGA improves the strength of the material, reduces hydrophobicity and enhances the ability of cells to adhere to the surface of the material.⁵⁹ Tricalcium phosphate increases the biocompatibility of the material and the total degradation time of PLGA/TCP material is similar to the natural bone formation.⁶⁰

Bioresorbable polycaprolactone scaffold in the 3D technology

The initial phase of research uses 3D selective laser melting polycaprolactone (PCL) scaffold containing 4% HA.¹⁸ Polycaprolactone is a biocompatible and biodegradable synthetic polymer that has a high mechanical strength and low production cost. The process of PCL degradation in a living body is slow and involves hydrolysis. The decomposition products do not cause acidification.¹⁹ Polycaprolactone scaffold can be sterilized with ethylene oxide.

Rasperini et al. used a scaffold made in 3D technology using patients CBCT to cover the recession of lower canines' root that occurred as a result of the loss of connective tissue attachment.¹⁸ After full-thickness flap detachment, mechanical instrumentation of the root was done and EDTA agent was applied. Then, a solution of human recombinant platelet-derived growth factor-BB (rhPDGF BB) was applied on its surface. The PCL scaffold was immersed in the solution for 15 min and then filled with blood derived from the recipient region. The scaffold was fixed with resorbable poly-D and L-lactide pins. The operation area was covered with a flap and sutured using non-resorbable sutures.¹⁸

No inflammatory process or dehiscence was detected during the control visit after 12 months. In the abovementioned study, 3 mm tissues attachment and partial coverage of the tooth root was obtained. During 13 months, exposure of the scaffold has been observed. Despite the use of professional oral hygiene tools, amelogens gel and systemic administration of antibiotics, it was necessary to remove the scaffold – partially at first, and then completely. After 14 months, there was initial healing of the connective tissue and minimal bone reparation.¹⁸

According to the authors, the scaffold should have a greater porosity to allow vascularization and less dense structure to undergo faster resorption, and thus prevent dehiscence, exposure, and bacterial infection.¹⁸

Summary

Reconstructing the vertical dimension of the mandibular ridge requires great competence from the surgeon performing the surgery. The emergence of new reconstruction techniques allows the functional and esthetic reconstruction even when there is extensive bone loss. The aim of this treatment is to produce a fully functional bone to enable proper stability and retention for dental implants and prosthetic devices. The choice of method depends on the bone and soft tissue loss extension, availability of autogenous bone to be harvested and access to modern technology – stereolithography, CAD/CAM, or osteodistractors.

References

- Perdijk FBT, Meijer GJ, van Strijen PJ, Koole R. Complications in alveolar distraction osteogenesis of the atrophic mandible. *Int J Oral Maxillofac Surg.* 2007;36(10):916–921.
- Mangano F, Macchi A, Caprioglio A, Sammons L, Piattelli A, Mangano C. Survival and complication rates of fixed restorations supported by locking-taper implants: A prospective study with 1 to 10 years of follow-up. *J Prosthodont.* 2014;23(6):434–444.
- Mangano F, Shibli JA, Sammons RL, Veronesi G, Piattelli A, Mangano C. Clinical outcome of narrow-diameter (3.3-mm) locking-taper implants: A prospective study with 1 to 10 years of follow-up. *Int J Oral Maxillofac Implants.* 2014;29(2):448–455.
- Poli PP, Beretta M, Ciccu M, Maiorana C. Alveolar ridge augmentation with titanium mesh. A retrospective clinical study. *Open Dent J.* 2014;8:148–158.
- Misch CM. Comparison of intraoral donor sites for onlay grafting prior to implant placement. *Int J Oral Maxillofac Implants.* 1997;12(6):767–776.
- Mehta RKP, Deschler DG. Mandibular reconstruction in 2004: An analysis of different techniques. *Curr Opin Otolaryngol Head Neck Surg.* 2004;12(4):288–293.
- Keith JD, Salama MA. Ochrona i augmentacja wyrostka zębodołowego zwiększa przewidywalność i poprawia efekt estetyczny leczenia implantologicznego. *Implants.* 2010;5(2):20–26.
- Szadowski M, Popowski W, Frank S, Nieckula P, Kamiński A, Wojtowicz A. Odbudowa ubytku kostnego w przednim odcinku szczęki allogennym blokiem kostnym wzbogaconym PRP. *Implants.* 2015;10(2):18–24.
- Dudek D, Żaba M, Barć-Czarnecka M, et al. Augmentacja kości szczękowych z zastosowaniem kości ludzkiej świeżo mrożonej – kliniczne doświadczenia własne. *Implants.* 2015;10(2):30–37.
- Yun KI, Choi H, Wright RF, Ahn HS, Chang BM, Kim HJ. Efficacy of alveolar vertical distraction osteogenesis and autogenous bone grafting for dental implants: Systematic review and meta-analysis. *Int J Oral Maxillofac Implants.* 2016;31(1):26–36.
- Teng F, Zhang Q, Wu M, Rachana S, Ou G. Clinical use of ridge-splitting combined with ridge expansion osteotomy, sandwich bone augmentation, and simultaneous implantation. *Br J Oral Maxillofac Surg.* 2014;52(8):703–708.
- Engelke WG, Diederichs CG, Jacobs HG, Deckwer I. Alveolar reconstruction with splitting osteotomy and microfixation of implants. *Int J Oral Maxillofac Implants.* 1997;12(3):310–318.
- Kao DW, Fiorellini JP. Comparison of ridge expansion and ridge splitting techniques for narrow alveolar ridge in a Swine cadaver model. *Int J Periodontics Restorative Dent.* 2015;35(3):e44–49.
- Simion M, Fontana F, Rasperini G, Maiorana C. Vertical ridge augmentation by expanded-polytetrafluoroethylene membrane and a combination of intraoral autogenous bone graft and deproteinized anorganic bovine bone (Bio Oss). *Clin Oral Implants Res.* 2007;18(5):620–629.
- Cordaro L, Amadé DS, Cordaro M. Clinical results of alveolar ridge augmentation with mandibular block bone grafts in partially edentulous patients prior to implant placement. *Clin Oral Implants Res.* 2002;13(1):103–111.
- Mangano FG, Zecca PA, van Noort R, et al. Custom-made computer-aided-design/computer-aided-manufacturing biphasic calcium-phosphate. *Case Rep Dent.* 2015;2015:941265.
- Moldovan I, Juncar M, Dinu C, et al. Mandibular reconstruction using free vascularized iliac crest grafts and dental implants. *Clujul Med.* 2015;88(3):391–394.
- Rasperini G, Pilipchuk SP, Flanagan CL, et al. 3D printed bioresorbable scaffold for periodontal repair. *J Dent Res.* 2015;94(Suppl 9):1535–1575.
- Rong D, Chen P, Yang Y, et al. Fabrication of gelatin/PCL electrospun fiber mat with bone powder and the study of its biocompatibility. *J Funct Biomater.* 2016;7(1):6.
- Pilling E, Mai R, Theissig F, Stadlinger B, Loukota R, Eckelt U. An experimental in vivo analysis of the resorption to ultrasound activated pins (Sonic weld) and standard biodegradable screws (ResorbX) in sheep. *Br J Oral Maxillofac Surg.* 2007;45(6):447–450.
- Le B, Rohrer MD, Prasad HS. Screw “tent-pole” grafting technique for reconstruction of large vertical alveolar ridge defects using human mineralized allograft for implant site preparation. *J Oral Maxillofac Surg.* 2010;68(2):428–435.
- Nocini PF, De Santis D, Fracasso E, Zanette G. Clinical and electrophysiological assessment of inferior alveolar nerve function after lateral nerve transposition. *Clin Oral Implants Res.* 1999;10(2):120–130.
- Kan JY, Lozada JL, Goodacre CJ, Davis WH, Hanisch O. Endosseous implant placement in conjunction with inferior alveolar nerve transposition: An evaluation of neurosensory disturbance. *Int J Oral Maxillofac Implants.* 1997;12(4):463–471.
- Sharma R. Trigeminal Nerve Injuries. *Medical Journal, Armed Forces India.* 2015;71(1):42.
- Hoffman GR, Islam S, Eisenberg RL. Microvascular reconstruction of the mouth, face and jaws. Oromandibular reconstruction – free fibula flap. *Aust Dent J.* 2012;57(3):379–387.
- Goh BT, Lee S, Tideman H, Stoeltinga PJ. Mandibular reconstruction in adults: A review. *Int J Oral Maxillofac Surg.* 2008;37(7):597–605.
- Hidalgo DA. Fibula free flap: A new method of mandible reconstruction. *Plast Reconstr Surg.* 1989;84(1):71–79.
- Marchetti C, Bianchi A, Mazzoni S, Cipriani R, Campobassi A. Oromandibular reconstruction using a fibula osteocutaneous free flap: Four different “preplating” techniques. *Plast Reconstr Surg.* 2006;118(3):643–651.
- Kokosis G, Schmitz R, Powers DB, Erdmann D. Mandibular reconstruction using the free vascularized fibula graft: An overview of different modifications. *Arch Plast Surg.* 2016;43(1):3–9.
- Chim H, Salgado CJ, Mardini S, Chen HC. Reconstruction of mandibular defects. *Semin Plast Surg.* 2010;24(2):188–197.
- Boyd JB, Caton AM, Mulholland RS, Tong L, Granzow JW. The sensate fibula osteocutaneous flap: Neurosomal anatomy. *J Plast Reconstr Aesthet Surg.* 2013;66(12):1688–1694.
- Maiorana C, Santoro F, Rabagliati M, Salina S. Evaluation of the use of iliac cancellous bone and anorganic bovine bone in the reconstruction of the atrophic maxilla with titanium mesh: A clinical and histologic investigation. *Int J Oral Maxillofac Implants.* 2001;16(3):427–432.
- Navarro Cuellar C, Caicoya SJ, Acero Sanz JJ, Navarro Cuellar I, Muela CM, Navarro Vila C. Mandibular reconstruction with iliac crest free flap, nasolabial flap, and osseointegrated implants. *J Oral Maxillofac Surg.* 2014;72(6):1226.e1–15.

34. Thoma A, Khadaroo R, Grigenas O, et al. Oromandibular reconstruction with the radial-forearm osteocutaneous flap: Experience with 60 consecutive cases. *Plast Reconstr Surg.* 1999;104(2):368–378.
35. Kumar KAJ, Masrom AK, Patil K, Kunusoth R, Begum F, Venkatesh V. Evaluation of vertical bone gain following alveolar distraction osteogenesis in the anterior edentulous mandible: A clinical study. *J Maxillofac Oral Surg.* 2014;13(4):539–545.
36. Gerber-Leszczyszyn H, Pawlak W, Łuczak K. Wykorzystanie wewnątrzustnych dystraktorów kostnych w leczeniu ubytków pourazowych wyrostka zębodołowego żuchwy – opis przypadku. *Dent Med Probl.* 2003;40(1):155–157.
37. Perdijk FB, Meijer GJ, Strijen PJ, Koole R. Complications in alveolar distraction osteogenesis of the atrophic mandible. *Int J Oral Maxillofac Surg.* 2007;36(10):916–921.
38. Mampilly MO, Rao LP, Sequiera J, Sripathi Rao BH, Chandra J, Rai G. Rehabilitation of edentulous atrophic anterior mandible – The role of vertical alveolar distraction osteogenesis. *J Clin Diagn Res.* 2014;8(11):ZR01–ZR03.
39. Li J, Zhang L, Lv S, Li S, Wang N, Zhang Z. Fabrication of individual scaffolds based on a patient-specific alveolar bone defect model. *J Biotechnol.* 2011;151(1):87–93.
40. Ciocca L, De Crescenzo F, Fantini M, Scotti R. CAD/CAM and rapid prototyped scaffold construction for bone regenerative medicine and surgical transfer of virtual planning: A pilot study. *Comput Med Imaging Graph.* 2009;33(1):58–62.
41. Liu YF, Zhu FD, Dong XT, Peng W. Digital design of scaffold for mandibular defect repair based on tissue engineering. *J Zhejiang Univ Sci B.* 2011;12(9):769–779.
42. Yamada H, Nakaoka K, Horiuchi T, et al. Mandibular reconstruction using custom-made titanium mesh tray and particulate cancellous bone and marrow harvested from bilateral posterior ilia. *J Plast Surg Hand Surg.* 2014;48(3):183–190.
43. Rocuzzo M, Ramieri G, Spada MC, Bianchi SD, Berrone S. Vertical alveolar ridge augmentation by means of a titanium mesh and autogenous bone grafts. *Clin Oral Implants Res.* 2004;15(1):73–81.
44. Rocuzzo M, Ramieri G, Bunino M, Berrone S. Autogenous bone graft alone or associated with titanium mesh for vertical alveolar ridge augmentation: A controlled clinical trial. *Clin Oral Implants Res.* 2007;18(3):286–294.
45. Lizio G, Corinaldesi G, Marchetti C. Alveolar ridge reconstruction with titanium mesh: A three-dimensional evaluation of factors affecting bone augmentation. *Int J Oral Maxillofac Implants.* 2014;29(6):1354–1363.
46. Miyamoto I, Funaki K, Yamauchi K, Kodama T, Takahashi T. Alveolar ridge reconstruction with titanium mesh and autogenous particulate bone graft: Computed tomography-based evaluations of augmented bone quality and quantity. *Clin Implant Dent Relat Res.* 2012;14(2):304–311.
47. Proussaefs P, Lozada J. Use of titanium mesh for staged localized alveolar ridge augmentation: Clinical and histologic-histomorphometric evaluation. *J Oral Implantol.* 2006;32(5):237–247.
48. Zaffe D, D'Avenia F. A novel bone scraper for intraoral harvesting: A device for filling small bone defects. *Clin Oral Implants Res.* 2007;18(4):525–533.
49. Yildirim M, Spiekermann H, Handt S, Edelhoff D. Maxillary sinus augmentation with the xenograft Bio-Oss and autogenous intraoral bone for qualitative improvement of the implant site: A histologic and histomorphometric clinical study in humans. *Int J Oral Maxillofac Implants.* 2001;16(1):23–33.
50. Poli PP, Beretta M, Cicciù M, Maiorana C. Alveolar ridge augmentation with titanium mesh. A retrospective clinical study. *Open Dent J.* 2014;8:148–158.
51. Shikinami Y, Matsusue Y, Nakamura T. The complete process of bioresorption and bone replacement using devices made of forged composites of raw hydroxyapatite particles/poly l-lactide (F-u-HA/PLLA). *Biomaterials.* 2005;26(27):5542–5551.
52. Matsuo A, Chiba H, Takahashi H, Toyoda J, Abukawa H. Clinical application of a custom-made bioresorbable raw particulate hydroxyapatite/poly-L-lactide mesh tray for mandibular reconstruction. *Odontology.* 2010;98(1):85–88.
53. Louis P, Holmes J, Fernandes R. Resorbable mesh as a containment system in reconstruction of the atrophic mandible fracture. *J Oral Maxillofac Surg.* 2004;62(6):719–723.
54. Lan Levensgood SK, Polak SJ, Poellmann MJ, et al. The effect of BMP-2 on micro- and macroscale osteointegration of biphasic calcium phosphate scaffolds with multiscale porosity. *Acta Biomater.* 2010;6(8):3283–3291.
55. Dominiak M, Gedrange T. New ways of reconstructing complex bone defects in the alveolar ridge. In: Dominiak M, Gedrange T, eds. *Esthetics in Implantology.* Wrocław: BF Remigiusz Dyrka; 2013;193–214.
56. Mangano F, Macchi A, Shibli JA, et al. Maxillary ridge augmentation with custom-made CAD/CAM scaffolds. A 1-year prospective study on 10 patients. *J Oral Implantol.* 2014;40(5):561–569.
57. Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. *Growth Factors.* 2004;22(4):233–241.
58. Spath S, Drescher P, Seitz H. Impact of particle size of ceramic granule blends on mechanical strength and porosity of 3D printed scaffolds. *Materials (Basel).* 2015;8(8):4720–4732.
59. Jansen JA, Vehof JW, Ruhe PQ, et al. Growth factor-loaded scaffolds for bone engineering. *J Control Release.* 2005;101(1–3):127–136.
60. Ruhe PQ, Hedberg EL, Padron NT, Spauwen PH, Jansen JA, Mikos AG. rhBMP-2 release from injectable poly(DL-lactic-co-glycolic acid)/calcium-phosphate cement composites. *J Bone Joint Surg Am.* 2003;85-A(Suppl 3):75–81.
61. Kramer FJ, Dempf R, Bremer B. *Clin Oral Implants Res.* 2005;16(1):80–88.