Bone Substitutes used in Implant Dentistry

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Introduction:

Bone is a dynamic organ with remarkable regenerative potential. The continuous cycle of bone formation and resorption is carried out by osteoblasts, osteocytes, and osteoclasts under the directive influence of the bone-signaling pathway.[1] In certain situations the host cycle of bone repair is inadequate and hence requires the assistance of biomimetic biomaterials which comprise bone grafts and their substitutes. Bone graft is a very popular transplantation tissue second only to blood. More than 2.2 million bone grafting procedures are undertaken worldwide to repair bone defects in relation to orthopedics, neurosurgery and dentistry. More than 60% of the population in industrialized countries need dental prosthetic replacements, ideally with implants and about 10-20% of the patients who need treatment with dental implants, require bone regeneration procedures before implant placement.[2]

Eighty percent of bone is made up of the outer, compact (cortical)bone, while 20% remaining is inner spongy (trabecular) bone.[3] Therefore, analyzing the content of compact bone will focus the therapy on healing the larger portion of the bone. Knowing that compact bone is 70%inorganic mineral (chiefly hydroxyapatite), 22% organic protein (collagen, cells, hyaluronic acid [HA]), and 8% water allows for bone graft design to focus on one compartment. (Fig 1)

History:

For centuries, the idea of replacing missing bone tissue has prevailed. During the 17th century, Dutch surgeon Job Van Meekeren reported the first incident in bone grafting where a piece of bone was harvested from a dog's skull to repair a cranial defect in a soldier.[4] Gradually, studies were conducted on bone grafting and in the year 1821 in Germany, the very first autograft was used. Later in 1881, MacEwen restored ahumeral defect with an allograft harvested from tibia. In 1991, the first commercial demineralized bone matrix was made available.

Need for bone substitutes:

After tooth extraction an average alveolar bone loss of 1.5–2 mm (vertical) and 40%–50% (horizontal) occurs within 6 months. Most of alveolar dimensional changes occur during the first 3 months. If no treatment to restore the dentition is provided, then continued bone loss occurs and up to 40%–60% of ridge volume is lost in first 3 years. The loss of vertical bone height leads to great challenges to dental implant placement due to surgical difficulties and anatomical limitations. This lack of sufficient bone volume and height if unresolved

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eventually proves to be detrimental to the final treatment outcome with respect to implant success and survival. Hence there is need for bone substitute.

Selection criteria:

Selection criteria may be studied from two aspects: biomaterial properties and patient-related factors[5]

Fundamental considerations on bone substitutes:

There are four main characteristics considered ideal in bone regeneration

- osteogenesis or osteogenic activity (ability of bone formation from viable osteoblasts or pre-osteoblasts derived from the graft donor area, that are capable of generating cellular proliferation and producing new bone).
- osteoconduction (the capacity of the graft for support or allow cell migration, formation of blood vessels and the bone growth in surface).
- osteoinductivity (refers to the ability of a graft to induce nondifferentiated stem cells or osteoprogenitor cells to differentiate into osteoblasts).
- osseointegration, (refers to contact between the bone and implant without intervening fibrous tissue)

It is fundamental that a bone substitute should present at least one of the characteristics described above and only autogenous bone presents them all. Other characteristics considered ideal include: the remodeling of the bone initially formed in mature lamellar bone, ability to stabilize implants when installed simultaneously to the grafting procedure, low risk of infection, good availability, low antigenicity and physiologically stable, not cause rejection and be ideally be absorbed after the regeneration.[6,7]

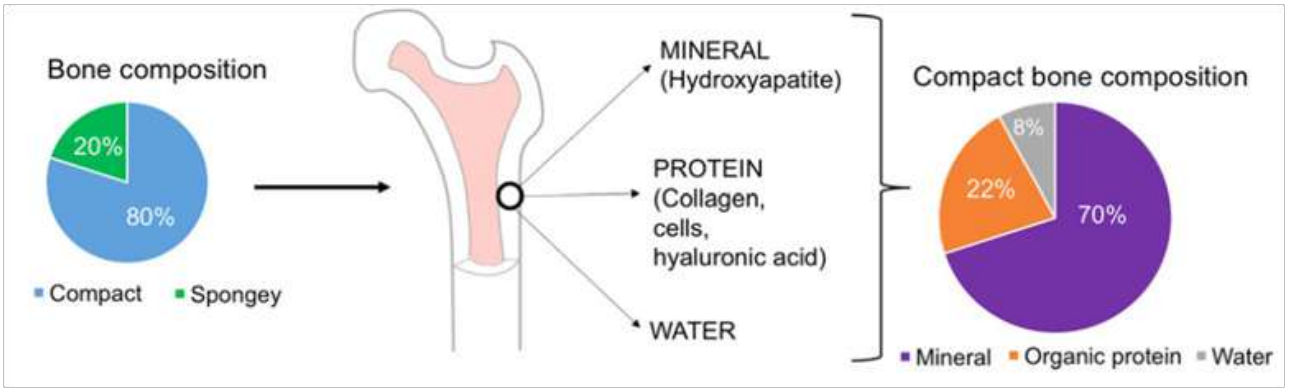


Fig 1. Schematic representation showing composition of bone and further evaluation of cortical bone

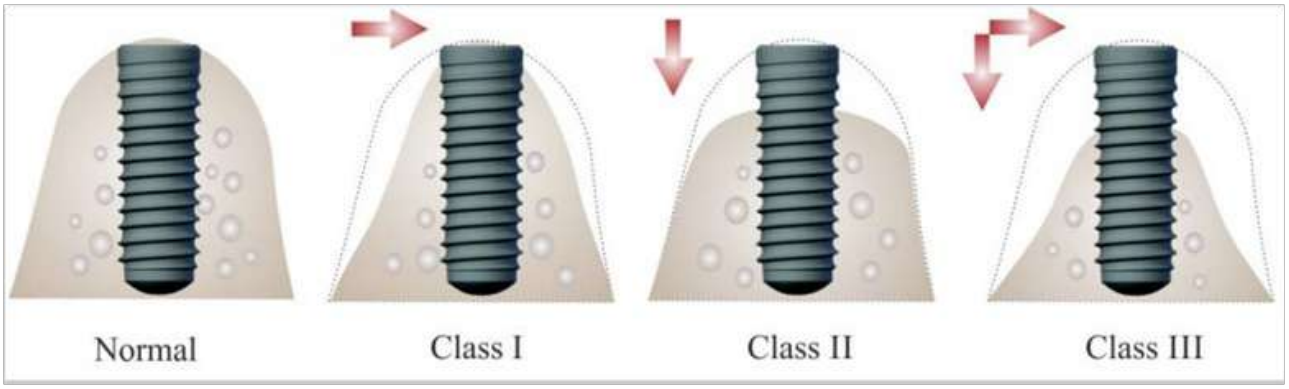


Fig2. Bone volume insufficiency for implant placement. In Siebert class I ridge defects there is horizontal bone loss with adequate height, which leads to insufficient bone volume for successful placement of regular diameter implants. In class II there is vertical bone loss with adequate width, which leads to insufficient bone volume for proper positioning of regular length implants in correct prosthetic corono-apical position. In class III there is vertical and horizontal bone loss that prevents placement of successful implants in all spatial dimensions.

Biomaterials used for bone regeneration in implant dentistry:

Autograft:

Autograft is a bone tissue that is separated from one site and implanted in other location in the same individual. They offer a wide pool of growth factors that induce mesenchymal stem cells to differentiate into osteogenic progenitor cells and are subdivided in two groups:

1. Cancellous autografts.
2. Cortical autografts.

Cancellous autografts are retrieved mainly from cancellous bone and upon transplantation, the majority of cells present in the grafts die as result of ischemia.

Table 1. Selection criteria and contributing factors for bone graft application

Patient aspect	Biomaterial aspect
•Age •General health •Size and anatomical site of the defect •Functional load at defect •Purpose of application •Patient cooperation •Financial issue	•Biomimetic materials •Chemica lnature •Physical properties •Chemical properties •Mechanical properties •Biodegradation rate •Osteoconductuve / osteoinductive •Availability •Cost

Table 2.Bone graft and bone graft substitutes[8]

Class	Grafting material	Properties of action
Autograft based	Cortical and cancellous autologous graft	Osteoconductive Osteoinductive Osteogenic
Allograft based	Fresh allograft Frozen allograft Frozen-dried allograft Graft	Osteoconductive Osteoinductive
Growth factor based	BMP and other growth factors TGF-β, PDGF, FGF, BMP	Both osteoconductive and osteoinductive with carrier materials Platelet-rich plasma (PRP) or autologous platelet concentrate
Cell based	Stem cells Collagen Gene	Osteogenic Both osteoconductive and osteoinductive with carrier materials
Ceramic based	Calciumhydroxyapetite(HA) Tricalcium phosphate Bioactive glass Calcium sulfate	Osteoconductive Limited osteoconductive when mixed with bone marrow
Polymer based	Natural or synthetic polymers Degradable or non-degradable polymers	Osteoconductive Limited osteoconductive when mixed with bone marrow

However, the mesenchymal stem cells present in the bone marrow are resistant to ischemia and may survive the grafting procedure.[2] The stem cells capacity of survival and proliferation after exposure to changes in the oxygen tension, pH and cytochine environment are the main reason behind the reliability of cancellous bone autograft interventions.

Cortical autografts are segments of cortical bone composed of necrotic bone that provides an osteoconductive support for bone formation, but does not supply significant amounts of living cells. For this reason, revascularization and integration of cortical autografts is slow. The main advantage of cortical autografts is the mechanical support that it provides at the graft site.

Autogenous bone transplants are very osteogenic and are the best according to all theoretical bone regeneration requirements. However, there are some disadvantages:

1. Need for second surgical procedure to obtain the graft
2. Donor site morbidity
3. Need for general anesthesia to obtain extra-oral donor sites

Other disadvantages include occurrence of bleeding, infections, neuralgias, edema, infection, and hematoma and it is time-consuming

Allografts:

Allograft is defined as tissue that has been harvested from one individual and implanted into another individual of the same species. These are best available alternative to autografts due its similar characteristics. Despite the superior properties of autografts, they are

Table 3.Carranza (1999) classification of bone graft materials[9]

Autogenous bone		Allograft	Xenograft	Non bone graft material	Alloplast
Bone from intraoral site-Osseous coagulum, Bone blend Intraoral cancellous bone marrow transplant Bone swaging	Bone from Extraoral sites Iliac crest Tibia	Freeze dried Decalcified freeze Dried bone allograft	Calf bone Kiel bone Anorganic bone	Sclera Cartilage Plaster of paris Calcium phosphate Biomaterials Hydroxyl apatite Tricalcium	Porous hydroxyapatite Non - porous hydroxyapatite HTR polymer Beta tricalcium phosphate Bio-active glass ceramics

Table 4. Summary of bone autograft properties as a function of their anatomical origin

Bone graft	Origin	Availability	Reabsorption	Graft form
Extraoral autograft				
Calvaria	IM	+++	++	Block/particulate
Iliac crest	EC	+++	+++	Block/particulate
Tibia	EC	+++	+++	Particulate
Intraoral autograft				
Ramus	IM	++	++	Block
Symphisis	IM	+	++	Block/particulate
tuberosity	IM	+	+++	Particulate

IM:Intramembranous bone, EC: Endochondral bone

usually preferred by patients as bone grafting material because of the problems associated to donor site surgery in autografts.

Types: Allografts are obtained from cadaver tissue banks for mineralized freeze-dried (FDBA) or decalcified freeze-dried (DFDBA) bone. Both FDBA and DFDBA are obtained from cortical bone of long bones due to its high content of bone inductive proteins and less antigenic activity than cancellous bone

Available forms: Powder, cortical chips, cancellous cubes, and cortical granules. The granulated form is obtained by milling the cortical bone under sterile conditions to obtain a particle size ranging from 250µm to 750µm. Milled forms present an open structure that facilitate invasion by blood cells, enhance graft incorporation and allows mixing with blood, platelet concentrates and other graft materials forming composites.

They are processed through several methods including physical debridement to remove soft tissue and reduced cellular load, ultrasonic washing to remove remnant cells and blood, ethanol treatment in order to denaturalize proteins and viral deactivation, antibiotic wash to kill bacteria, and sterilization through gamma-radiation and ethylene oxide for spore elimination.

FDBA: Mineralized bone matrix has no active bone morphogenetic proteins (BMPs) and therefore it lacks osteoinductive properties, Graft incorporation is qualitatively similar to autograft, but occur more slowly.

DFDBA: These are processed by acid demineralization in 0.5 to 0.6 molar hydrochloric acid. As a result, 40% of the mineral content is removed leaving the organicmatrix intact. This process preserves the BMPs present in bone, and therefore maintains some of the inherent osteoinductive properties. Moreover, the collagen matrix present in DFDBA acts as a scaffold that provides osteoconductive properties apart from the osteoinductive behavior

Xenografts:

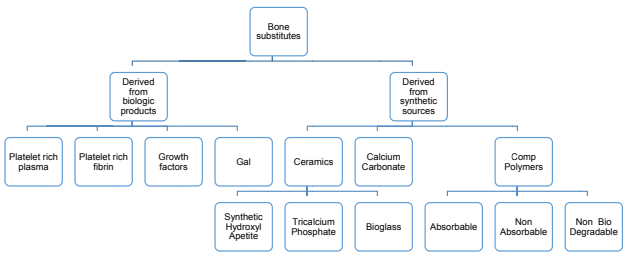
Xenograft transplants are taken from other species individuals than the recipient. Typically transplanted materials are natural hydroxyapetite and deorganated bovine bone. These grafts have excellent osteoconductive properties. Xenograft is a bone substitute material derived from deprotienized bone marrow with the hydroxyapetite structure of the highly porous bone similar to cortical bone of human species. The organic component is chemically and thermally treated. These grafts have pore system with a particle size of 0.25-1mm that can be easily invaded by blood vessels resulting in osteoblastic migration the structure consists of a wide interconnections.[10] The procedure of processing this may vary and some grafts are treated at high temperature while others are treated at low temperature. Xenogenous transplant treated at low temperature (300°C) after post transplantation will be fully integrated into human bone tissue,therefore it is called as most physiological transplant.

Limitations:

- Higher risk of recipient's immunologic reaction
- Possible migration
- Resorption is slow
- Risk of infection

Bone substitutes

To avoid all the limitations presented with various bone grafts,the use of synthetic bone substitutes are being increasing popular.



Bone substitutes derived from biological products:

Platelet rich plasma (PRP): Platelet-rich plasma (PRP) is generally used as a gel that is easily obtained with the patient's blood. Blood is centrifuged through gradient density, and the resulting blood platelets are mixed with thrombin and calcium chloride. Hence, PRP includes an important concentration of platelets and fibrinogen, as well as growth factors such as platelet derived growth factors, vascular endothelial growth factor (VEGF), IGF and TGF. PRP is expected to show pro-coagulant effects due to platelets; however, there is no evidence in the literature of benefits for the addition of PRP to accelerate bone healing.[11] Even if PRP shows limited infectious risks and adverse effects by its origin (autologous

blood),it does not present any mechanical resistance and is not validated as a stand-alone bone substitute. PRP is rather used as a supplement to other materials.

Platelet Rich Fibrin:

Platelet Rich Fibrin (PRF) is a quite modern platelet concentrate. It is achieved with a simplified preparation, with no biochemical manipulation of blood. This technique does not require anticoagulants or bovine thrombin (or any other gelling agent).This feature make this product easily usable with a low rate of mistakes during the preparation stage

Growth factors:

Among various growth factors widely used, BMP (Bone Morphogenic Proteins) requires special mention as Bone morphogenetic proteins (BMPs) are osteoinductive growth factors included in the transforming growth factor β (TGF-β) super family. They are produced by osteoblasts and are largely involved in the skeletogenic process enabling ectopic bone formation. BMP play a role in the recruitment of osteoprogenitor cells in bone formation sites. Genetic engineering allows to synthetize recombinant human BMP (rhBMP-2 and rhBMP-7), [12] which can be produced in large quantities and limit risks of contamination. rhBMP-2 and rhBMP-7 are allowed by the Food and Drug Administration (FDA) for clinical use. Other growth factors apart from BMP include:

1. Platelet derived growth factor
2. Transforming growth factor-β
3. Insulin-like growth factor (1)
4. Vascular endothelial growth factor
5. Fibroblast growth factor.

Thus, due to the variability of the needed dosage which is patient- and site-dependant, the use of BMP is still surrounded by a blur. Moreover, BMPs require molecular carriers to deliver and maintain them at their intended osseous targets, their mechanical properties are not biomimetic of the native bone tissue, and their high cost makes their use prohibitive in most settings.

Hydroxyapatite:

Hydroxyapatite (HA) is part of the apatites family, which are crystalline compounds with crystalline hexagonal lattice. HA has the specific formula (Ca10 (PO4)6(OH)2) and is the primary mineral component of teeth and bones.[13,14,15] Thus, HA is extremely biocompatible and does not promote an inflammatory response. Natural HA is porous with a various porosity depending on the bone site that is extracted (for example 65% porosity and pores from 100 to 200 μm for trabecular bone), which allows osteoconductive properties. Indeed, HA resorption is very slow and the material is usually maintained atleast up to 3 years after implantation,allowing a slow bone in growth progress and cell colonization.. Some composite materials containing HA and collagen exist as well, and their combination enhances osteoblasts differentiation and accelerates osteogenesis. HA-collagen composites have some mechanical advantages over HA used alone.

Coral:

Corals have interconnected pores and a skeleton quite similar to cortical and spongy bones, and their use as bone substitute has been approved by the FDA in 1992. Coral-based substitutes are mainly calcium carbonate that can be transformed industrially into HA, or they can retain their original state which allows a better resorption by the natural bone. Coralline HA can be used as growth factors carrier, such as BMP, TGF-β, or FGF. It can be found in different forms like granules or blocks. Despite its slow resorption, it does not induce adverse effects like inflammatory responses.[16] Coralline HA is osteoconductive and can show an excellent bone-bonding capacity, avoids donor site morbidities, and is unlikely to promote disease transmissions or risks of deep infections.

Bone substitutes derived from synthetic sources:

Ceramics

- Synthetic calcium hydroxyapetite:

Primary inorganic natural bone. The ratio of calcium to phosphorous:10:6

Chemical features depend upon calcium and phosphorous ratio,recipient area,pH. The solubility depends upon crystal structure and porosity affects the blood permeability and vessels in growth into transplant. 250-350 micrometer porosity is ideal for bone in growth.

- Tricalcium phosphate :

TCP is chemically similar to HA.[17] The ratio of Ca and P:3:2. The speed of resorption depends on material

chemical structure. TCP have 2 phases:

- Alfa phase
- Beta phase

When TCP is heated to 900ºC, beta phase is produced which is fully resorbable and is transformed to natural bone after 8-12 months and when heated higher than 1180 degrees : alpha is produced (less recommended in clinical practice).

TCP is used in places without any inflammation and best results are produced when combined with autogenous bone.

- Bioactive glass:

It comprises of calcium salts, phosphate, sodium salts and silicon. The size of pellets varies from 90 – 710 μm with the mean of 300 – 355 μm.[18] At the junction of bone and transplant the collagen layer with the mean thickness of 0.3 μm appears which is similar to natural periodontal ligament according to dimensions.

- Calcium carbonate:

Inorganic material which is composed of aragonite (more than 98% CaCO3) which is porous more than 45%.The mean porosity size is about 150 μm. The material is slowly resorbable. Calcium carbonate transplants show better hemostasis features and are prone to keeping the position and don't migrate from recipient zone. The main limitation of this material is fragility.

- Composite polymers:

Absorbable

- Synthetic absorbable polymers are well known in medical practice. Many years before suture materials, fixation screws and other products were manufactured from polilacetate and polyglycolic acids. Most polymers are high molecular mass compounds with slow resorption (~3y). The final decomposition products of these materials are carbon dioxide and water. Polymer's biologic decomposition depends on many factors: patient's age, immune system, tissue tolerance, localization of the defects and surface configuration. Slow density polilactate and polyglycolic acidic copolymers are decomposed in 3-8 months. They can be found in three different forms; powder, gel and sponge, which can be combined with each other to allow the reconstruction of different defects. Powders are used in three walls defects, sponges – in two and three walls bone defects. These materials are mixed with saline water or patient's blood and are formed with a sharp instrument before the insertion into the bone defects. The gel is used in deep bone defects reconstruction. Small transplant's mass and wide surface allow easy fibroblasts penetration and absorption initiation as well as cells colonization. It is easy to work with this material, however usually GTR membranes should be used with these materials.

Non-absorbable:

Non-absorbable composite polymers are the compounds of polymethylmethacrylate (PMMA), polihydroxyethilmethacrylate (PHEMA), small amounts of barium sulphate (roentgenocontrastic) and calcium hydroxide, which directly interact with recipient's bone, creating CaCO3 appetites. PMMA is a synthetic polymer, which is used in medical practice for long time. Intraocular lenses, artificial heart valves, etc. are produced from this material. A primary internal layer of this transplant is covered with hydrophilic PHEMA polymer. PHEMA has unique hollow spherical structure. It lets the bone tissue to in grow into the material and around the material. After the healing, only 10-12% of the reconstructed defect is composed of this material and 88-90% is newly formed bone. Synergic action of compounds' materials determines unique features. The main feature – negative electric charge of the surface (-10mV). It was found that negative electric charge of surface ease and improve the healing and formation of the bone. Even though this material does not have bacteriostatic or bactericidal features, bacteria hardly colonize the surface, because of the transplant, same as the bacteria, have negative electric charge of the surface, which results in the inflammation prevention effect. The negative charge also provide material adhesion to recipient's bone surface, which has positive electric charge, it attracts the pluripotentive stem cells, which transform into osteoblasts, it gives better adhesion to metals, which improves osteointegration. This transplant does not migrate to surrounding structures after the augmentation and does not have to be covered with GTR membranes.

Nano composite based biodegradable polymer:

The inclusion of nanoparticles into the biopolymer matrix has the dual objective of improving the mechanical properties as well as incorporating Nano topographic features that mimic the nanostructure of natural bone.[19]

Recent advances

Bone tissue engineering:

The complex biology behind the nanostructure and microstructure of bones and their repair mechanisms, which involve various types of chemical and biome-

TABLE 3.Examples of commercially available graft biomaterials and their detailed properties

Name	Biodegradation	Phase	Crystal-linity	Physical properties	Mechanical
Bioresorb®	99% β-TCP, traces of α-TCP and calcium pyrophosphate	Moderate	High	Porous granule (particle size: 0.5–2 mm	Low
Chronos®	99% β-TCP, traces of α-TCP and HA	Moderate	High	Porous granule (particle size of 0.5– 1.4 mm and pore sizes of 100–500 µm; 60% pore volume)	Low
Ceros®	99% β-TCP, traces of α-TCP and HA	Moderate	High	Porous granule (particle size of 0.5– 1.4 mm and pore sizes of 100–500 µm; 60% pore volume)	Low
Cerasorb®	100% β-TCP	Moderate	High	Porous granule (pore size>5 µm, particle size 0.05– 2mm *Macroporous block	Low High
Vitoss®	98.8% β-TCP, traces of calcium pyrophosphate, and 1.2 % organic bone matrix	Moderate	High	Porous granule (pore size 10–1000 µm; porosity 90%; particle size 3–5 mm)	Low
PepGen®	100% HA coated with a P-15	Slow	High	Porous granule (particle size of 0.25–0.42 mm)	Low
Endobon® Cerabones®	100% HA, traces of calcium oxide	Slow	High	Porous block (pore size 1mm porosity 50%)	High
Algipore®	95% HA, 2.4% organic matrix, 2.3 % CaCO3	Moderate	Moderate	Porous granule (particle sizes of 0.3– 2mm, pores of 5–10 mm	Low
Ostims®	59.6% nanoHA dispersed in 40% H2O	Fast	Nano	Fluid paste with nanoscale apatite particles	None
BioOss® 3	3% H2O, 3.4% CaCO3, 93.6% carbonated HA ± 10% collagen	Fast	Nano	Porous granule (granule size of 0.25–2 mm), *Cancellous bone block (1x1x2 cm)	Low
Tutoplast® *	Bovine= 9% H2O, 26% organic matrix, 8%CaCO3, 57% HA. *Human= 9.5% H2O, 34% organic matrix, 7.5% CaCO3, 49% HA	Fast	Nano	*Porous block/cylinder (pore size >100 µm) *Granulate (particle size 0.25–2 mm)	High

Evidence based results: (20)

Reference	Study design	Number of patients	Graft materials	Number of implants	Timing of implant placement	Follow up implant survival (%)	Implant success (%)
JoseLuis CebrianCarretero	Case series	4	Fibula, iliac crest and scapula free flaps	19	6-12 months after reconstruction	100	100
Balaji SM	Case report	1	BMP rhBMP2	6	No data	100	100
Emir Yuzbaşıoğlu	Case report	1	Iliac bone graft	3	4 years 6 months after reconstruction	No data	No data
Kristian Rude	Case report	1	Free vascularized fibula flap	5	Oral rehabilitation was carried out 12 months Post-operatively	100	100
Hisahiro Kamoi	Case report	1	Rib bone	5	Dented implants inserted simultaneously during surgery	100	100
Po-Sung Fu	Case report	1	Autogenous bone harvested from the chin	1	4 months after socket augmentation	100	100
Pedro Infante Cossio	Case report	1	Composite bone graft of autogenous bone, xenograft, and autologous PRP	2	24 months after augmentation	100	100
Hideshi Sekine	Case report	1	Iliac bone block and PCBM	5	On the right side, two Implants were placed 4 months after bone grafting. On the left side, three implants were placed simultaneously after bone grafting	100	100
		1					
Masako Sawaki, et al	Case report	1	A PCBM graft and RBOG	2	5 months after bone grafting	100	100
Juliano de Alenear Vasconcelos, et al.	Case report	1	Bone tissue collected during the osteotomies and drilling processes	2	Bone graft placed at the same time of implant placement	100	100
Dr. Eugenio Miguel Pereira	Case series	1	Fresh-frozen bone allograft from the iliac crest	8	5 months after grafting	100	100
Francesco Grecchi	Case report	1	Femur homografts	12	8 weeks after grafting	100	100

Gui-Youn Cho-Lee	Case report	1	Free vascular-ized fibular flap	3	Implants placed after 3 months	100	100
Pedro Infan-te-Cossio	Case report	1	Iliac crest graft	3	6 months and 2 weeks after grafting	100	100
Po-Sung Fu	Case report	1	Chin graft	1	Implant placed after 4 months of grafting		
Dr. Gregory taylor	Case report	1	Ramus graft	1	Implant placed after 6 months of grafting		
Mario Santa-gata1	Case series	11	Particulate bone graft				
Jee-Won Moon	Case report	1	Bovine bone, mixed with fibrin adhesive	3	Placed immediately		
Mi-Ra Ahn	Case series	11	Irradiated can-cellous bone and mar-row	27	Placed after 5 months	99	97.5
Devorah Schwartz-Arad	Retrospec-tive study	214	Autologous Intraoral block OBG augmentations, combined with Bio-Oss mixed with PRP, and cov-ered by PPP - as scaf-fold	633	4-6 months	93.4	83
Thomas J. Balshi	Case report	1	Iliac crest bone graft	2	Implants placed subsequently	50	0
Matteo Chiapasco	Case series	3	Iliac crest	22	5-6 months	100	100
Eduardo Anitua	RCT	23	PDG and TGF-β		Placed immediately	100	100

Michael Peleg	RCT	63	Autogenous composite bone graft consisting of combination of 50% membranous bone harvested from the symphysis and 50% DFDBA	160	Placed immediately	100	100
Ji-Min Kim	Case series	63	Fibrin-rich block with concentrated growth factors	74	After 5 months	100	98.6
Gerry M. Raghoebar	Case series	14	Zygomatic rim	14	No data	100	100
Stefan Lundgren	Case series	11	Bone flap	21	Placed immediately	98.7	100
Mats Sjostrom	Case series	29	Free iliac crest grafts	192	6-8 months after grafting	90	61.8
Federico Hernandez-Alfaro	Case series	14	Mandibular bone block graft and biomaterials	108	14-16 weeks after grafting	88.4	77.99
DongSeok Sohn	Case series	53	Fibrinrich blocks with CGF	113	Placed simultaneously	99	98.2
JeeWon Moon	Case series	14	Peripheral venous blood	31	Placed simultaneously	95.1	93.5

CGF: Concentrated growth factor, DFDBA: Demineralized freeze-dried bone allograft, PDGF: Platelet-derived growth factor, TGF-β: Transforming growth factor-β, rhBMP2: Recombinant human bone morphogenetic protein-2, PCBM: Particulate cancellous bone and marrow, RBOG: Ramus bone onlay grafting, OBG: Onlay bone graft, PPP: Platelet-poor plasma, RCT: Randomized controlled trials, PRP: Platelet-rich plasma, BMP: Bone morphogenetic protein

chanical signaling amongst different cells, has set strong requirements for biomaterials to be used in bone tissue engineering. When considering for bone tissue engineering, it is important to recognize that bone is load-bearing tissue and the extent of bone mineral

Density is load dependent. Compressive loading of engineered construct significantly increases the synthesis of mineralized organic matrix. Tissue engineering may be used to regenerate bone by combining cells from the body with growth factors and scaffold cells from the body with growth factors and scaffold biomaterials. This combination of cells, signaling molecules and scaffold is often referred to as the tissue engineering triad. Hydrogels are desirable scaffold materials for bone tissue engineering due to their high water content, cytocompatibility, and mechanical properties to resemble natural tissues.[22,23,24] Cell-laden hydrogels have been used for tissue engineering of bone, muscle, cartilage,and other tissues. By adding cells into a hydrogel precursor prior to gelling process, cells can be distributed homogeneously within the hydrogel scaffold. In general, hydrogels from natural sources are derived from polymers such as collagen,gelatin, keratin, hyaluronic acid, fibrin, alginate, agarose, chitosan, or synthetic hydrogels such as Poloxamer, polyethylene glycol, or combination of natural and synthetic hydrogels such as gelatin.

Gene therapy

Gene therapy resembles the genetic information transferring to desired target cells, which results in a secure and efficient biological effectiveness leading to the rapid recovery of bone healing. It also adapts for distribution of growth factors in tissue Engineering delivered nucleicacids can induce specific osteogenic growth factors

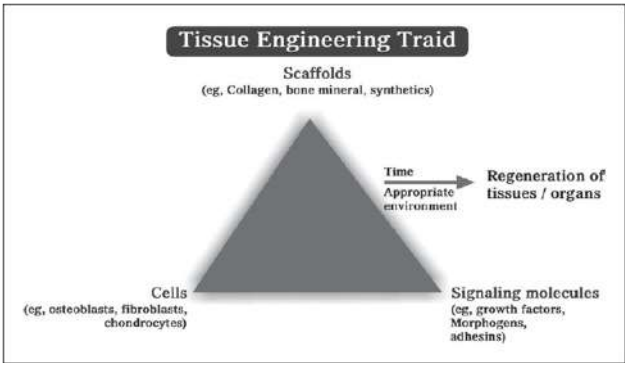


Figure 3: Tissue engineering triad that includes cells, scaffolds, and signalling molecules. This triad is essential for regeneration

Bio – printing / 3d printing of bone:

3D printers can print bone tissue tailored to the requirements of the patient and can act as biomimetic scaffolds for bone cell enhancement and tissue growth and differentiation in bone regeneration procedures 3D printed alginate peptide hybrid scaffolds provide a stable environment for growth of stem cells.[25] Also composite powders can be printed into scaffolds. Calcium phosphate powders mixed with 3d printing powder based on Calcium sulphate can also be used as bone augmentation material.

Conclusion

The extensive need for the bone grafts has resulted in the introduction of a number of materials with varied applications.

Both natural and synthetic materials have found favourable results in obtaining bone augmentation[26]. No singular technique or graft material can claim unconditional success in ridge reconstruction Both treatment protocols and Biomaterials require constant revisions to adapt to challenging situations that arise at a faster pace.

References

1. Fillingham Y, Jacobs J. Bone grafts and their substitutes. The bone & joint journal. 2016 Jan; 98(1_Supple_A): 6-9.
2. Torres J, Tamimi F, Alkhraisat M, Prados-Frutos JC, Lopez-Cabarcos E. Bone substitutes. InImplant dentistry-the most promising discipline of dentistry 2011. InTech.
3. Brett E, Flacco J, Blackshear C, Longaker MT, Wan DC. Biomimetics of bone implants: the regenerative road. BioResearch open access. 2017 Jan 1; 6(1):1-6.
4. Rodriguez R, f Hartmann N, Weingart D. Current concepts of bone regeneration in implant dentistry. J Surg 2015; 10:227-8.
5. Ebrahimi M. Bone Grafting Substitutes in Dentistry: General Criteria for Proper Selection and Successful Application.Iosr-Jdms.2017;16(4):75-79
6. Kumar J, Jain V, Kishore S, Pal H. Journey of Bone Graft Materials in Periodontal Therapy: A Chronological Review. J Dent Allied Sei. 2016; 5:30-4.
7. Cardoso CL, Curra C, Santos PL, Rodrigues MF, Ferreira-Júnior O, de Carvalho PS. Current considerations on bone substitutes in maxillary sinus lifting. Revista Clínica de Periodoncia, Implantología y Rehabilitación Oral. 2016 Aug 1; 9(2):102-7.
8. Hasan A, Byambaa B, Morshed M, Cheikh MI, Shakoor RA, Mustafy T, Marei H. Advances in osteobiologic materials for bone substitutes. Journal of Tissue Engineering and Regenerative Medicine. 2018 Apr 27.
9. Carranaza FA, Newman MG. Reconstructive Osseous Surgery.

In: Clinical Periodontology. Philadelphia, USA: WB Saunders Company. 1999; 8:622-39.
10. Raghavan R, Shajahan PA, Raj JS, Reini Raju MV, Jishnu S. Review on recent advancements of bone regeneration in dental implantology.International journal of applied dental sciences 2018;4(2):161-163
11. Andrius Geguzis, Inesa Astramskaite, Dovile Gabseviciute. Bone Substitute Materials in Modern Dentistry. International Annals of Medicine. 2017; 1(4).
12 .Teresa M, Kamakshi V. Bone Grafts and Bone Substitutes. Int J Pharm Pharm Sci, Vol 6, Suppl 2, 88-91
13 .Kim CS, Kim JI, Kim J, et al. Ectopic bone formation associated with recombinant human bone morphogenetic proteins-2 using absorbable collagen sponge and beta tricalcium phosphate as carriers. Biomaterials 2005;26:2501–2507
14 .Engelke WG, Diederichs CG, Jacobs HG, Deckwer I Alveolar reconstruction with splitting osteotomy and microfixation of implants. Int J Oral MaxillofacImplants. 1997; 12:310-318.
15 .Roberts TT and Rosenbaum AJ. Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing Organogenesis 2012; 8(4): 114–124.
16 .Finkemeier CG. Bone-grafting and bone-graft substitutes.J Bone Joint Surg Am 2002; 84-A: 454–464.
17 .Kattimani et al. Hydroxyapatite—Past, Present, and Future in Bone Regeneration. Bone and Tissue Regeneration Insights 2016:7 9–19
18 .Saikia KC, Bhattacharya TD, Bhuyan SK, et al. Calcium phosphate ceramics as bone graft substitutes in filling bone tumor defects. Indian J Orthop 2008; 42(2): 169–172.
19 Fernandez de Grado G, Keller L, Idoux-Gillet Y, Wagner Q, Musset AM, Benkirane-Jessel N, Bornert F, Offner D. Bone substitutes: a review of their characteristics, clinical use, and perspectives for large bone defects management. sw Journal of tissue engineering. 2018 Jun 2; 9: 1–18.
20 .Elakkiya S, Ramesh AS, Prabhu K. Systematic analysis on the efficacy of bone enhancement methods used for success in dental implants. The Journal of Indian Prosthodontic Society. 2017 Jul 1; 17(3):219.
21 .Mygind T, Stiehler M, Baatrup A, et al. Mesenchymal stem cell ingrowth and differentiation on coralline hydroxyapatite scaffolds. Biomaterials. 2007; 28:1036–1047
22 .Christopherson GT, Nesti LJ. Stem cell applications in military medicine. Stem cell research & therapy. 2011 Dec;2(5):40
23 .Anderson JM. The future of biomedical materials. J MaterSci Mater Med 2006;17:1025–1028
24 .Gurtner GC, Callaghan MJ, Longaker MT. Progress and potential for regenerative medicine. Annu. Rev. Med. 2007 Feb 18;58:299-312.
25 .Heo EY, Ko NR, Bae MS, Lee SJ, Choi BJ, Kim JH, Kim HK, Park SA, Kwon IK. Novel 3D printed alginate–BFP1 hybrid scaffolds for enhanced bone regeneration. Journal of Industrial and Engineering Chemistry. 2017 Jan 25; 45:61-7.
26 .Sheikh Z, Sima C, Glogauer M. Bone replacement materials and techniques used for achieving vertical alveolar bone augmentation. Materials. 2015 May 27; 8(6):2953-93.