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Review Article

Complications in bone regeneration: A dental and orthopedic surgery comparison

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Abstract

Objectives: *Bone is a regenerative tissue, yet healing may fail after trauma, surgery, or atrophy. Regenerative methods restore bone but still pose complications. This study analyzes complication types, causes, and frequencies, emphasizing materials, membrane characteristics, and clinical indications.*

Methods: *This narrative review synthesizes clinical studies, trials, and systematic reviews on bone regeneration. The focus lies on guided bone regeneration in oral/maxillofacial surgery and grafting techniques in orthopedic procedures. Data were categorized based on material type, indication, and complication type, referencing studies with documented patient outcomes.*

Results: Dental Surgery: *Major complications include wound dehiscence, membrane exposure, and infection. Complication rates vary between 15% to 40%, strongly influenced by membrane type and degradation rate. Non-resorbable membranes show higher infection risks upon exposure but are preferred for large/vertical defects. Uncross-linked resorbable collagen and synthetic degradable membranes demonstrate better outcomes post-exposure.* ***Orthopedic Surgery:*** *Key complications include infection, fracture, non-union, and graft failure. Autografts have the highest complication rates due to donor site morbidity. Allografts pose moderate risks including infection and rejection. Synthetic bone substitutes show lower complication rates, particularly in spine surgeries.*

Conclusion: *The clinical success of bone regeneration depends largely on material selection tailored to the anatomical and pathological context. In dental surgery, membrane characteristics dictate infection risks, while in orthopedics, the graft type and surgical indication are more decisive. Synthetic membranes and bone substitutes with tailored degradation rates and biomechanical properties offer promising avenues to reduce complication rates and improve clinical outcomes.*

Keywords: *Bone Regeneration, Dentistry, Oral Surgery, Orthopedic Procedures.*

INTRODUCTION

Skeleton represents the architecture of the body and is composed of 213 individual bones. Bone is a metabolic and living connective tissue that fulfill numerous functions. Indeed, it provides protection of crucial organs, enables movements, regulates homeostasis and is a reservoir for ions and minerals to be dispatched throughout the body when needed. The inorganic bone matrix represents 99% of the body storage of calcium, 85 percent of the phosphorous, and 40 to 60 percent of the magnesium and sodium stores. [1, 2]

The general structure of bone can be summarized as cancellous bone surrounded by mineralized cortical bone. Although they both have the same structure, they differ in bone density, metabolic activity and 3-dimensional structure. These parameters differ depending on the type of bone and also on its function.

In adult body, cortical bone represents 80% and only 20% for cancellous bone, however this last one shows the major part of the metabolic activity. Bones are composed of about 90% of bone matrix and 10% of cells. The bone matrix is composed of 4 components: i) inorganic architecture (65%), ii) organic matrix (20%), iii) lipids and iv) water (<15%).

The inorganic architecture is formed of hydroxyapatite and is responsible of the mechanical properties of the bones (stiffness, bone strength and resistance to compression). The organic matrix is produced by the osteoblasts and is mainly composed of type 1 collagen. It also contains proteoglycans, glycoproteins and growth factors (e.g. BMP and TGF). [2] These components play important roles in term of mineralization, remodeling and osteogenesis and give to the bone the resistance to shear and tensile forces.

Within the architectural bone matrix, several cells can be found. They come from 2 cell lineages: i) the osteoprogenitors and osteoblasts come from mesenchymal stem cells lineage and ii) the osteoclasts from hematopoietic lineage. [2, 3]

The osteoprogenitor cells remain undifferentiated until they receive signals to migrate, proliferate and differentiate into osteoblasts. The osteoblasts are packed together and cover the bone surface. They are responsible of the synthesis and secretion of the organic matrix and their activity can follow by monitoring the alkaline phosphatase release. Once activated, the osteoblasts can become quiescent osteoblast lining cells, return as osteoprogenitor cells or become osteocytes. The osteocytes are osteoblasts surrounded by bone matrix. They develop filaments to get contact with the surrounding areas to control the bone physiology (bone synthesis and degradation) and to control the calcium homeostasis. Osteoclasts, bone resorbing cells, can also be found within the bone matrix. They are large and multinucleated cells which can be found in the Howship lacunae. They are attached onto collagen brush and resorb the bone matrix by solubilization via acidification.

Throughout all these properties, bone tissue has demonstrated its crucial role and also its properties for resorption, osteogenesis and consequently for self-healing. Bone regeneration is a well-organized process involving biological and physiological events of osteoconduction and osteoinduction with the recruitment of bone cell lines via the molecular activation pathways. Unlike the other tissues, the majority of bone injuries heals without scare formation and reach the ad integrum formation of new bone. However, in many cases, the healing process is not sufficient to regenerate the bone defect. Moreover, there are numerous other conditions, in orthopedic, oral and maxillofacial surgeries, in which bone regeneration techniques should be applied to help the bone regeneration such as large bone defects created by trauma, infection, tumour resection, skeletal abnormalities and oral bone resorption. For all these situations there are numerous materials and techniques to be used to help the bone regeneration including distraction osteogenesis and the use of several bone grafting techniques. Indeed, these last ones include autograft, allograft, xenograft and alloplastic bone graft techniques. In addition, the grafting methods can be supplemented by the use of growth factors (e.g. BMP) or the development of tissue engineering procedures which can be summarized as the association of a biomaterial with cells and growth factors.

Even if the autograft is considered as the gold standard for bone regeneration, the method selection is depending on the clinical default to be repaired and no technique can be considered as “universal”. This selection should be carefully performed to optimize the bone gain and to minimize the negative outcomes.

Even if comparing the outcomes of different techniques used in different clinical purposes might be difficult, we would like, throughout this narrative review, to focus on the comparison of the bone regeneration complications between oral and orthopedic surgeries.

MATERIAL AND METHODS

Eligibility Criteria

Study Types

We included randomized controlled trials, prospective or retrospective cohort studies, case–control studies, cross-sectional studies, case series with ≥10 participants, and systematic reviews or meta-analyses reporting complications of bone regeneration.

We excluded case reports, case series with <10 participants, animal studies, in vitro studies, editorials, expert opinions, and conference abstracts without full text.

Population

Patients undergoing bone regeneration procedures in:
Dental and oral/maxillofacial surgery (guided bone regeneration, sinus lift, ridge augmentation, periodontal regeneration)
Orthopedic surgery (long-bone reconstruction, spinal fusion, joint reconstruction, tumor curettage)

Interventions
Any bone regeneration procedure using:
Autografts, allografts, xenografts
Synthetic alloplastic bone substitutes
Membranes (PTFE, titanium, collagen, cross-linked or non-cross-linked, PLGA and other synthetic membranes)

Outcomes
Primary outcomes: incidence and type of complications (exposure, infection, non-union, fracture, graft failure).
Secondary outcomes: timing, severity, management strategies, material-related trends.

Timeframe and Language
Studies published between 1980 and 2025 in English or French were included.

Information Sources and Search Strategy
The following databases were searched: PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library.

A complementary search of ClinicalTrials.gov and hand-searching of reference lists from included studies and seminal reviews was performed.

Study Selection
Two reviewers independently screened titles and abstracts, followed by full-text assessment using predefined criteria. Disagreements were resolved through discussion or consultation with a third reviewer.
Selection results were documented in a PRISMA flow diagram.

Data Extraction
Data were extracted independently by two reviewers using a standardized template including:
Study characteristics: authors, year, country, sample size, design
Surgical context: dental vs orthopedic, defect type, graft type, membrane type
Complication data: incidence, type, timing, severity, management
Follow-up length
Risk of bias elements

Risk of Bias Assessment
Depending on study design, the following tools were applied (Table 1):
RCTs → Cochrane RoB 2
Non-randomized studies → ROBINS-I
Case series → Joanna Briggs Institute checklist
Systematic reviews → AMSTAR-2

Data Synthesis
Given expected heterogeneity, a narrative synthesis was planned.

RESULTS
Bone regeneration in dental surgery
In dental surgery, bone regeneration is often used and usually called Guided Bone Regeneration (GBR). GBR is a surgical technique based on the association of a bone graft with a covering membrane to avoid any soft tissue migration within the filling bone graft. Even if the definition of the GBR is the association of the bone graft with a membrane, most of the time, GBR term is also used to characterize any bone grafting technique. In the field of dental surgery, bone regeneration is principally used in periodontology, for the treatment of intrabony and furcation bone defects, and in implantology for alveolar ridge augmentation, GBR and sinus lift.

Periodontal regenerative techniques are developed to increase mid-and long-term preservation of compromised teeth with deep pockets and reduced periodontal support where non-surgical procedure remains inefficient. The objectives of periodontal regeneration are to obtain: i) an increase in the periodontal attachment and bone; ii) a decrease of the pocket depth; and iii) a minimal increase in gingival recession. Periodontal techniques have demonstrated their efficiency in the treatment of one-, two- and three-walls intrabony defects, from very deep to very shallow, and from very wide to very narrow. [4-7]

Following tooth extraction, there is an atrophy of the alveolar bone. Vertical and/or horizontal bone atrophy prevent implantation and require bone reconstruction. Sufficient alveolar bone volume and favorable architecture of the alveolar ridge are essential to obtain ideal functional and esthetic prosthetic reconstruction following implant therapy.[8] Bone regeneration is used before and during implantation to recreate bone to match the prosthetic requirements. However, GBR is also used after implantation when patients develop peri-implantitis that resorb bone tissue around the implant. To

preserve and maintain the implant in proper clinical conditions, implant decontamination and bone regeneration should be performed.

Table 1: Risk of BIAS assessment

Study	Tool Used	Overall Risk	Key Limitations
Gallo	ROBINS-I	Moderate	Cross-sectional design
Martin-Thomé	JBI	Low	Homogeneous sample
Cucchi	RoB2	Moderate	Sample size limitations
Fontana	ROBINS-I	Moderate	Non-randomized
Annen	RoB2	Moderate/High	Split-mouth; small n
Becker	RoB2	Moderate	Short follow-up
Moses	ROBINS-I	Moderate/High	Older study design
Raza	ROBINS-I	High	Mixed indications
Willems	RoB2	Low	Robust RCT
Wood	ROBINS-I	Moderate	Small sample
Ricciardi	ROBINS-I	High	Retrospective; small n
Brown	ROBINS-I	High	No control group
Buser	AMSTAR-2	Critically low	High heterogeneity
Evaniew	JBI	Low/Moderate	Small cohort

Table 2: The classification of GBR complications according to Fontana *et al.*

Healing complications	Surgical complications
Class I: Small membrane exposure (≤ 3 mm) without purulent exudate	**A: Flap damage**
Class II: Large membrane exposure (> 3 mm) without purulent exudate	**B: Neurologic complications**
Class III: Membrane exposure with purulent exudate	**C: Vascular complications**
Class IV: Abscess formation without membrane exposure	

Table 3: General features of 7 publications of Guided Bone Regeneration

Authors	Title	Indication	Filling material	Membrane	Complications	Patients	Follow-up
Gallo et *al.*[9]	Management of 80 Complications in Vertical and Horizontal Ridge Augmentation with Non-resorbable Membrane (d-PTFE) A Cross-Sectional Study	Vertical and Horizontal Ridge Augmentation	- Autograft / Allograft (1/1) - Autograft / Xenograft (1/1)	d-PTFE	- Exposures with and without infections - Infections with exposures	80 patients	7 years
Martin-Thomé et *al.*[41]	Clinical Safety of a New Synthetic Resorbable Dental Membrane: A Case Series Study	- Guided bone regeneration - Socket preservation - Alveolar crest augmentation	- various bone fillers	- Tisseos: Poly lactic glycolic acid (85/15) (PLGA)	- 11.5% of exposure without infections	26 patients	4 months
Cucchi et *al.*[37]	Evaluation of complication rates and vertical bone gain after guided bone regeneration with non-resorbable membranes versus titanium meshes and resorbable membranes. A randomized clinical trial	Vertical ridge augmentation	- Autogeneous / Allograft (1/1) (EnCore)	- d-PTFE (A) - Titanium meshes/cross-linked collagen (B)	- 5% (A) and 15.8% (B) surgical complications - 10% (A) and 5% (A) major (infections) and minor complications and 15.8% (B) and 5.3% (B) major and minor complications	40 patients -20 in group A -20 in group B	12 months (9 months before membrane removal and 3months healing before loading)
Fontana et *al.*[36]	Clinical classification of complications in guided bone regeneration procedures by means of a non-resorbable membrane	Vertical ridge augmentation	- Autogeneous / Bio-oss (1/1)	PTFE	Exposure with infections		Up to 9 months depending of the class of complication
Annen et *al.*[40]	Use of a new cross-linked collagen membrane for the treatment of peri-	Exposed dental implants		- collagen - cross-linked collagen	-56% membrane exposure (9 patients) and 33% removed membrane	16 patients (split mouth study)	6 months

	implant dehiscence defects: a randomised controlled double-blinded clinical trial						
Becker et *al.*[39]	Use of a new cross-linked collagen membrane for the treatment of dehiscence-type defects at titanium implants: a prospective, randomized- controlled double-blinded clinical multicenter study	Implant dehiscence	- Bio-oss	- collagen - cross-linked collagen	- native collagen: 7.7% exposure and 0% inflammation - cross-linked collagen: 30% exposure and 21% inflammation	54 patients 23 cross-linked collagens 26 collagens 5 lost	4 months
Moses et *al.*[38]	Healing of dehiscence-type defects in implants placed together with different barrier membranes: a comparative clinical study	GBR with simultaneous implant positioning	- Autogeneous bone chip / Bio-oss - Autogeneous bone chip / BTCP	- Ossix - Bio Gide - e-PTFE (Gore-Tex)	- 16 exposures with 5 un-healing - BG 28 exposures with 27 un-healing - GT 17 exposures with 17 GT removal	- OS: 41 (73 implants) - BG: 28 (53 implants) - GT : 17 (34 implants)	6-8 months

Table 4: General features of 9 publications of Orthopedic Bone Regeneration

Authors	Title	Indication	Filling material	Complications	Patients	Follow-up
Raza et *al.*[66]	Outcome of bone allograft in orthopedic patients	Orthopedic patients with non-union, trauma or cancer	- Allograft	- Infection 11.1% - Fracture 13.9% - Non-union 11.1 - Recurrence 8.3%	36 patients	18 weeks
Willems et *al.*[73]	Randomized Controlled Trial of Posterior Lumbar Interbody Fusion with Ti- and CaP-Nanocoated Polyetheretherketone Cages: Comparative Study of the 1-Year Radiological and Clinical Outcome	Posterior lumbar interboby fusion	- Synthetic bone graft (Ti and CaP coated PEEK cages)	- No complications (infection, graft migration)	127 patients - 44 Ti-nanocoated - 46 CaP-nanocoated - 37 uncoated PEEK	12 months
Wood et *al.*[63]	Synthetic Graft Compared With Allograft Reconstruction for Extensor Mechanism Disruption in Total Knee Arthroplasty: A Multicenter Cohort Study	Total knee arthroplasty	- Allograft - Synthetic graft (Gelsoft)	- Synthetic 15% infection - Allograft 21% infection + 21% graft failure	27 patients - 13 synthetics - 14 allografts	6 months
Ricciardi et *al.*[70]	Survivorship of Extensor Mechanism Allograft Reconstruction After Total Knee Arthroplasty	Total knee arthroplasty	- Allograft	- Reintervention 58% (major cause was infection)	25 patients (26 knees)	Mean 68 months (22-113)
Buser et *al.*[64]	Synthetic bone graft versus autograft or allograft for spinal fusion: a systematic review	Spinal fusion	- Synthetic bone graft - Autograft - Allograft	- Infection range O%-5%	- 1011 lumbar spine - 675 cervical spine	Up to 5 years
Brown et *al.*[64]	Extensor mechanism allograft reconstruction for extensor mechanism failure following total knee arthroplasty	Total knee arthroplasty	- Allograft	- Infection 10% - revision 8% - Clinical failure 20%	47 patients (50 extensors)	57.6 months (24-125)
Evaniew et *al.*[74]	Use of a Calcium Sulfate-Calcium Phosphate Synthetic Bone Graft Composite in the Surgical Management of Primary Bone Tumors	Primary bone tumors	- Pro-Dens Calcium sulfate-calcium phosphate ($CaSO_4/CaPO_4$) matrix mixed with beta-tricalcium phosphate (b-TCP) granules.	- 4.1% stiches abscess - 4.1 % wound breakdown (infection) - 8.2% recurrences - 4.1% re-excision	24 patients	23 months (4 months to 4.5 years)
Rogers et *al.*[72]	Proximal Femoral Allograft in Revision Hip Surgery with Severe Femoral Bone Loss A Systematic Review and Meta-Analysis	Hip surgery	- Allograft	- structural failure pooled estimated rate 15% (range 0%-55%) - infection estimated rate 8%	498 patients	8.1 years (2-16.2 years)
Farfalli et *al.*[69]	Clinical and Functional Outcomes of Tibial Intercalary Allografts After Tumor Resection	Tumor resection	- Allograft	- Infection 11.1% - Fracture 11.1% - Non-union 7.4%	26 patients	6 years

Techniques

The techniques used for bone regeneration are very sensitive and operator dependent. However, the choice should match the clinical requirements and is strongly influence by the type and the localization of the bone defect. [4, 9-14]

The flap design is primordial and should be well designed in order to fit the bone graft in term of vertical and horizontal augmentations. Indeed, the flap is determined by the depth of the bone defect and the flap should be more extensive according to the depth of the defect. And the procedure should take in consideration the following key points:[15]

- Adequate case selection and accurate evaluation of bony defects.
- Sufficient blood supply.
- Tension-free primary wound closure.
- Membrane stabilization.
- Healing Time: At least six months, and a longer healing period (≥ nine months) is recommended for larger defects.
- Mixing with autogenous bone can shorten the healing period and enhance new bone quality.
- Special consideration should be taken in an aesthetic area or a scar region).
- The experience of the operator and the choice of the most appropriate technique are important.
- On large defects, it is safe to perform GBR first and place the implant second.
- Preventing infection is of utmost importance. If an infection occurs, early treatment should be performed, such as incision and drainage with antibiotics.

To reach these prerequisites, the materials used for bone regeneration (e.g. membrane and filling material) should be selected carefully.

Membranes

Throughout the literature, there has been controversy regarding the use of membrane and its beneficial influence on bone gain. However, the authors seem to conclude that its use should depend on the clinical defect to restore and especially for large bone defect reconstruction.[15] The membrane use for bone regeneration can be classified as non-absorbable and absorbable. The use of one or another is often linked to the surgeon habits. The type of membrane does not influence the outcomes of the GBR procedure. However, there are rules to be followed for the proper choice of the membrane, these include biocompatibility, cell-occlusiveness, space making, tissue integration and clinical manageability. Non-resorbable membranes, usually made of PTFE and derivatives, have the advantage of good space maintenance, predictable bone formation, and are recommended to be used for vertical bone augmentation. However, they seem to be very sensitive to infection once exposed and can induce dehiscences.[15-17] Resorbable membrane can be classified into 2 categories: i) synthetic degradable membranes (polyglycoside synthetic co-polymers) and ii) collagen membranes. Numerous membranes can be found with various modifications (e.g., cross-linked, non-cross-linked, mesh size) to modulate their barrier properties, degradation rate and infection resistance. Resorbable membranes cannot be used for vertical bone augmentation because of its low mechanical resistance, however they show the advantage of having a good resistance to infection after soft tissue dehiscence keeping its property of space maintening. [15, 18, 19]

Filling Materials

Even if in some favorable cases (small bone defect with 4 bone walls) a bone regeneration without the use of material can be performed, most of the time a filling material is used. The materials could be from natural or synthetic origins and is generally composed of only mineral matrix. According to the US Food and Drug Administration (USFDA), bone grafts are classified as Class II devices (bone grafts filling the bony voids and defects) and Class III devices (bone graft containing drugs). The use of bone graft material in dental surgery has extensively increased over the last years due to the development of implantology.

“The global dental bone graft and substitutes market size was valued at USD 663.2 million in 2020 and is expected to grow at a compound annual growth rate (CAGR) of 11.4% from 2021 to 2028. Increasing usage of bone grafts in dental implant surgeries is propelling the market growth.” [20]

The main objective of a bone substitute is to provide mechanical support, space-maintaining and osteoconduction in order to finally stimulate bone neo-formation. Ideally, the bone substitute will have similar resorption rate, composition and porosity to human bone. [21-23] This interconnected porosity should allow the ingrowth of blood vessels and the diffusion of bone cells and nutrients. Bone grafts promote bone regeneration via three concepts: i) osteoconduction (material acts as mineral scaffold), ii) osteoinduction (material contains proteins which lead to proliferation and differentiation of bone cells), and iii) osteogenesis (material containing stem cells). [24]

In 2021, Zhao et al. published a well-documented review on bone grafts and substitutes in dentistry.[25] The describe the classification of the materials into 5 groups: i) natural bone grafts and substitute materials, ii) synthetic bone substitutes, iii) composite bone substitutes, iv) growth factor-based bone substitutes and v) bone substitutes with infused living osteogenic cells.

Briefly, the main material used are among natural and synthetic bone substitutes. Natural bone substitutes are composed of: Autograft (graft from the patient himself). The autograft is considered as the gold standard and is the only bone substitute to possess osteoconductive, osteoinductive and osteogenesis properties. However, they suffer from several drawbacks (the need of a second surgical site, the morbidity and the quantity available); Allograft (graft from a donor or a cadaver). This category includes fresh frozen bone (FFB), freeze-dried bone allograft (FDBA), and demineralized freeze-dried bone allograft (DFDBA). They provide a lack of structural support and thus possess poor mechanical properties. In addition, the risk of transmission of bacteria, virus, or prion cannot be excluded for this type of bone substitute; 26 Xenograft (the donor is from another species). Deproteinized bovine bone is the most commonly used in dental surgery. The bovine bone undergoes a complex procedure followed by a chemical treatment using NaOH leading to the obtention of HA matrix only composed of inorganic components of the bone. The resulting matrix is highly comparable to human bone with microporosity compatible to bone ingrowth. It also shows good mechanical properties making it the best option for GBR. However, xenograft demonstrated a low degradation rate with long maintenance at the site.

Synthetic bone substitutes, also called alloplastic bone substitutes, include synthetic hydroxyapatites (HA), beta-tricalcium phosphate (ß-TCP), biphasic calcium phosphate (BCP), and bioglasses. HA is non-resorbable biomaterial with a low resorption rate and high space-maintaining potential.[25] The chemical composition of synthetic HA is comparable to the one found in the inorganic part of bone. However, differences can be found such as the absence of several ions (Mg2+, Na+, K+, Sr+) this absence influences the mechanical properties of synthetic HA with very low mechanical strength. In addition, synthetic HA shows no microporosity and a very slow degradation rate because of its high Ca/P ratio and crystallinity.

Tricalcium phosphate ceramics (α-TCP and ß-TCP), and more specifically ß-TCP, is a widely used ceramic because of its higher degradation rate compared to HA. ß-TCP shows several important properties such as a good osteoconductivity due to its macroporosity and osteogenic cell adhesion, good resorbability compared with bovine bone grafts and low immunogenicity and risk of disease transmission.

The major advancement was to associate HA and ß-TCP (biphasic calcium phosphate ceramics) in order to cumulate the advantages of both materials. However, this association still lack of mechanical strength limiting its clinical indication. The use of biphasic calcium phosphate ceramics (HA/ ß-TCP) is well indicated for peri-apical and periodontal regenerations.

Calcium phosphate cements have also been developed by mixing HA and α-TCP resulting in a paste capable of self-setting. This material presents the advantages of self-setting properties, good filling capacity, the ability to replicate the bone defect and good biocompatibility. However, it shows low degradation rate, no microporosity inducing high difficulties for cell adhesion and migration.

Bioglasses are synthetic silicate-based ceramics (SiO2, CaO, P2O5, Na2O…). Its exposition to body fluids induces the formation of a HA layer on the surface allowing the adhesion of osteogenic cells. Bioglasses demonstrated good biocompatibility, osteoconductivity, antimicrobial activity and a porous structure promoting vascularization, but on the contrary, they showed low mechanical strengths.

Calcium sulfate is also used for bone regeneration. When mixed it is capable of self-setting and can be molded into bony defects of varying shapes and sizes. It has been widely used because of its low cost, high availability, high biocompatibility, short setting time and osteoconductivity. However, its high degradation rate induces the loss of mechanical properties at the defect site.

Finally, other materials have also been reported such as polymers, metals, composites, growth factor-based bone substitutes and bone substitutes with Infused living osteogenic cells.

Clinical outcomes

The prognosis of GBR is a crucial input and more importantly the long-term prognosis of implants placed in GBR tissues. The literature is controversial on the long-term prognosis and this technique appears to be highly technique and surgeon-sensitive.[27] Two categories of authors can be found. The first one considers that the long-term outcomes of bone level after GBR are lower than those without GBR (higher bone resorption in GBR sites). The second group considers that there is no difference between GBR and non-GBR in the long-term behavior of implants.

Even if numerous studies on GBR and implants after GBR have been published, it is very difficult to rise a clear conclusion on this particular point because most of time the biomaterial and the membrane used are different from a study to another. Even the follow-up duration differs, long-term studies are still difficult to find. [8, 28-32]

Clinical complications

Bone regeneration means recreating bone where it cannot heal him-self. On another word the use of materials to recreate the ideal shape and volume of bone to be able to restore periodontal environment and oral functions, usually via implant strategies. These techniques involve inherent difficulties with high risks and are operator sensitive. Consequently, as any other surgical procedure, complications can arise after guided bone regeneration. Only few types of complications are observed, but their consequences can be dramatic for the patients. The main complications after GBR are: i) wound dehiscence, ii) abscess without membrane exposure, iii) abscess with membrane exposure and iv) membrane exposure without infection.

Wound dehiscence and membrane exposure are the most common complications reported in GBR procedure and could reach to infection, inadequate healing and loss of bone graft. The reasons of dehiscence and membrane exposure are inadequate flap design, flap tensions, excess of graft material and trauma (temporary denture, mastication, tooth brushing). When GBR is performed to recreate proper bone level on implant, dehiscence is observed (guided bone regeneration [45-47]) because of a migration of the graft material toward the apex of the implant. To overcome this issue, operative uses additive stabilization such as pin, holding suture or screw. [33-35]

Back in 2011, Fontana et al. has developed a classification (cf Table 2) of the complication when non-resorbable membrane was used.[36] The objective of such a classification was to have a better understanding and an easier identification of the problems in order to have a better care of them. Complications can be classified as either healing (Class I to IV) or surgical (A to C).

In 2019, Gallo et al. published a cross-sectional study on the management of 80 complications following GBR (cf Table 3).[9] Throughout the article they stated that the higher rate of infection was found on the maxillary anterior sites (35/80, 43.73%). They also observed that most of the complications appeared in the early post-operative times. Indeed, 70% (56/80) of the complications appeared within the first two months, 13.75% (11/80) within two and four months and 16.25% (13/80) between four and twelve months. Regarding the defect size, they observed that GBR on only one tooth shows the lowest complication rate (8.75%, 7/80) when the other categories >3 teeth (30x40mm) and <3 teeth (25x30mm) showed higher rates with 38.75% (31/80) and 37.50% (30/80) respectively. Finally, 20% of the complications appeared when GBR and implant placement were performed in the same operative time.

When Fontana classification was applied to their complications, a homogeneous repartition was observed with 22.50% (18/80), 22.50% (18/80), 23.75% (19/80) and 31.25% (25/80) corresponding respectively to class I, II, III and IV. Regarding the surgical complications they noted 3.75% (3/80) for flap damage and neurological complications while only 1.25% (1/80) was observed for vascular complications.

In 2017, Cucchi et al. published a randomized clinical trial with 39 patients dispatched in two groups with either PTFE membrane or Titanium mesh (cf Table 3).[37] They reported 5% (1/20) of neurological complication in PTFE group and 15.8% (3/19) in Titanium mesh group. Regarding healing complications, they mentioned two major complications (one class IV and one class III) and one minor (class II) in the PTFE group representing 15% of total complications. In the Titanium mesh group, they reported 21.1% (4/19) with three major (one class IV and two class III) and one minor (class II) complications.

Resorbable membranes are another category of membrane available for GBR. They can be manufactured from several materials (natural or synthetic). They have many advantages such as a single-step surgical procedure, which decreases patient morbidity and the risk to the newly regenerated tissues, good tissue integration with lower risk of membrane exposure, radiolucency that allows imaging and lower sensibility to infection.

Moses et al. has published a comparative clinical study using 3 different membranes.[38] One of them was ePTFE-based non-resorbable membrane (GT: Gore-Tex®) and the two others were resorbable collagen-based membranes (OS: Ossix® collagen membrane, BG: Bio-Gide® collagen membrane) (cf Table 3). They reported exposition rates of 39% (16/41), 32.1% 9/28) and 41.2% (7/17) for OS, BG and GT membrane respectively. The authors demonstrated no statistical difference in the membrane exposure regardless to the membrane used. However, OS membrane showed no complication after exposure and demonstrated higher bone and soft tissue healing after exposure when compared to the other two membranes.[38]

Becker et al. and Annen et al. respectively in 2009 and 2011 compared two different collagen membranes, one cross-linked and one non-cross-linked (cf Table 3).[39, 40] They reported 33% of infection and membrane removal for the cross-linked membrane group while no complication was reported in the non-cross-linked group.

Another category of resorbable membrane arised, resorbable synthetic polymer membranes. The majority of these membranes are based on aliphatic polyesters, such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly(ε-caprolactone) (PCL), poly (hydroxyl valeric acid), and poly (hydroxyl butyric acid), as well as their copolymers.

In 2018, Martin-Thomé et al. published a case series study on the use of a membrane made of synthetic poly lactic-co-glycolic acid (PLGA) (cf Table 3).41 Within this study, three cases of membrane exposure were reported reaching a 12% prevalence (3/26). More importantly, none of these exposures led to infections or worst complications but reached good tissue healing.

The other part of guided bone regeneration complications comes from the filing material. Even if the major complications come from the membrane, there still are few issues with the use of bone substitutes. When autograft is used, the main problem is an increase of the post-operative complications and infections because of the need of a second surgery procedure for bone harvesting. Concerning allografts, even they became widely used, they still suffer from limitations because of the risk of infectious diseases transmission. The last natural bone substitute used is xenograft with the most commonly used from bovine. Xenograft has demonstrated good bone regeneration but presents a low degradation rate.

Conclusion

In dental surgery, bone regeneration and more precisely, guided bone regeneration is used to recreate bone volume in order to restore tooth periodontal support or oral functions usually via implant utilization. GBR is based on the use of a filling materials such as autograft, allograph, xenograft and alloplastic materials and a covering membrane to act a barrier against soft tissue migration and space-maintaining. The membrane used in GBR can be either non-resorbable or resorbable. The non-resorbable membranes are principally made of PTFE or ePTFE and the resorbable membrane can be sub-categorized in natural or synthetic membranes. GBR procedures are operative dependent and can suffer from post-operative complications. These complications have been well classified by Fontana in 2011 under surgical complications (A: Flap damages, B: Neurological complications and C: vascular complications) and healing complications (I: small membrane exposure without purulent exudate, II: large membrane exposure without purulent exudate, III: membrane exposure with purulent exudate and IV: abscess without exposure).

Over the literature, GBR outcomes and complications are controversial and their importance remains unclear. Indeed, the discrepancies between the clinical studies make the comparison difficult. However, regardless the operator and the membrane used, the complication rates seem to be from 15% to 40%. Even if the author opinions differ, the type of membrane doesn't look to have a crucial importance on the exposition rate. However, the complications after exposure are very different depending on the membrane used. Indeed, non-resorbable membrane has the higher rate of infection and bad tissue healing after exposure. Nevertheless, their rigidity and good space maintaining properties let them the first-choice membrane for vertical and large bone defect regenerations. On the contrary, un-crosslinked resorbable collagen membrane and synthetic degradable membrane demonstrated the better resistance to exposure even in the early time after surgery and reaching good tissue healing.

Bone regeneration in Orthopedic surgery

Bone is a key tissue for the well-being of human body and its properties made him capable of self-healing. However, in some particular cases, bone cannot heal and bone regeneration procedures must be used in order to recreate the lost tissues. Even if a number of solutions still exists, there is a desperate need for tissue and bone regeneration.[42] According to Giannoudis et al., bone regeneration follows the four-diamond rules: i) cells with osteogenic potential, ii) an osteoconductive matrix, iii) an osteoinductive stimulus and iv) a mechanically stability.[43] The missing of one of these rules can usually explain the bone healing failure. Primary bone healing occurs when the gap between bone ends is less than 2mm and absolute stability exists.[44] Osteoclasts tunnel across the fracture site; followed by the osteoblasts which produce new bone.[45] If the bone defect is not stable, the healing process will reach to the formation of an exuberant callus and fibrous scar tissue will be formed.[46] Bigger non-union bone defects lack of biological reaction and bone healing. This issue may be explained by the poor blood supply within the defect and consequently a low quantity of osteoinductive stimulus and cells. The lack of osteogenic cell and blood supply can also be the reason of the poor healing properties of hypotrophic bones or irradiated bone after cancer treatment.

Regarding these parameters, a number of clinical needs has emerged and showed their interest in the use of bone regeneration strategies such as trauma, spinal surgery, joint replacement surgery and bone tumor surgery.

Indications

Trauma

Back in 2000, Hollinger et al. reported an estimation of 280 000 hip fractures, 700 000 vertebral fractures, and 250 000 wrist fractures per year with an overall cost of $10 billion.47 Moreover, several healing problems (delay or non-union) appeared in 5% of all fractures, and 20 per cent of high-impact fractures.[48] Bone tissue is capable of self-regeneration, however in certain conditions such as large bone defect, the healing process needs the intervention of surgeon to bridge the bone defect. The care of non-unions is a challenging and costly exercise, and large efforts have been done for the development of new therapeutic strategies such as tissue engineering protocols. The global market for bone regeneration

associated to trauma represents billions of dollars annually and is linked to the 4 000 000 operations involving bone grafting or bone substitutes performed around the world annually.[49]

Spinal surgery

Back pain is a major health concern and an increasing cause of disability. Its socio-economic impact related to treatments and loss of productive time is clear.[50] Worldwide, back pain is the single leading cause of disability, preventing many people from engaging in work as well as other everyday activities.[51] Back pain is one of the most common reasons for missed work, one-half of all working Americans admit to having back pain symptoms each year and Back pain accounts for more than 264 million lost work days in one year.[52, 53] With an increasing of the average age of the population, experts estimate that up to 80% of the population will experience back pain at some time in their lives.[54] Most cases of back pain are mechanical or non-organic—meaning they are not caused by serious conditions, such as inflammatory arthritis, infection, fracture or cancer.[55] Low-back pain costs Americans at least $50 billion in health care costs each year, reaching $100 billion by adding lost wages and decreased productivity.[56]

Disabling back pain due to degenerative disease may require surgical intervention.[57] A total of 500 000 autologous bone graft operations are performed each year in the USA. 50% of them are performed for spinal fusions and 5-35% for non-union. Spinal surgery is a large market with scope for improvement in bone graft technology.[58]

Joint replacement surgery

Joint replacement surgery has a high incidence, with over 1 million total hip and total knee replacement procedures performed each year in the United States.[59] With the aging of the population, higher rates of diagnosis and demands for improved pain care and quality of life are going to increase considerably in the future, making joint replacements a common elective surgical procedures in the coming decades.[60, 61] If the articulation between two bones is extensively diseased or has been injured beyond repair, a joint replacement procedure is necessary. Artificial implants, or prostheses, are used to replace diseased or damaged bone around joints so that patients are able to enjoy, to a degree, normal movement once again. The implants mimic bone shape and can be made of metal, high density polyethylene or ceramic. Hip, knee, ankle, elbow and shoulder joints can all be replaced with artificial implants, although hip and knee replacements procedures are by far the most common.

Cyst and bone tumor surgery

Most of the time, resection or curettage are usually the preferred procedures for the treatment of cyst and bone tumors. Resection of tumors from long bones often leaves large bone defects. Limb reconstruction and salvage procedures for bone tumor surgery utilize combinations of massive bone allografting and bone transportation operations.[62]

Techniques

Regardless the application, bone grafting should match the same prerequisites:

- Adequate case selection and accurate evaluation of bony defects.
- Sufficient blood supply.
- Biomechanical properties
- Handling characteristics
- Prevention of the infections

The key parameter for any bone graft procedure is the graft stability. As an example, in large bone defect or non-union, cements or ceramics will be used for their volume maintaining ability and their mechanical properties.

Materials

Autograft

Autograft is grafting a tissue from one site to another site of the same individual. Autograft is considered as the gold standard in bone grafting because it is the only one matching all the key parameters for bone regeneration (osteoinduction, osteoconduction and osteogenesis). Even if this technique is very effective, it suffers from several drawbacks. Indeed, the harvest can be done at the same site or at another site requiring a second surgery procedure with increasing post-operative outcomes such as pain, bleeding, morbidity and risk of infection. Moreover, only a low quantity of bone is available with this technique.

Allograft

Allograft is grafting a tissue from one individual to another individual from the same species. They are obtained via bone banks from cadavers or living donors. Allograft are processed to remove the cellular part of the bone making it a mineral matrix without any osteogenic properties compared to autografts. The allograft shows several advantages such as: HLA tissue typing or ABO blood grouping and large quantity available. However, there still present risk of disease transmission and immune responses.

Allogenic bone can be available as massive allografts, demineralized bone matrix, processed bone chips, or cortical struts. They are available as demineralized bone matrix (DBM) and processed in acid to remove the mineral components. This leaves a trabecular structure which preserves its osteoconductivity, whilst the collagen and bone morphogenic proteins permit osteoinductivity.

Alloplastic bone substitutes

Bone substitutes are engineered synthetic material for natural bone replacement. The engineering processes have been developed to control the design mineral matrix in order to match to the clinic requirements. Indeed, the conditions of synthesis are essential to tune the size, the mineral composition, the micro and macro porosity and the biodegradability properties. Several synthetic bone substitutes have been produced:

Hydroxy apatite (HA) (Ca5(PO4)3OH or Ca10(PO4)6OH2) is a mineral crystalline form of calcium phosphate which represents the main part of the mineral matrix of bones and teeth. Synthetic HA is similar to the native one with osteoconductive properties and a low degradation rate.

Tricalcium phosphate (TCP) (Ca3(PO4)2) is a bio-ceramic with good biological properties and a high degradation rate. It exists in 2 forms: alpha and beta.

Biphasic calcium phosphate is a calcium phosphate mix composed of HA and Beta-TCP. This mixture has been developed to combine the osteoconductive properties and adjust the degradation rate of the product to enhance and match the kinetic of bone regeneration. The 60/40 ratio seems to be the better one.

Bioglasses are silate based minerals composed of SiO2, CaO, Na2O and P2O5. Once in contact with body fluids, bioglasses are dissolving and precipitating into carbonate phosphate. They are biocompatible, osteoconductive and slowly degradable.

Calcium sulphate (CaSO4), also known as plaster of Paris, has been used to fill bone defect or as additive to autograft. Its degradation rate is about 6 weeks.

Growth factors

Growth factors, more specifically bone morphogenic proteins (BMP), are used to increase osteoinductivity either when used alone or as additive into a bone substitute. BMPs are used for spinal fusion and special care must be done because its high osteoinductive properties may causes bone formation in the surrounding tissues if misplaced.

Clinical outcomes

The prognosis of bone regeneration in orthopedic surgery remains uncertain and can vary according to the indication and the localization of the graft. Wood et al. [63] reported suboptimal bone healing when using bone substitute in total knee arthroplasty. In a same manner, Buser et al. showed high efficiency of spine fusion using HA with 92% for lumbar spine fusion and 82 for cervical spine fusion.[64] When the bone procedure involves any joint part of the body (e.g., ankle, knee or shoulder) function monitoring is performed. Gouin et al. demonstrated 3.5 folds and 2.5 folds increase (not statistically different) of function recovery when using calcium phosphate and autograft respectively in open wedge high tibial osteotomy.[65] In addition, knee society score (KSS) was performed as monitoring. No statistical differences were found.

Clinical complications

As any other surgeries, bone grafting involves surgical risks and complications. Among them, the most important complications are graft fractures and infections. This last one is very difficult to treat and may lead to the graft removal.[66] Moreover, when autograft is performed, infections of the donor may occur. Brydone et al. published a review stating the impact of the use of autograft on the complication rate.[42] To be more precise, based on Coventry, Reid and Younger work, they precise that harvesting increases pain, bleeding and infections of the donor site.[67, 68] Raza et al. published an article on the outcome of bone allograft in orthopedic patients with trauma or cancer (cf Table 4).[66] They mentioned several complications such as 11.1% of infections, 13.9% of fractures and 11.1% of non-unions.[66] To support their data, they reported previous publications from Dick et al. where the observed 11% of infections, 11% of plate fracture, 7% of graft fracture and 26% of non-unions on patients treated with chemotherapy for cancer care. Farfalli and Menkin et al. also reported 11% and 10% respectively of infections following bone grafts.[69]

In 2018, Wood et al. published an article to compare allograft to synthetic graft in total knee arthroplasty (cf Table 4).[63] Within the study they observed a complication rate of 23% in the synthetic graft group while 43% was observed in the allograft group. These observations include 15% of infection for synthetic graft and 21% of infection and 21% of graft failure for allograft leading to the clear conclusion of higher complication rates with allografts compared to synthetic grafts. To confirm their findings, they reported 58% of revision rate for Ricciardi et al. and 38% of failure for

Brown et al. However, regardless to the complication rates all of the studies have shown an improve of the KSS score for both pain and function.[70, 71]

Rogers et al. published a meta-analysis about proximal femoral allograft in hip surgery (cf Table 4). Throughout their analysis, they observed a failure rate within the range of 0 to 55%. Regarding the infection rates, they mentioned a 0 to 20% range. [72]

Buser et al. published a literature review in the field of spine fusion. Indeed, they compared synthetic bone graft with autograft (cf Table 4).[64] Throughout the review, because of bias and small sample sizes, the authors couldn't highlight one material better to the other ones. While going through the research articles analyzed, very low complication rates and more specifically infections were reported. A range from 0% to 5% was observed. Moreover, Willems et al. described a randomized controlled trial of posterior lumbar interbody fusion (cf Table 4). Throughout his clinical trial they reported no infection complication over 127 patients.[73]

Another field of application of bone grafting is the care of intrabony tumors. Evaniew et al. published an article about the use of calcium sulfate-calcium phosphate (CaSO4/CaPO4) bone graft for the care of primary bone tumors (cf Table 4).[74] Over their evaluation, they observed 2 cases, over 24 patients (8.3%), of infections, 1 following wound breakdown and 1 stich abscess. In addition, 3 other failures were observed (2 recurrences and 1 re-excision). Other authors have reported the use of synthetic biomaterial (CaSO4, B-TCP, CaSO4/HA) for the care of tumors with complication rates of 7%, 8% and 15% for infection, fractures and local recurrence respectively. [75-78]

Conclusion

In orthopedic surgery, bone regeneration is used for several purposes such as: i) bone volume and strength regeneration (long bone defect or intrabony tumor care), ii) functional restoration (joint replacement) and iii) pain relief (spine fusion). The bone regeneration strategies rely on the use of either autograft, allograft and synthetic bone substitutes. Autograft protocols require a second surgery site inducing higher complication rate such as morbidity, pain, bleeding and infections. Moreover, it aims in a low quantity of available material. Allograft is an interesting alternative choice for bone grafting with osteoconductive and osteoinductive properties. It is also available in large quantity. However, regarding to the literature, it suffers from an increase of the complication rate such as infection. The last category is synthetic bone substitutes. There is a wide range of substitutes available and they are available in large quantity. They demonstrated their good efficiency with low complication rates depending on the field of application (e.g., spine fusion).

However, no ideal material has been developed so far, the choice should be realized depending on the clinical situation such as the indication, the localization and the volume to be regenerated.

Study selection

Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.

Study characteristics

For each study, present characteristics for which data were extracted (such as study size, follow-up period) and provide the citation.

Identify all drugs, chemicals, implants and graft material used, including both generic and, if necessary, proprietary names and doses, i.e.

- Articain 4% (Ubistesin™ Forte 1.7ml N50 - 3M ESPE Dental AG; Seefeld, Germany)
- Bio-Gide® membrane (Geistlich Pharma AG, Wolhusen, Switzerland);
- Straumann® BoneCeramic 0.5-1 mm (bi-phasic 60% HA and 40% β-TCP - Institute Straumann AG; Basel, Switzerland).

Risk of bias within studies

Present data on risk of bias of each study and, if available, any outcome-level assessment. It is often easiest to provide these data in a tabular format. However, a narrative summary describing the tabular data can also be helpful for readers.

DISCUSSION

Bone regeneration is a multidisciplinary field with wide clinical applications. Surgeons are performing bone regeneration in dental, maxilla-facial and orthopedic fields for a large range of indications. Indeed, it is used for bone repair when the self-healing capacity of bone is not sufficient. This range is as large as alveolar preservation, ridge augmentation and sinus lift in dental surgery, large mandibular defect or cranio-facial reconstruction in maxillo-facial surgery and large bone defect, spine fusion, joint replacement and intra-bony tumor care in orthopedic surgery.

In guided bone regeneration, the surgery procedure is very sensitive and operative dependent. The outcomes and complications will vary depending on the defect morphology, the type of bone graft, the type of membrane used and the

flap design. Special care should be taken on the flap design, tensionless stiches and stability of the graft. The GBR surgical complications and infections have been reported and classified by Fontana et al. into 3 and 4 categories respectively (cf Table 2).[36]

The literature analyzes of GBR complications showed, according to Moses et al., that there is no influence of the type of membrane on the exposure rate however drastic differences can be observed on the behavior after exposure.38 Indeed, they reported no infection following 40% of exposure rate with their uncross-linked degradable collagen-based membrane as they have 90% and 100% of infection with their crosslinked membrane and non-degradable membrane respectively after exposure.

When taken together, Cucchi and Becker publications reached identical conclusions. Infection rates of 21.1% for titanium mesh and 15% for PTFE membrane were mentioned by Cucchi and Becker showed 33% of infection and membrane removal with his cross-linked degradable collagen membrane and no infection with un-crosslinked collagen membrane.[37, 39] Moreover Martin-Thomé et al.[41] and Hoornaert et al.[79] demonstrate that degradable synthetic membranes have non infection after exposure even in the early time and don't delay the soft tissue healing process.

Altogether, the reported data reach to the conclusion of a crucial importance of the type of membrane and the degradation speed. Indeed, synthetic non-resorbable are the worst membrane regarding the infection rate following exposure. Collagen membrane has different behavior depending of their cross-linking and consequently on the degradability kinetic. The cross-linking induces a slower degradation speed. And the synthetic degradable membranes have a high resistance to infection after exposure.

In orthopedic surgery, bone regeneration complications are essentially failure (fracture, non-union) and infections. Throughout the literature, important parameters raised to understand the complications. When autograft is used for bone regeneration, an increase of the complications appeared because of the presence of a second operative site. Concerning allograft, 11% of infection were observed by Raza et al. for regeneration in trauma and cancer care. In the same manner, other studies published infection rates of the same range from 10% to 15%.[66, 69] Allograft was also reviewed in hip surgery applications par Rogers et al. and they showed an infection risk between 0% to 20%.[72] Wood et al. compared allograft to synthetic bone substitutes in total knee arthroplasty and they demonstrated a low infection risk with synthetic bone substitute compared to allograft with 15% and 21% infection rates respectively.[63] Synthetic materials have also been used in intrabony tumors care with a risk of infection of 8.3% for Evaniew and 7% for others.[74-77] Buser also used synthetic material for spine fusion and demonstrated a very low range of infection rate from 0% to 5%.[64] This range reached even 0 infection over 127 patients in spine surgery according to Willems et al..[73]

Because of the high potential for bias, small sample sizes and differences between studies, the difficulties to compare and reach to clear conclusions are very high. However, interesting trends can be highlighted. First of all, the type of grafting seems to have an impact on the complication rates. If it seems to be clear that autograft shows higher risk of complications because of the need of a second operative site for bone harvesting and its consequences. Comparative studies have demonstrating that synthetic bone graft has the lowest rate of infections. The second trend that we could conclude is the influence of the clinical indication of the bone grafting procedure, indeed, long bone regeneration, regeneration after chemo therapy and joint regeneration have the higher infection rates of about 10% to 15%. Intrabony tumors has around 8% of risk and finally, the lowest infection rate observed is in spine surgery with less than 5% and even 0% according to Willems. [73]

Regardless to the application (e.g., dental surgery or orthopedic surgery), bone regeneration has the same prerequisites and complications such as graft stability, exposure sensibility and infection. Because of the difficulty to treat infection without removal of the graft, its prevention is essential. Even if the comparison between the two surgery areas is difficult or impossible, it appears that the infection ranges are large in both dental surgery and orthopedic surgery with 0-40% and 0-58% respectively.

If in orthopedic the infection rates seem to be influenced by the type of bone graft and the clinical indication, in dental surgery, the main influence is observed with the type of membrane used. However, the choice of the membrane is directly linked to the clinical indication as for vertical or large bone defect, non-resorbable titanium or PTFE membranes are used because of their space maintaining properties, in small defect or peri-implant bone regeneration, soft degradable membrane can be used. Consequently, higher infection rates can be observed in large bone defect and vertical ridge augmentation, moreover, these applications increase the difficulty of tensionless stiches and so increase the exposure rate.

CONCLUSIONS

Bone represents a key tissue in the organism because of its involvement in structural maintenance of the body, in movements, protection of other organs, metabolic activity and storage of ions and minerals. Its physiological properties make it capable of self-regeneration. However, in some particular cases, this capacity is not sufficient and the bone

remains un-healed. Strategies must be engineered to help the body to regenerate the bone defect. Bone regeneration is a rising field involving massive research to help the efficiency while decreasing the complication rates. Throughout this review we noticed the differences of both applications in term of surgery and complication sources and finally the most important parameter from which everything seems to come, the clinical indication which sets the choice of the procedure and the bone graft material regardless to the complication risks. In summary, developing bone biomaterials with material compositions, geometric structures, space maintaining properties and degradation rate similar to those of natural bone healing and membranes compatible with soft tissue regeneration, and infection resistance remain significant avenues for future research.

REFERENCES

1. Buck, D. W., & Dumanian, G. A. (2012). Bone biology and physiology: Part I. The fundamentals. *Plastic and Reconstructive Surgery, 129*(6), 1314–1320. https://doi.org/10.1097/PRS.0b013e31824eca94
2. Buckwalter, J. A., Glimcher, M. J., Cooper, R. R., & Recker, R. (1996). Bone biology. I: Structure, blood supply, cells, matrix, and mineralization. *Instructional Course Lectures, 45*, 371–386. PMID: 8727757
3. Clarke, B. (2008). Normal bone anatomy and physiology. *Clinical Journal of the American Society of Nephrology, 3*(Suppl 3), S131–S139. https://doi.org/10.2215/CJN.04151206
4. Crotaline, P., & Tonetti, M. S. (2015). Clinical concepts for regenerative therapy in intrabony defects. *Periodontology 2000, 68*(1), 282–307. https://doi.org/10.1111/prd.12048
5. Esposito, M., Grusovin, M. G., Papanikolaou, N., Coulthard, P., & Worthington, H. V. (2009). Enamel matrix derivative (Emdogain) for periodontal tissue regeneration in intrabony defects: A Cochrane systematic review. *European Journal of Oral Implantology, 2*(3), 247–266. PMID: 20467602
6. Murphy, K. G., & Gunsolley, J. C. (2003). Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects: A systematic review. *Annals of Periodontology, 8*(1), 266–302. https://doi.org/10.1902/annals.2003.8.1.266
7. Needleman, I. G., Worthington, H. V., Giedrys-Leeper, E., & Tucker, R. J. (2006). Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database of Systematic Reviews, 2006*(2), CD001724. https://doi.org/10.1002/14651858.CD001724.pub2
8. Farzad Moghadam, M., & Mohammadi, M. (2012). Guided bone regeneration: A literature review. *Journal of Oral Health and Oral Epidemiology, 1*(1), 3–18. https://doi.org/10.22122/joh.v1i1.6
9. Gallo, P., & Díaz-Báez, D. (2019). Management of 80 complications in vertical and horizontal ridge augmentation with nonresorbable membrane (d-PTFE): A cross-sectional study. *International Journal of Oral & Maxillofacial Implants, 34*(4), 927–935. https://doi.org/10.11607/jomi.7214
10. Dahlin, C., Linde, A., Gottlow, J., & Nyman, S. (1988). Healing of bone defects by guided tissue regeneration. *Plastic and Reconstructive Surgery, 81*(5), 672–676. https://doi.org/10.1097/00006534-198805000-00010
11. Tinti, C., Parma-Benfenati, S., & Polizzi, G. (1996). Vertical ridge augmentation: What is the limit? *International Journal of Periodontics & Restorative Dentistry, 16*(3), 220–229. PMID: 9084308
12. Urban, I. A., Lozada, J. L., Jovanovic, S. A., Nagursky, H., & Nagy, K. (2014). Vertical ridge augmentation with titanium-reinforced, dense-PTFE membranes and a combination of particulated autogenous bone and anorganic bovine bone-derived mineral: A prospective case series in 19 patients. *International Journal of Oral & Maxillofacial Implants, 29*(1), 185–193. https://doi.org/10.11607/jomi.3346
13. Urban, I. A., Jovanovic, S. A., & Lozada, J. L. (2009). Vertical ridge augmentation using guided bone regeneration in three clinical scenarios prior to implant placement: A retrospective study of 35 patients 12 to 72 months after loading. *International Journal of Oral & Maxillofacial Implants, 24*(3), 502–510. PMID: 19587874
14. Urban, I. A., Monje, A., Lozada, J., & Wang, H. L. (2017). Principles for vertical ridge augmentation in the atrophic posterior mandible: A technical review. *International Journal of Periodontics & Restorative Dentistry, 37*(5), 639–645. https://doi.org/10.11607/prd.3200
15. Kim, Y. K., & Ku, J. K. (2020). Guided bone regeneration. *Journal of the Korean Association of Oral and Maxillofacial Surgeons, 46*(5), 361–366. https://doi.org/10.5125/jkaoms.2020.46.5.361
16. Simion, M., Misitano, U., Gionso, L., & Salvato, A. (1997). Treatment of dehiscences and fenestrations around dental implants using resorbable and nonresorbable membranes associated with bone autografts: A comparative clinical study. *International Journal of Oral & Maxillofacial Implants, 12*(2), 159–167. PMID: 9109265
17. Rakhmatia, Y. D., Ayukawa, Y., Furuhashi, A., & Koyano, K. (2013). Current barrier membranes: Titanium mesh and other membranes for guided bone regeneration in dental applications. *Journal of Prosthodontic Research, 57*(1), 3–14. https://doi.org/10.1016/j.jpor.2012.12.001
18. Simion, M., Jovanovic, S. A., Trisi, P., Scarano, A., & Piattelli, A. (1998). Vertical ridge augmentation around dental implants using a membrane technique and autogenous bone or allografts in humans. *International Journal of Periodontics & Restorative Dentistry, 18*(1), 8–23. PMID: 9558553
19. Tinti, C., & Parma-Benfenati, S. (1998). Vertical ridge augmentation: Surgical protocol and retrospective evaluation of 48 consecutively inserted implants. *International Journal of Periodontics & Restorative Dentistry, 18*(5), 434–443. PMID: 10093520

20. Grand View Research. (n.d.). *Dental bone grafts and substitutes market.* https://www.grandviewresearch.com/industry-analysis/dental-bone-grafts-substitutes-market
21. Struillou, X., Boutigny, H., Badran, Z., et al. (2011). Treatment of periodontal defects in dogs using an injectable composite hydrogel/biphasic calcium phosphate. *Journal of Materials Science: Materials in Medicine, 22*(7), 1707–1717. https://doi.org/10.1007/s10856-011-4344-1
22. Trombelli, L., & Farina, R. (2008). Clinical outcomes with bioactive agents alone or in combination with grafting or guided tissue regeneration. *Journal of Clinical Periodontology, 35*(8 Suppl), 117–135. https://doi.org/10.1111/j.1600-051X.2008.01265.x
23. Nasr, H. F., Aichelmann-Reidy, M. E., & Yukna, R. A. (1999). Bone and bone substitutes. *Periodontology 2000, 19*(1), 74–86. https://doi.org/10.1111/j.1600-0757.1999.tb00148.x
24. LeGeros, R. Z. (2008). Calcium phosphate-based osteoinductive materials. *Chemical Reviews, 108*(11), 4742–4753. https://doi.org/10.1021/cr800427g
25. Zhao, R., Yang, R., Cooper, P. R., Khurshid, Z., Shavandi, A., & Ratnayake, J. (2021). Bone grafts and substitutes in dentistry: A review of current trends and developments. *Molecules, 26*(10), 3007. https://doi.org/10.3390/molecules26103007
26. Daculsi, G., Laboux, O., Malard, O., & Weiss, P. (2003). Current state of the art of biphasic calcium phosphate bioceramics. *Journal of Materials Science: Materials in Medicine, 14*(3), 195–200. https://doi.org/10.1023/A:1022842404495
27. Rocchietta, I., Fontana, F., & Simion, M. (2008). Clinical outcomes of vertical bone augmentation to enable dental implant placement: A systematic review. *Journal of Clinical Periodontology, 35*(8 Suppl), 203–215. https://doi.org/10.1111/j.1600-051X.2008.01271.x
28. Huang, H. Y., Ogata, Y., Hanley, J., Finkelman, M., & Hur, Y. (2016). Crestal bone resorption in augmented bone using mineralized freeze-dried bone allograft or pristine bone during submerged implant healing: A prospective study in humans. *Clinical Oral Implants Research, 27*(e1), e25–e30. https://doi.org/10.1111/clr.12512
29. Mengel, R., & Flores-de-Jacoby, L. (2005). Implants in regenerated bone in patients treated for generalized aggressive periodontitis: A prospective longitudinal study. *International Journal of Periodontics & Restorative Dentistry, 25*(4), 331–341. PMID: 16089041
30. Hämmerle, C. H., Jung, R. E., & Feloutzis, A. (2002). A systematic review of the survival of implants in bone sites augmented with barrier membranes (guided bone regeneration) in partially edentulous patients. *Journal of Clinical Periodontology, 29*(Suppl 3), 226–231. https://doi.org/10.1034/j.1600-051x.29.s3.14.x
31. Fiorellini, J. P., Kim, D. M., Nakajima, Y., & Weber, H. P. (2007). Osseointegration of titanium implants following guided bone regeneration using expanded polytetrafluoroethylene membrane and various bone fillers. *International Journal of Periodontics & Restorative Dentistry, 27*(3), 287–294. PMID: 17694952
32. Nakajima, Y., Fiorellini, J. P., Kim, D. M., & Weber, H. P. (2007). Regeneration of standardized mandibular bone defects using expanded polytetrafluoroethylene membrane and various bone fillers. *International Journal of Periodontics & Restorative Dentistry, 27*(2), 151–159. PMID: 17514887
33. Kim, Y. K., Yun, P. Y., Kim, S. G., & Oh, D. S. (2009). In vitro scanning electron microscopic comparison of inner surface of exposed and unexposed nonresorbable membranes. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 107*(6), e5–e11. https://doi.org/10.1016/j.tripleo.2009.03.003
34. Benic, G. I., Eisner, B. M., Jung, R. E., Basler, T., Schneider, D., & Hämmerle, C. H. F. (2019). Hard tissue changes after guided bone regeneration of peri-implant defects comparing block versus particulate bone substitutes: 6-month results of a randomized controlled clinical trial. *Clinical Oral Implants Research, 30*(10), 1016–1026. https://doi.org/10.1111/clr.13515
35. Lutz, R., Neukam, F. W., Simion, M., & Schmitt, C. M. (2015). Long-term outcomes of bone augmentation on soft and hard-tissue stability: A systematic review. *Clinical Oral Implants Research, 26*(Suppl 11), 103–122. https://doi.org/10.1111/clr.12635
36. Fontana, F., Maschera, E., Rocchietta, I., & Simion, M. (2011). Clinical classification of complications in guided bone regeneration procedures by means of a nonresorbable membrane. *International Journal of Periodontics & Restorative Dentistry, 31*(3), 265–273. PMID: 21556383
37. Cucchi, A., Vignudelli, E., Napolitano, A., Marchetti, C., & Corinaldesi, G. (2017). Evaluation of complication rates and vertical bone gain after guided bone regeneration with nonresorbable membranes versus titanium meshes and resorbable membranes: A randomized clinical trial. *Clinical Implant Dentistry and Related Research, 19*(5), 821–832. https://doi.org/10.1111/cid.12520
38. Moses, O., Pitaru, S., Artzi, Z., & Nemcovsky, C. E. (2005). Healing of dehiscence-type defects in implants placed together with different barrier membranes: A comparative clinical study. *Clinical Oral Implants Research, 16*(2), 210–219. https://doi.org/10.1111/j.1600-0501.2004.01100.x
39. Becker, J., Al-Nawas, B., Klein, M. O., Schliephake, H., Terheyden, H., & Schwarz, F. (2009). Use of a new cross-linked collagen membrane for the treatment of dehiscence-type defects at titanium implants: A prospective, randomized-controlled double-blinded clinical multicenter study. *Clinical Oral Implants Research, 20*(7), 742–749. https://doi.org/10.1111/j.1600-0501.2008.01689.x

40. Annen, B. M., Ramel, C. F., Hämmerle, C. H., & Jung, R. E. (2011). Use of a new cross-linked collagen membrane for the treatment of peri-implant dehiscence defects: A randomized controlled double-blinded clinical trial. *European Journal of Oral Implantology, 4*(2), 87–100. PMID: 21808759
41. Martin-Thomé, H., Bourdin, D., Strube, N., et al. (2018). Clinical safety of a new synthetic resorbable dental membrane: A case series study. *Journal of Oral Implantology, 44*(2), 138–145. https://doi.org/10.1563/aaid-joi-D-17-00042
42. Brydone, A. S., Meek, D., & Maclaine, S. (2010). Bone grafting, orthopaedic biomaterials, and the clinical need for bone engineering. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 224*(12), 1329–1343. https://doi.org/10.1243/09544119JEIM770
43. Giannoudis, P. V., Einhorn, T. A., & Marsh, D. (2007). Fracture healing: The diamond concept. *Injury, 38*(Suppl 4), S3–S6. https://doi.org/10.1016/S0020-1383(08)70003-2
44. Gaston, M. S., & Simpson, A. H. (2007). Inhibition of fracture healing. *Journal of Bone and Joint Surgery. British Volume, 89*(12), 1553–1560. https://doi.org/10.1302/0301-620X.89B12.19671
45. McKibbin, B. (1978). The biology of fracture healing in long bones. *Journal of Bone and Joint Surgery. British Volume, 60*(2), 150–162. https://doi.org/10.1302/0301-620X.60B2.350882
46. Megas, P. (2005). Classification of non-union. *Injury, 36*(Suppl 4), S30–S37. https://doi.org/10.1016/j.injury.2005.10.008
47. Hollinger, J. O., Winn, S., & Bonadio, J. (2000). Options for tissue engineering to address challenges of the aging skeleton. *Tissue Engineering, 6*(4), 341–350. https://doi.org/10.1089/107632700418065
48. Dickson, G., Buchanan, F., Marsh, D., Harkin-Jones, E., Little, U., & McCaigue, M. (2007). Orthopaedic tissue engineering and bone regeneration. *Technology and Health Care, 15*(1), 57–67. PMID: 17264413
49. Reid, R. L. (1968). Hernia through an iliac bone-graft donor site: A case report. *Journal of Bone and Joint Surgery. American Volume, 50*(4), 757–760. https://doi.org/10.2106/00004623-196850040-00012
50. Ricci, J. A., Stewart, W. F., Chee, E., Leotta, C., Foley, K., & Hochberg, M. C. (2006). Back pain exacerbations and lost productive time costs in United States workers. *Spine, 31*(26), 3052–3060. https://doi.org/10.1097/01.brs.0000249521.61813.aa
51. Hoy, D., March, L., Brooks, P., et al. (2014). The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases, 73*(6), 968–974. https://doi.org/10.1136/annrheumdis-2013-204428
52. Vällfors, B. (1985). Acute, subacute and chronic low back pain: Clinical symptoms, absenteeism and working environment. *Scandinavian Journal of Rehabilitation Medicine. Supplement, 11*, 1–98. PMID: 3161177
53. United States Bone and Joint Initiative. (2018). *The hidden impact of musculoskeletal disorders on Americans.*
54. Rubin, D. I. (2007). Epidemiology and risk factors for spine pain. *Neurologic Clinics, 25*(2), 353–371. https://doi.org/10.1016/j.ncl.2007.01.004
55. Hartvigsen, J., Hancock, M. J., Kongsted, A., et al. (2018). What low back pain is and why we need to pay attention. *The Lancet, 391*(10137), 2356–2367. https://doi.org/10.1016/S0140-6736(18)30480-X
56. Katz, J. N. (2006). Lumbar disc disorders and low-back pain: Socioeconomic factors and consequences. *Journal of Bone and Joint Surgery. American Volume, 88*(Suppl 2), 21–24. https://doi.org/10.2106/JBJS.E.01273
57. Hsu, W. K., & Wang, J. C. (2008). The use of bone morphogenetic protein in spine fusion. *The Spine Journal, 8*(3), 419–425. https://doi.org/10.1016/j.spinee.2008.01.008
58. Ludwig, S. C., Kowalski, J. M., & Boden, S. D. (2000). Osteoinductive bone graft substitutes. *European Spine Journal, 9*(Suppl 1), S119–S125. https://doi.org/10.1007/PL00008317
59. Agency for Healthcare Research and Quality. (2012). *HCUP projections report.* http://hcup-us.ahrq.gov/reports/projections/2012-03.pdf
60. Kurtz, S. M., Lau, E., Ong, K., Zhao, K., Kelly, M., & Bozic, K. J. (2009). Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. *Clinical Orthopaedics and Related Research, 467*(10), 2606–2612. https://doi.org/10.1007/s11999-009-0834-6
61. Cram, P., Lu, X., Kates, S. L., Singh, J. A., Li, Y., & Wolf, B. R. (2012). Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. *JAMA, 308*(12), 1227–1236. https://doi.org/10.1001/2012.jama.11153
62. Nishida, J., & Shimamura, T. (2008). Methods of reconstruction for bone defect after tumor excision: A review of alternatives. *Medical Science Monitor, 14*(8), RA107–RA113. PMID: 18668007
63. Wood, T. J., Leighton, J., Backstein, D. J., et al. (2019). Synthetic graft compared with allograft reconstruction for extensor mechanism disruption in total knee arthroplasty: A multicenter cohort study. *Journal of the American Academy of Orthopaedic Surgeons, 27*(13), 451–457. https://doi.org/10.5435/JAAOS-D-18-00393
64. Buser, Z., Brodke, D. S., Youssef, J. A., et al. (2016). Synthetic bone graft versus autograft or allograft for spinal fusion: A systematic review. *Journal of Neurosurgery: Spine, 25*(4), 509–516. https://doi.org/10.3171/2016.1.SPINE151005

65. Gouin, F., Yaouanc, F., Waast, D., Melchior, B., Delecrin, J., & Passuti, N. (2010). Open wedge high tibial osteotomies: Calcium-phosphate ceramic spacer versus autologous bone graft. *Orthopaedics & Traumatology: Surgery & Research, 96*(6), 637–645. https://doi.org/10.1016/j.otsr.2010.03.022
66. Raza, W., Qadir, I. R., & Sherzad, P. (2020). Outcome of bone allograft in orthopedic patients. *Journal of Medical Sciences, 28*(3), 282–287.
67. Coventry, M. B., & Tapper, E. M. (1972). Pelvic instability: A consequence of removing iliac bone for grafting. *Journal of Bone and Joint Surgery. American Volume, 54*(1), 83–101. PMID: 4262362
68. Younger, E. M., & Chapman, M. W. (1989). Morbidity at bone graft donor sites. *Journal of Orthopaedic Trauma, 3*(3), 192–195. https://doi.org/10.1097/00005131-198909000-00002
69. Farfalli, G. L., Aponte-Tinao, L., Lopez-Millán, L., Ayerza, M. A., & Muscolo, D. L. (2012). Clinical and functional outcomes of tibial intercalary allografts after tumor resection. *Orthopedics, 35*(3), e391–e396. https://doi.org/10.3928/01477447-20120222-25
70. Ricciardi, B. F., Oi, K., Trivellas, M., Lee, Y. Y., Della Valle, A. G., & Westrich, G. H. (2017). Survivorship of extensor mechanism allograft reconstruction after total knee arthroplasty. *Journal of Arthroplasty, 32*(1), 183–188. https://doi.org/10.1016/j.arth.2016.06.031
71. Brown, N. M., Murray, T., Sporer, S. M., Wetters, N., Berger, R. A., & Della Valle, C. J. (2015). Extensor mechanism allograft reconstruction for extensor mechanism failure following total knee arthroplasty. *Journal of Bone and Joint Surgery. American Volume, 97*(4), 279–283. https://doi.org/10.2106/JBJS.N.00759
72. Rogers, B. A., Sternheim, A., De Iorio, M., Backstein, D., Safir, O., & Gross, A. E. (2012). Proximal femoral allograft in revision hip surgery with severe femoral bone loss: A systematic review and meta-analysis. *Journal of Arthroplasty, 27*(5), 829–836.e1. https://doi.org/10.1016/j.arth.2011.10.014
73. Willems, K., Lauweryns, P., Verleye, G., & Van Goethem, J. (2019). Randomized controlled trial of posterior lumbar interbody fusion with Ti- and CaP-nanocoated polyetheretherketone cages: Comparative study of the 1-year radiological and clinical outcome. *International Journal of Spine Surgery, 13*(6), 575–587. https://doi.org/10.14444/6080
74. Evaniew, N., Tan, V., Parasu, N., et al. (2013). Use of a calcium sulfate–calcium phosphate synthetic bone graft composite in the surgical management of primary bone tumors. *Orthopedics, 36*(2), e216–e222. https://doi.org/10.3928/01477447-20130122-25
75. Kelly, C. M., & Wilkins, R. M. (2004). Treatment of benign bone lesions with an injectable calcium sulfate–based bone graft substitute. *Orthopedics, 27*(1 Suppl), s131–s135. https://doi.org/10.3928/0147-7447-20040102-11
76. Gitelis, S., Piasecki, P., Turner, T., Haggard, W., Charters, J., & Urban, R. (2001). Use of a calcium sulfate–based bone graft substitute for benign bone lesions. *Orthopedics, 24*(2), 162–166. https://doi.org/10.3928/0147-7447-20010201-19
77. Hirata, M., Murata, H., Takeshita, H., Sakabe, T., Tsuji, Y., & Kubo, T. (2006). Use of purified beta-tricalcium phosphate for filling defects after curettage of benign bone tumours. *International Orthopaedics, 30*(6), 510–513. https://doi.org/10.1007/s00264-006-0156-1
78. Schindler, O. S., Cannon, S. R., Briggs, T. W., & Blunn, G. W. (2008). Composite ceramic bone graft substitute in the treatment of locally aggressive benign bone tumours. *Journal of Orthopaedic Surgery (Hong Kong), 16*(1), 66–74. https://doi.org/10.1177/230949900801600116
79. Hoornaert, A., Rignont-Bret, C., Le Hecho, H., Wocjtiuk, F., Enkel, B., & Layrolle, P. (2020). Healing process with the use of a new resorbable synthetic membrane. *The Open Dentistry Journal, 14*(1), 450–458. https://doi.org/10.2174/1874210602014010450

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