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Bioactive materials for craniofacial tissue repair in pediatric dentistry. A short review

Materiales bioactivos para la reparación del tejido craneofacial en odontología pediátrica. Una revisión breve

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ABSTRACT: The craniofacial structures are most crucial aspect of a person's appearance from an aesthetic standpoint even in children too. Defects in this area cause visible malformations in patients, which are both physically and psychologically damaging. Although advances in grafting and tissue transfer procedures have improved surgical outcomes, we still have limitations in our ability to entirely regenerate missing or faulty tissue. Tissue engineering therapies based on the supporting action of biomaterials combined with the synergistic action of osteo-inductive chemicals and recruited stem cells that can be driven to the process of bone regeneration have emerged. The goal of this narrative review is to highlight the approaches for reconstructing craniofacial bone deformities for child patients.

KEY WORDS: Bioactive materials, cleft lip and palate, congenital craniofacial bone defects, growth factors.

INTRODUCCIÓN

Craniofacial bone defect abnormalities affect both soft and hard tissues and can be caused by trauma, tumour and cyst-induced bone recession, or congenital ailments. Craniofacial abnormalities have a major negative impact on the quality of life and self-esteem of an individual. Cleft lip and palate (CL/P) is the most prominent congenital craniofacial abnormality caused by abnormal embryonic development of soft and hard tissues around the mouth cavity and face (Martín-del-Campo *et al*., 2019). Calvarial defect reconstruction is a prevalent issue in the treatment of congenital malformations, craniofacial trauma, and oncologic surgery (Bekisz *et al*., 2017).

In Present scenario autografts are indeed the gold standard for bone repair and replacement in current times. However, autografts have certain limitations, such as additional expenditure and trauma to the patient, the probability of donor site morbidity, and limited supply. Allografts have also been reported to be successful, but viral transmission and immunogenicity are pertinent concerns, in addition to the reduced availability and high expenses. Hence, there was a pressing need to design bone substitute materials that mimicked bone's characteristics while overcoming the shortcomings of autografts and allografts. Metals, polymers, corals, Calcium Phosphate (CaP) of natural (from corals or bovine bone) or synthetic origin, bioactive glasses (specially formulated silica-based glasses), and polymer and CaP composites have all been used in commercial and experimental materials for bone repair, substitution, or augmentation in recent times (LeGeros, 2002).

Biomaterials-based osteoconductive techniques, frequently in conjunction with modulation of the biomolecular mechanisms of bone formation, present a potential answer for bone tissue creation. Compounds such as hydroxyapatite

and tricalcium phosphate (TCP) have been used in the development of bioactive ceramic-based approaches (Dutta *et al*., 2003; Wilson *et al*., 2004).

Adenosine receptor agonists have recently showed potential in improving osteogenesis, particularly through the adenosine A2A receptor (A2AR), which inhibits osteoclasts and inflammation while also activating osteoblasts. The use of dipyridamole-coated 3DPBC scaffolds to fill cranial lesions enhanced bone regeneration as effectively as BMP-2, without the worrying effects of BMPs such as osteolysis, ectopic bone development, and craniosynostosis (Bekisz *et al*., 2017).

Bekisz *et al*. (2017) in their study, showed that dipyridamole improved the calvarial bone regeneration capacity of 3D-printed bioactive ceramic scaffolds, they further observed that significant enhancement in the bone formation in dipyridamole-containing samples at 3 and 6 weeks post-operative period.

Many studies have reported the efficacy of new tissue engineering methods, but very few are documented in literature from pediatric perspectives. This review is an attempt to emphasise on advanced/ newer approaches for the management of craniofacial defects in Children incorporating advanced bioactive materials.

Scaffold-guided bone tissue regeneration

Growth factor delivery (GFD) is a strategy intended to compensate for the low osteoinductivity of guided bone regeneration approaches and to mediate the cellular response to the scaffold microenvironment. GFs are soluble polypeptides that adhere to their cell membrane receptors and interfere with cellular activity. Bone morphogenetic proteins (BMPs), fibroblast growth factor-2 (FGF-2), transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF) are among the GFs that have a role in osteogenesis. As a result, they're commonly used in bone regenerative therapies to guide cell differentiation and tissue creation toward bone tissue regeneration. Vascularization, which is aided by angiogenic GFs like as PDGF and TGF-b, FGF-2, and vascular endothelial growth factor (VEGF), is another critical component for the long-term viability of new regenerated bone tissue (Teven *et al*., 2015; Duruel *et al*., 2017; Wang *et al*., 2018) (Table I).

Scaffold-mediated GFD is a pioneering delivery technique that allows for more precise injection profiles, release kinetics, and therapeutic factor localisation. Tissue healing and morphogenesis are improved by a GFD release profile that more closely resembles the natural environment. Multiple GFs are supplied in a sequential or simultaneous spatiotemporal pattern via GBR delivery devices that release the Growth Factors (GF) according to a predetermined therapeutic time profile optimal for repairing bone tissue, in order to overcome this problem. Release of a combination of BMP-2 and TGF-or BMP and VEGF for bone regeneration stimulation is one of the most well-known sequential GF delivery patterns (Pilipchuk *et al*., 2015; Teven *et al*., 2015; Duruel *et al*., 2017; Wang *et al*., 2018; Tahmasebi *et al*., 2020).

Bone marrow stromal stem cells (BMSSCs) have been shown to be effective in inducing new bone formation in critical-size defects in animal models when compared to other stem cells with the desired osteoblastic activity (Yamada *et al*., 2004; Meinel *et al*., 2005; Mankani *et al*., 2006; Liu *et al*., 2014). Indeed, scaffold-type constructs, tri-dimensional forms, and cell culture all demonstrate the ability of those cells to stimulate bone production. Several matrices have been used in recent years, ranging from nonresorbable biomaterials like hydroxyapatite in various relationships with BMSSCs, such as layers encapsulated in hydrogel (Liu *et al*., 2013) or calcined bovine bone (Wang *et al*., 2014), to resorbable ones like b-TCP or calcium phosphate (CaP) (Özdal *et al*., 2015). CaP matrices rather than hydroxyapatite, had a better in vivo and i*n vitro* response on improved trabecula development, cell density, and decreased fibrosis (Scarano *et al*., 2017).

Craniofacial-derived MSCs (CDMSCs) could be utilized in craniofacial and non-craniofacial tissue engineering, and could even serve as prototypes for non-craniofacial structures. They enable bone tissue engineering in specific shapes and dimensions, which has a lot of potential for correcting segmental abnormalities in the appendicular bones (Liu *et al*., 2014; Machado *et al*., 2012). Despite the fact that CDMSCs and appendicular MSCs (BMMSCs) have similar differentiation capacities, more research is needed to assess their ability to efficiently regenerate craniofacial structures and treat non-craniofacial abnormalities (Machado *et al*., 2012) (Table II).

Table I. Applications of biologic and organic materials in bone regeneration.

Scaffold	Stem cells/growth factor	Method	outcome
2010- Biological Scaffolds Mineralized bone xenografts and allografts	Recombinant human bone morphogenetic protein-2/acellular collagen sponge	Grafts and GFs combination for maxillary sinus augmentation and the vital bone formation, and bone graft density and stability were analysed.	New woven bone was formed after 6 months. Minimal traces of remained allograft were observed showing to be accelerated remodelling or undergoing resorption
2011 Organic bovine bone cancellous blocks and Organic bovine bone cortical granules		Assessed osseus repair after filling epiphyseal rabbit femur defects with either the blocks, granules, or only blood clots.	In histomorphometry and radiographic investigations, the experimental groups initially demonstrated a modest reduction in the healing time that did not persist over time.
2011 Cortical porcine bone xenograft		The xenograft was used for sinus augmentation. Specimens were extracted from increased sinuses and analysed histologically and histomorphometrically.	The grafted biomaterial was incorporated into the regenerated bone, illustrating that it is a biocompatible osteoconductive material for enhancing the maxillary sinus that ideally does not obstruct the normal bone-restoring procedures.
2011 Demineralized bone matrix and poly (70 L-lactide-co30DL-lactide) copolymer	Stromal vascular fraction (SVF)	combination implanted in rat calvarial defect models and the new bone formation was histologically evaluated.	Both the combined matrix and the SVF demonstrated significant new bone growth. SVF is a viable replacement for cell-based regenerative tissue engineering therapies because it was shown that undifferentiated adipose-derived stem cells are responsible for the production of new bone.
2012 Demineralized bone matrix	Adipose-derived stem cells (ASCs)	osteogenesis properties were evaluated using rat critically-sized calvarial defect models	ASCs accelerated greater osteogenic regeneration in vivo compared to undifferentiated ASCs, suggesting that induced ASCs may be suitable for clinical tissue regeneration. ASCs enhanced osteogenic differentiation.
2013 Xenograft composed of oragraft and Bio-Oss	PTH injection	Xenograft grafted in the sockets and the intermittent PTH was administered in different timings	Immediately following tooth extractions, intermittent PTH therapy shown a great potential for encouraging bone growth in the sockets and supporting a successful ridge preservation technique.
2013 New highly purified bovine allograft called Laddec	Platelet-rich plasma (PRP)	PRP and Laddec filled into the bone defects	Laddec enhanced bone regeneration in conjunction with PRP and demonstrated potential for routine clinical regenerative uses for treating cystic bony defects.
2013 Xenogenic Gen-Ox-lyophilized bovine bone organic graft and Gen-Ox-lyophilized bovine bone organic matrix	Autologous platelet-rich plasma	The effect of grafts on the bone-healing process was evaluated histologically using autologous PRP in artificial intrabony lesions in the rabbit femur bone filled with matrix or left unfilled.	Compared to the graft alone, the xenogenic matrix/plasma combination dramatically improved neovascularization and accelerated the production of new bone.
2014 Demineralized freeze-dried bone allograft vs anorganic bovine bone xenograft		Scaffolds grafted in human infrabony periodontal defects.	Both demonstrated the ability to repair periodontal infrabony defects. Except for having a higher adhesion level, demineralized freeze-dried bone allograft was just as successful as anorganic bovine bone xenograft.

2015 Human mineralized perforated allograft bone in particulate form and type I porcine collagen membranes		Allografts filled into the sockets and the membranes used as guided bone regeneration barrier	The resulting new bone regeneration varied from 1.8–43% and the number of sites stated to be too small to determine their significance.
2016 Decellularized natural bone matrix particles	Rat mesenchymal stem cell	matrix and stem cells implanted in the orthotopic in vivo model.	In vitro and in vivo, matrix particles successfully stimulated cell growth, osteogenesis, and bone repair, offering potential as a biological bone graft.
2016 Modified demineralized bone matrix	Collagen-binding stromal-cell-derived factor-1α	combined matrix was implanted in rat femur defect models.	The modified scaffolds were demonstrated to recruit endogenous stem cells and enhance bone repair.
2017 Decellularized dental pulp ECM from swine	Human dental pulp SCs	Decellularization was carried out using Triton X-100 and 10 % sodium dodecyl sulphate. Nude mice received subcutaneous transplants of implanted ECM.	Decellularized ECM successfully induced SC proliferation and differentiation, demonstrating a promising potential for dental pulp disease restoration.
2017 Acellular bovine cancellous bone matrix	Rabbit fetal osteoblasts	The rabbit foetal osteoblast cells were cultured and characterized using a specific marker and their adhesion, proliferation, and penetration were investigated.	With the help of the matrix filopodial extensions through the tissue core, the scaffold effectively supported cell growth and proliferation.
2017 A novel biologically active bone graft	Freeze-dried bone marrow stem cells	mandibular bone defects were repaired using autogenous rib grafts and a new biologically active bone graft.	Following tumour removal, the newly created biologically active bone graft and bone marrow stem cells demonstrated promising potentials for rebuilding the mandibular bone deficiencies.
2018 Bone decellularized extracellular matrix, Polycaprolactone, beta-tricalcium phosphate		The capacity of guided bone regeneration of the composite was evaluated *in vitro*	The composite scaffold showed outstanding potential as bone graft replacement for effective bone regeneration
2018 Bio-Oss and freeze-dried human bone		The bone grafts were implanted into 3-mm artificially created calvarial defects on the parietal bone	Both bone grafts induced bone regeneration and Bio-Oss proved to be highly osteoconductive.
2018 Cancellous bone of porcine femurs		Porcine cancellous bone was decellularized via a new method.	generated porcine-derived bone scaffold was proposed as a possible bone graft.
2019 Bovine derived xenograft and biphasic calcium sulphate/hydroxyapatite		The grafts were randomly implanted in the tooth extracted site.	Biphasic calcium sulphate/hydroxyapatite showed equal or better results in socket preservation compared to the xenograft.
2019 Chitosan combined with simvastatin-loaded nanoparticles		*In vitro* and *in vivo* studies were conducted on the properties of various composite formulations as well as their effects on cell proliferation and differentiation	Simvastatin-loaded nanoparticles combined with chitosan resulted in significant early collagen enhancement and enhanced bone repair.
2019 Gelatin-chitosan, hydroxyapatite, _-tricalcium phosphate	Mesenchymal stem cells	mechanical, physiochemical, and osteogenic properties of the nanoceramic composite scaffolds were tested *in vitro*	gelatin-chitosan composites containing 30 wt.% hydroxyapatite showed the best bioactivity and bone substitution potentials.

Table II. Different Materials used for Cleft Repair in child.

Type of material	Author
Adipocyte stem cells (ADSCs)	Pourebrahin *et al*. (2013) proposed the use of adipose tissue in maxillary alveolar cleft defects, due to their potential for differentiation, the easy accessibility to this source of cells, and their capability to rapidly expand in vitro. They reported ADSCs as promising solution for the reconstruction of human maxillofacial bone defects in the case of limited autograft availability or morbidity at the donor site.
BMSC and dental pulp	Korn *et al*. (2017) demonstrated that BMSCs could be used to promote bone formation in a maxillary defect through their osteogenic differentiation mediated by BMP-4
PRFs	Al-Ahmady *et al.* (2018) introduced a novel strategy for alveolar cleft reconstruction by combining BMSCs seeded on a collagen sponge with platelet-rich fibrin (PRF) and nanohydroxyapatite
Bioceramics	In a bilateral alveolar goat cleft model, Janssen *et al.* (2017) reported osteoinductive microstructured TCP granules embedded in a glycerol matrix as an alternative to autologous bone grafts for alveolar cleft repair since they can stimulate bone growth when implanted at heterotopic sites.
Polymeric Biomaterials poly (_-caprolactone) (PCL), poly (lactic acid) (PLA), poly (glycerol sebacate) (PGS), poly (lactide-co-glycolide) (PLGA), or polyhydroxyalkanoates (PHA)	Flores-Cedillo *et al*. prepared membrane composites made of multiwall carbon nanotubes (MWCNTs) with PCL, demonstrating their ability to allow adhesion and proliferation of human dental pulp stem cells (HDPSCs), and enhancing their osteogenic development toward phenotypes that are similar to b one, allowing for bone regeneration and making them appropriate for CL/P
	Hoshi *et al.* (2017) developed an implant-type tissue-engineered cartilage using a PLA based scaffold and evaluated it clinically by inserting it into subcutaneous areas of nasal dorsum in three patients to correct cleft lip–nose deformity. The maintenance of the patients' dorsum and apical morphology was subsequently confirmed one year following implantation
	Puwanun *et al*. (2018) but using biodegradable electrospun PCL scaffolds with the ability to support bone-forming cells and within cleft palate bone
	Zaky *et al*. (2017) aimed to enhance biocompatibility, biodegradability, and material elasticity by creating a biomimetic cellular niche based on poly glycerol sebacate (PGS) in which bone marrow stromal cells were mechanically stimulated to produce their own extracellular matrix leading to a biochemically mimicking environment of bone.
Cryogel scaffolds	Hixon *et al.* (2017) described cryogel scaffolds as tissue-engineered constructs formed at sub-zero temperatures, with excellent potential for the treatment of patient-specific bone defects. They used patient-specific 3D-printed molds derived from computed tomography for scaffold fabrication during the thawing of the cryogels, resulting in a macroporous, sponge like products for creating site specific implants for treating CL/P
Folic Acid Derivatives	Fernandez Villa *et al.* (2018) highlighted the potential of folic acid as a key bioactive compound to enhance the effectiveness of biomaterial performance and biological functions for the regeneration of tissues and organs. The potential for novel folic acid derivatives holding bioactive cations like Sr or Zn to speed up bone growth in craniofacial abnormalities and reduce inflammation has also been demonstrated.
	Rojo *et al*. (2015) developed a carrier for Sr based on folic acid with a remarkable capacity of enhancing bone tissue formation and synergic benefits on cell replication and differentiation processes.
	Martín-del-Campo *et al.* (2016) demonstrated that the incorporation of strontium folate within 3D porous bio-hybrid scaffolds for regeneration of bone tissue in craniofacial area

Bioactive Materials For Cleft Repair

Orofacial clefts result from the failure of developing embryonic facial and palatal processes to ultimately merge or fuse (Fig.1). The most prevalent congenital craniofacial defect observed in children is CL/P, which requires early surgery and face reconstruction procedures that may be amended during childhood and infancy which can be done via tissue engineering approaches based on the synergic trio of employing functional biomaterials, vehiculation and local distribution of bioactive restorative chemicals, and guided or recruited stem cells (Figs. 2 and 3). These are progressively providing successful regenerative therapies for managing CL/P (Table III) (Martín-del-Campo *et al*., 2019).

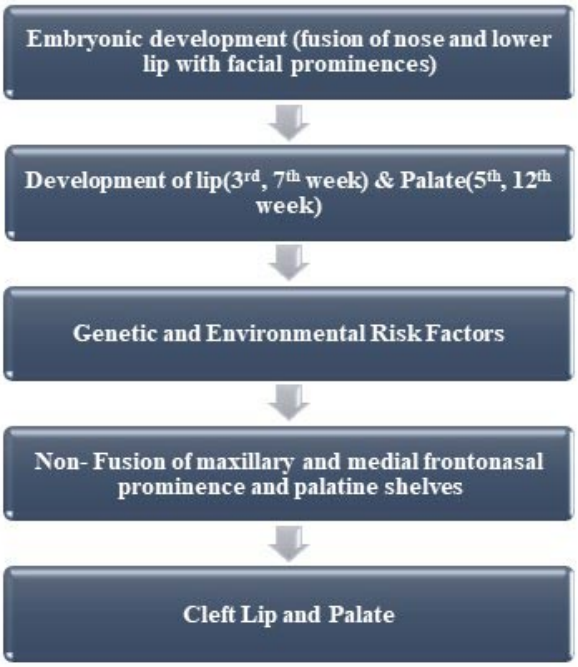

Fig. 1. Etiopathogenesis of CL/P.

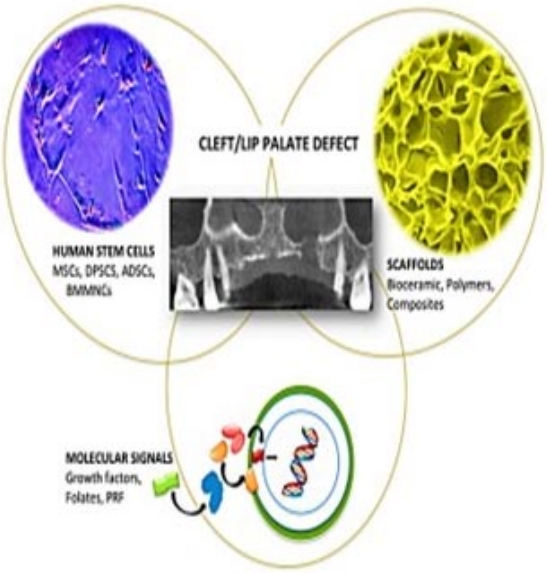

Fig. 2. Human stem cells, biomimetic scaffolds, and regenerative molecule signals as fundamental pieces of the tissue engineering puzzle for cleft/lip palate regeneration (Martín-Del-Campo *et al*., 2019).

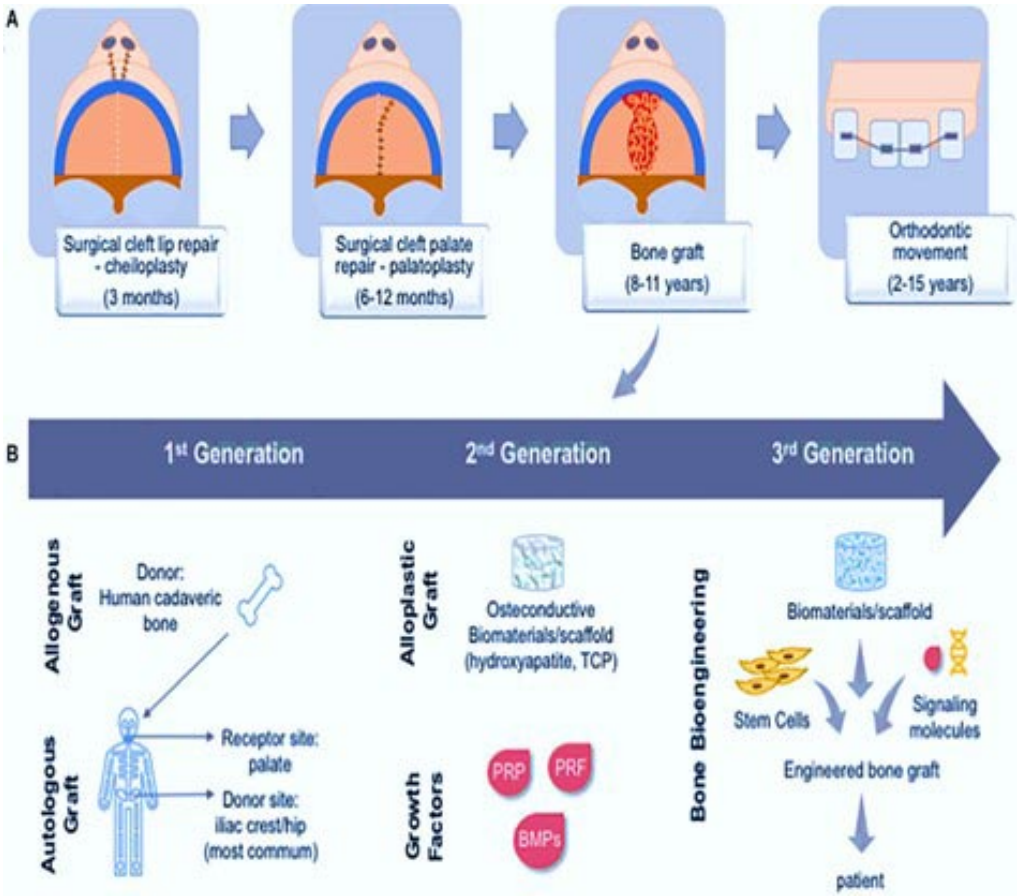

Fig. 3. Chronological management over time and types of bone graft. (A) lip reconstruction (around 3 months); followed by palate reconstruction (between 6–12 months); primary bone graft in the hard palate (between 8–11 years); and, then orthodontic movement (between 2–15 years). (B) autologous and allogenous graft (1st generation), osteoconductive biomaterials and recombinant growth factors or natural adjuvants (2nd generation), and bone bioengineering [stem cells from patient, biomaterials and signalling molecules to create an in vitro engineered bone graft] (3rd generation) (Paiva *et al*., 2019).

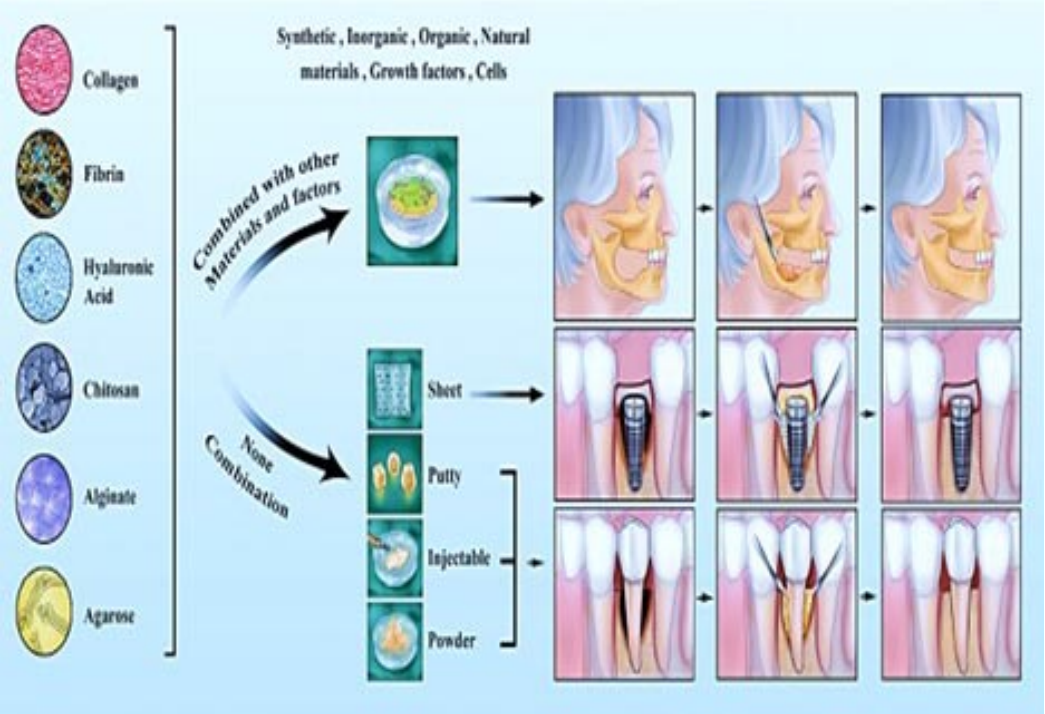

Fig. 4. Popular organic biomaterials used for bone regeneration (Tahmasebi *et al*., 2020).

Table III. Various materials used for craniofacial bone repair.

Material	Benefits	Drawbacks	Novel developments
Zinc	Biocompatible	Low mechanical properties	Porous structures
	Antibacterial	Releases large zinc ions harmful to cells	Calcium phosphate coatings
Bioglass	Bioactive	Brittle, Low fracture toughness	Metal doping
	Osteoconductive	Poor osteoinductivity	
	Integration with host bone		
	Antibacterial		
Calcium phosphates	Osteoinductive	Brittle, Slow resorption	Metal doping
	Resorbable	Limited mechanical strength	Addition to polymers as coatings
	Injectable as a cement, shapeable	Risk of infection	
Silica nanomaterials	Low cytotoxicity	Crystallinity impacts biocompatibility	Surface modifications
	High porosity	Aggregation of nanoparticles	Combination with polymers
	High mechanical strength	High concentrations can result in particle formation and	
	Biocompatible	cytotoxicity.	
	Tunable pore size	Concentration limits	
	Drug delivery vehicles	Risk of infection	
	Osteogenic Promotes vasculature		
Polylactic acid (PLA)	Biocompatible	Acidic degradation products may cause inflammation	Coat with calcium phosphate
	Biodegradable	Risk of infection	Blend with multiple polymers
	Easily 3D-printed into specific shapes and porosities		
	Shorter degradation time than PCL (6 + months)		
	High mechanical properties		
Polycaprolactone (PCL)	Flexible	Low mechanical stiffness	Blend with multiple polymers
	Biocompatible	Long degradation times	Use different polymer
	Biodegradable	Acidic degradation products	conformations (star)
	Easily 3D-printed into specific shapes and porosities	High transition temperature for shape actuation	
	Shape-memory fabrication	Risk of infection	
Collagen	Tunable pore size	Low mechanical properties	Reinforce with stronger materials
	Biocompatible	Disease transmission risk	Collagen derived from marine
	Sequester growth factors easily	Need mineral to induce osteogenesis	sources
		Risk of infection	Add calcium phosphate
Chitosan	Antibacterial	Poor mechanical properties	Reinforce with stronger materials
	Anti-inflammatory	Low cell attachment	Modify fabrication (granular
		Poor osteoconductivity	hydrogels)
		Need mineral to induce osteogenes	

CONCLUSION

Incorporating biomaterials to improve scaffold qualities and improving structure through more environmentally sustainable bio-based materials and computer-aided designs allows us to emulate the configuration, morphologic traits, and mechanical function of bone. Advances in disclosing the osteogenic ability of different stem cells, as well as discovering more easily accessible and abundant sources of stem cells, are providing promising prospects for craniofacial bone repair. Incorporation of growth factors, particularly BMP, has been extensively investigated and has frequently demonstrated promise in terms of enhancing bone regeneration. Innovations in GFD methods and vectors have the potential to improve bone regeneration, but safety concerns remain and must be addressed before it can replace autologous grafting approaches.**REFERENCES**

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RESUMEN: La estructura craniofacial es el aspecto mas importante de la apariencia de las personas desde un punto de vista estético, incluyendo también a los niños. Defectos en esta área como las malformaciones traen requerimientos físicos y psicológicos. Aunque avances en injertos óseos y transferencia de tejidos han mejorado los resultados, aun existen limitaciones en la capacidad de regenerar la estructura perdida. Terapias con ingeniería de tejidos son basadas en la acción de biomateriales convinados con la acción sinérgica de materiales osteoconductivos reclutando celular madre que pueden llevar a los procesos de regeneración emergente. El objetivo de esta revisión narrativa es la de conocer las aproximaciones para la reconstrucción craneofacial de deformidades óseas en pacientes pediátricos.

PALABRAS CLAVE: Material bioactivo, labio y paladar fisurado, defectos óseos creaneofaciales congénitos.

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