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SYSTEMATIC REVIEWS

Update on synthetic biomaterials combined with fibrin derivatives for regenerative medicine: Applications in bone defect treatment: Systematic review

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Abstract

BACKGROUND

Bone regeneration is a central focus of regenerative medicine, with applications in orthopedics and dentistry, particularly for treating bone defects caused by trauma, infection, or congenital anomalies. Synthetic biomaterials, often combined with fibrin derivatives, offer promising solutions for bone healing and restoration.

AIM
To Explore the increasingly important role of the association of synthetic biomaterials with fibrin in bone regeneration.

METHODS
Search terms included: "synthetic biomaterials AND fibrin sealant", "hydroxyapatite AND fibrin sealant", "tricalcium phosphate AND fibrin sealant", and "synthetic biomaterials AND platelet-rich fibrin (PRF)", resulting in 67 articles. After rigorous screening, 21 articles met the inclusion criteria.

RESULTS
The reviewed studies assessed biomaterials like hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), and fibrin-based products. Key findings highlighted the enhanced osteoconductivity and biocompatibility of HA and β-TCP, especially when combined with fibrin sealants. These composites show significant potential for improving cellular adhesion, promoting osteogenic differentiation, and accelerating bone regeneration. The antimicrobial properties and structural support for cell growth of certain biomaterials indicate a promising potential for clinical applications.

CONCLUSION
This systematic review emphasizes the growing role of fibrin-based biomaterials in bone regeneration and urges continued research to improve their clinical use for complex bone defects.

Key Words: Biomaterials; Bone regeneration; Fibrin sealant; Hydroxyapatite; Orthopedics; Dentistry; Regenerative medicine

Core Tip: The integration of synthetic biomaterials and fibrin composites is a promising strategy in regenerative medicine, demonstrating high biocompatibility and effectiveness in bone formation. It also represents progress in the pursuit of more accessible and clinically applicable solutions for bone reconstruction.

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INTRODUCTION

Bone defects present a major challenge in orthopedic medicine, causing high hospitalization rates and financial costs. These defects are often caused by high-energy trauma and result in bone loss and infection[1,2]. Tissue engineering has evolved over the years, and research has focused on bone defects and healing from conditions such as tumors, infections, osteoporosis, osteonecrosis, osteotomies, and congenital abnormalities[3,4]. In this context, new strategies for bone repair have been constantly explored. Recent advances in biomaterials and manufacturing techniques have enabled the development of natural and synthetic polymer scaffolds for improved clinical application in bone defect repair and regeneration[5,6].

Polymeric scaffolds combine properties that influence their clinical applicability; they show both advantages and disadvantages. Their mechanical properties should provide rigidity comparable to natural tissue. Because of the variable multicellular composition, it is ideal to create adjustable polymeric matrices that allow for mechanical changes over time [7]. Natural and synthetic polymeric biomaterials have been widely used in tissue engineering. In orthopedic medicine, the use of hydroxyapatite (HA), bioglass, and bioceramics is particularly common.

HA is a chemical analog of bone mineral; it is widely studied in various forms and has long been an ideal inorganic material for synthetic applications in orthopedics and bone tissue engineering. Its interconnected porous structure, high tensile strength, biocompatibility, and resorption capability make it an effective scaffold. However, conventional synthetic HA has coarser crystals than natural bone apatite[8-10]. As research advances, nano-structured HA has gained attention, as its nanometric particles enhance protein adsorption, cell adhesion, and surface roughness, thus improving mechanical and biological properties for tissue healing[8,9,11,12].

Calcium phosphates have been used as bone substitutes for over a century, and calcium phosphate cements (CPCs) began to be explored in the 1980s. Early studies by Brown and Chow (1986)[13,14] investigated a self-setting CPC made from tetracalcium phosphate combined with dehydrated dicalcium phosphate cement. The dissolution–precipitation mechanism forms this type of CPC, primarily driven by the nucleation and growth of calcium phosphate compounds. CPCs are commercially available synthetic materials that pose no immunological risks, are resorbable, and whose

dissolution products can be assimilated by the human body[15,16].

Beta-tricalcium phosphate (β-TCP) is a promising material for bone regeneration, known for its biocompatibility, osteoconductivity, and osteoinductivity. It is often used in composite grafts for periodontal and alveolar bone regeneration. For example, β-TCP combined with HA creates a biomimetic material for bone regeneration. β-TCP can dissolve in acids released by osteoclasts or macrophages[17,18].

Another promising material in regenerative medicine is bioadhesives, which are used for bonding or sealing injured tissues. These biomaterials, known as glue, adhesive, sealant, or fibrin biopolymer (FB), have positively impacted tissue regeneration. Human fibrin glue (FG) is synthesized from two lyophilized components. The first is a coagulation protein concentrate, such as fibrinogen, fibronectin, and Factor XIII—reconstituted with a solution of aprotinin, a tissue fibrinolysis inhibitor. The second component, thrombin, is combined with calcium chloride to form a substance essential for hemostasis and wound healing. This combination provides hemostatic, sealing, and biological stimulation properties vital for the formation of a new tissue matrix[19,20]. Many bioadhesives are commercially available (*e.g.*, BioGlue®, CoSeal®, Evicel®, FloSeal®, Progel™ PALS, Tisseel®, and TissuGlu®). Their formulations contain natural and synthetic compounds like albumin, cyanoacrylate, fibrin, thrombin, gelatin, glutaraldehyde, polyethylene glycol, chitosan, and urethanes. Each formulation has distinct properties and was developed and validated for specific applications[21] (Figure 1).

Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) are important advancements in surgery, particularly for growth factor-mediated osteoinduction. Early studies showed promise, but combining PRP with synthetic materials failed to yield statistically significant benefits, causing some controversy[22]. Outcomes depend on preparation techniques, dosage, and application methods. PRF, a second-generation platelet concentrate, is less studied but offers advantages similar to ceramics, such as ease of handling and tolerance. The main difference between PRF and PRP lies in the biochemical manipulation of blood. Whereas PRP requires anticoagulants and bovine thrombin, PRF does not, thus eliminating potential risks associated with bovine thrombin use. The PRF clot forms a dense three-dimensional fibrin matrix that retains platelets and leukocytes, dissolving slowly after application. This matrix is gradually remodeled, resembling a natural blood clot, and this process results in a slow release of growth factors[23,24].

Research in regenerative medicine is advancing quickly, necessitating that professionals stay up to date. Accordingly, we conducted a literature update on the use of the main synthetic biomaterials combined with fibrin derivatives as valuable resources in bone regenerative medicine.

MATERIALS AND METHODS

Protocol and study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the PubMed/MEDLINE database for articles published after 2013 using the following descriptors: "synthetic biomaterials AND fibrin sealant", "hydroxyapatite AND fibrin sealant", "tricalcium phosphate AND fibrin sealant", and "synthetic biomaterials AND PRF". We initially reviewed the titles and abstracts of all identified manuscripts based on eligibility criteria.

This review included studies that were: (1) Conducted using animal models or human subjects; (2) published in English; (3) fully accessible; and (4) Relevant to the research objective. We excluded duplicate articles, unrelated studies, those not using biomaterials, non-English articles, restricted access articles, letters to the editor, and literature reviews.

After the initial selection, we carefully examined the full texts of the remaining articles to confirm their adherence to the eligibility criteria and the review objectives. This step ensured that the methodologies used in the reviewed articles aligned with our aims.

Study selection and data extraction

Study selection and data extraction were conducted independently by two reviewers (Marcelie Priscila de Oliveira Rosso and Bruna Trazzi Pagani) to ensure rigorous and consistent application of predefined eligibility criteria to minimize potential sources of bias. Following full-text screening, relevant data were extracted and organized into standardized tables. Disagreements between reviewers were resolved through consensus based on a re-evaluation of the established criteria. The study selection process is illustrated in the PRISMA flowchart in Figure 2.

RESULTS

Study selection process

Our search retrieved 68 articles published since 2013. After removing eight duplicates, we thoroughly analyzed 60 articles as follows: Nine literature reviews, two articles without full-text access, and 28 articles that did not meet the eligibility criteria. We then excluded all of them from our review. Twenty-one studies met the eligibility criteria and were included in this systematic review. This selection process is summarized in the PRISMA flowchart (Figure 2), ensuring transparency and replicability of the methodology.

Study designs and experimental models

The included studies used diverse methodological approaches. We reviewed 21 articles, consisting of eight human experi-

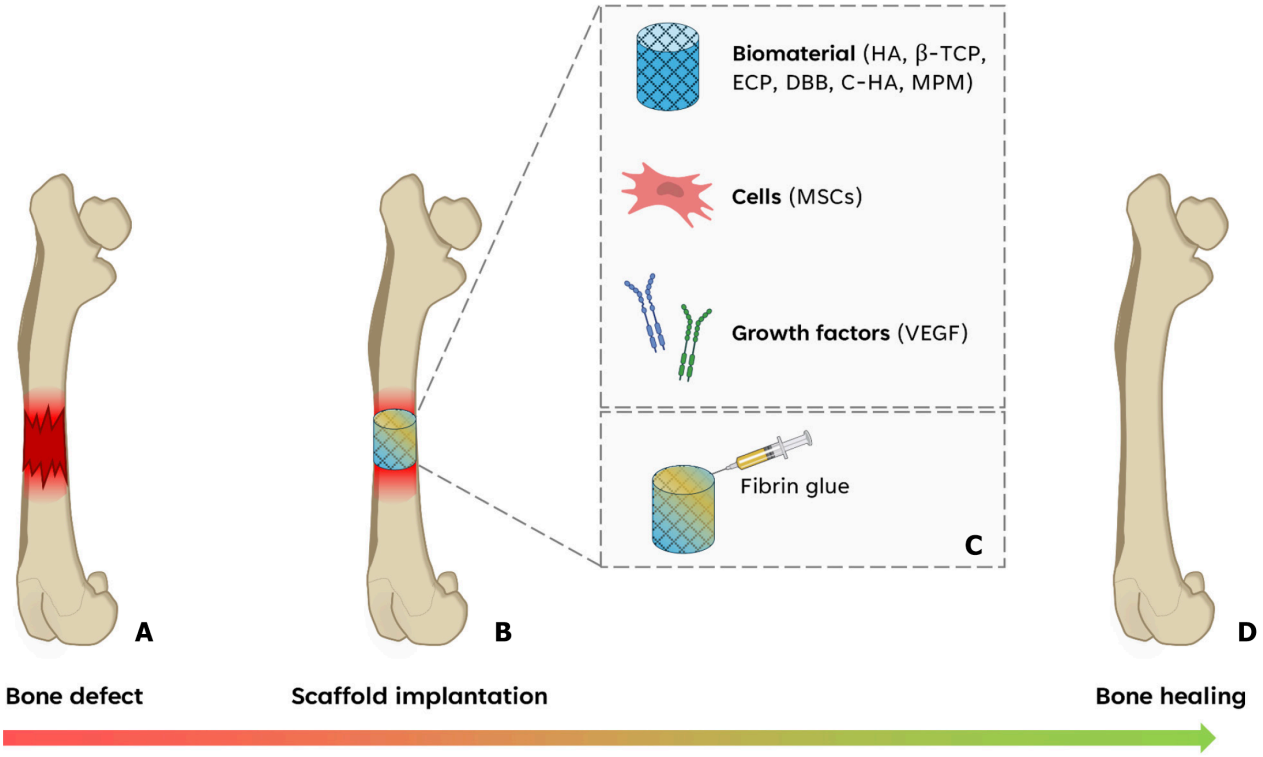

Figure 1 Schematic representation of the bone regeneration process facilitated by biomimetic scaffold implantation combined with fibrin derivatives. A: Illustration of a critical bone defect, characterized by the loss of structural integrity and the need for regenerative intervention; B: Implantation of a bioactive scaffold at the defect site, creating a microenvironment conducive to cellular adhesion, proliferation, and tissue growth; C: Multicomponent strategy to enhance bone regeneration, incorporating synthetic biomaterials such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), experimental calcium phosphate (ECP), deproteinized bovine bone (DBB), collagen-hydroxyapatite (C-HA), and mineralized plasmatic matrix (MPM). This approach is further optimized by integrating mesenchymal stem cells (MSCs), vascular endothelial growth factor (VEGF), and fibrin sealants, which collectively improve scaffold stabilization, cellular recruitment, osteoconductivity, and angiogenesis; D: Final stage of the bone repair process, demonstrating the formation of structurally integrated, mature bone tissue, restoring the biomechanical properties of the affected region. HA: Hydroxyapatite, β-TCP: β-tricalcium phosphate; ECP: Experimental calcium phosphate; DBB: Deproteinized bovine bone; C-HA: Collagen-hydroxyapatite; MPM: Mineralized plasmatic matrix; MSCs: Mesenchymal stem cells; VEGF: Vascular endothelial growth factor.

mental studies, ten animal experimental studies, two *in vitro* studies, and one combined *in vitro* and *in vivo* study. Of the eight studies with humans, two were *ex vivo* (on cadavers). Of the ten studies with animal models, five used rats, three used rabbits, two used sheep, and one used pigs. Most analyzed articles used *in vivo* approaches (76.19%; n = 16), either in animal models or human subjects, whereas the remaining studies used *in vitro*, *ex vivo*, or a combination of *in vitro* and *in vivo* approaches (Figure 3). In terms of animal models, rats were the most frequently used (23.81%; n = 5 studies), followed by rabbits (14.29%; n = 3), sheep (9.52%; n = 2), and pigs (4.76%; n = 1) (Figure 4). This classification underscores the scientific effort to evaluate biomaterials in both controlled laboratory conditions and biologically relevant settings. These studies represent clinical scenarios of reconstructive surgery and trauma repair.

Anatomical sites and bone defect models

A broad anatomical distribution of bone defect models was observed. Studies using human subjects examined the following anatomical regions: The nasal dorsum[25], orbital floor fractures[26], knees (condyles and trochlea)[27], ACI knee[28], maxillary alveolar bone[29], and femoral head[30]. These studies also focused on fractures of the mandible, maxilla, and zygomatic bone[31], as well as late fractures in the humerus, femur, and tibia[32]. In animal studies, defects were induced in the parietal bones[33-36], femur[23,37,38], radius[39], mandible[40,41], and tibia[42]. These models were selected to replicate either cortical or trabecular bone healing environments, allowing the evaluation of regenerative potential under different mechanical and biological challenges.

Types and combinations of biomaterials used

The reviewed studies explored multiple biomaterials and their combinations, as follows: HA alone or combined with other biomaterials [such as β-TCP, Poly (D,L-lactide-co-glycolide) (PLGA), deproteinized bovine bone, Collagen-HA, mineralized plasma matrix (MPM)], monocortical autogenous bone, and phosphoserine-modified cement.

Fibrin sealants were applied in various forms, including heterologous FB derived from snake venom, commercially available human blood-derived fibrin sealant, fibrin-platelet glue derived from PRP, fibrin-collagen adhesive, fibronectin derived from bovine plasma, and L-PRF.

Other materials used included PRP, PRF, bone marrow-derived mesenchymal stem cells (MSCs), adipose tissue-derived mesenchymal cells, autologous adipose tissue, collagen membranes, bovine cortical bone membrane (referred to as the guided bone regeneration method), PLGA, and combinations with PBM using gallium-aluminum-arsenide[33,36].

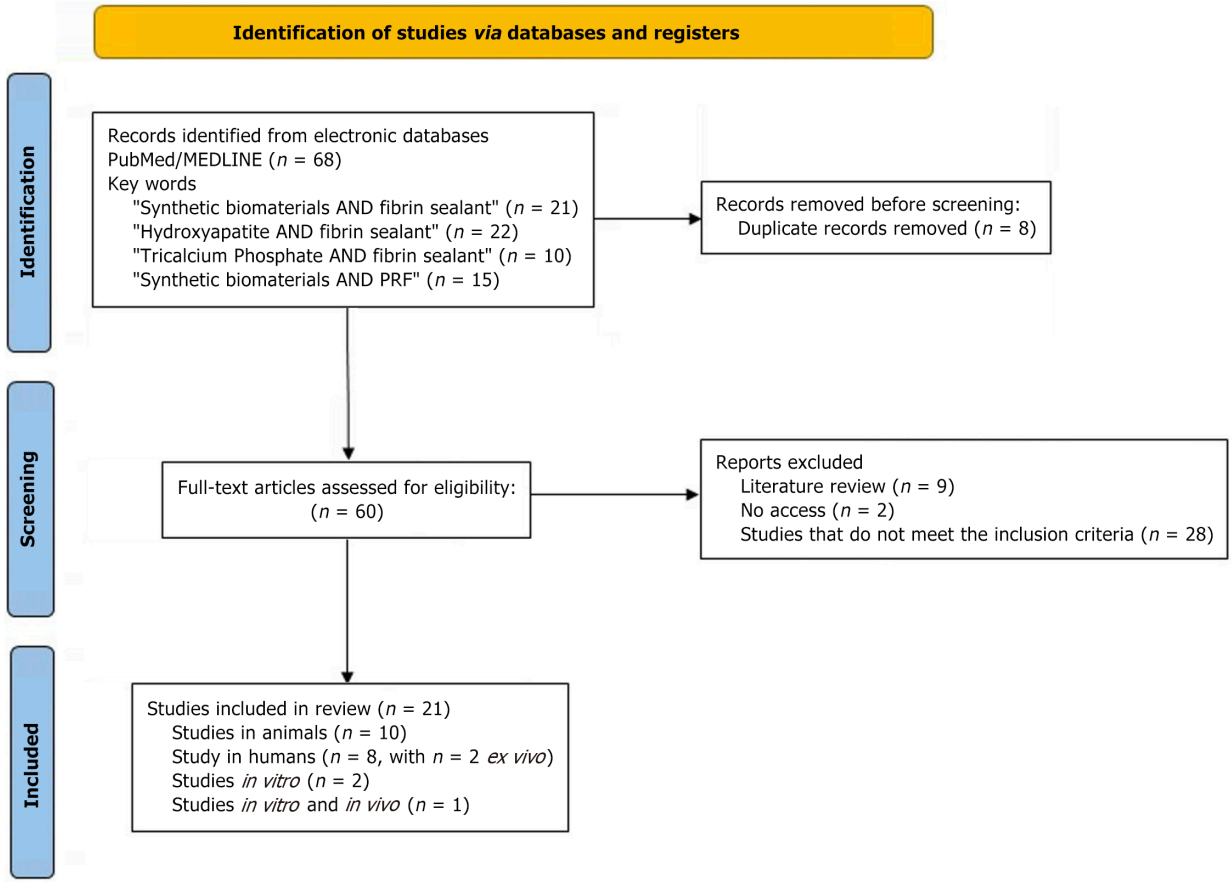

Figure 2 Identification and organization of articles from databases through the PRISMA flow diagram. PRF: Platelet-rich fibrin.

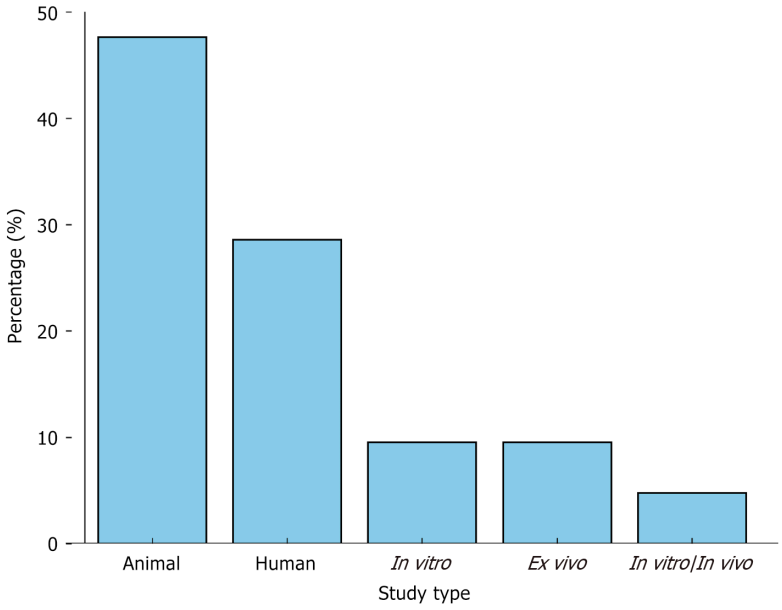

Figure 3 Distribution of studies published since 2013 by type of experimental model.

Figure 5 illustrates the distribution of biomaterials identified in this review: PRF (61.90%, 13 studies), HA (57.14%, 12 studies), β-TCP (42.86%, 9 studies), fibrin, including FG (47.62%, 10 studies), PLGA/PGA (19.05%, 4 studies) and biphasic bioceramic (14.29%, 3 studies). Here we consider that some studies used more than one type of biomaterial.

Synthesis of findings and clinical implications

Table 1 synthesizes all included studies according to the Population, Intervention, Comparison, Outcome strategy, detailing sample size, defect site, biomaterial formulation, experimental model, and main outcomes.

Table 1 Studies published since 2013 on synthetic biomaterials combined with fibrin derivatives in bone

Ref.	Objective	Study type	Biomaterial	Methods	Outcome measures
Studies with HA as the main component					
Reis *et al*[33], 2022	To evaluate the ceramic biomaterial with heterologous FB and PBM	*In vivo* (animal model: Male Wistar rats)	HA/tricalcium phosphate (BP) ceramic (B); FB; PBM with gallium-aluminum-arsenide	Parietal osteotomies (5 mm) were performed on 56 rats. Four groups were established: Biomaterial only, biomaterial + FB, biomaterial + PBM, and biomaterial + FB + PBM	PBM with low-level laser therapy positively influenced the repair of bone defects filled with FB associated with BCP
Meimandi-Parizi *et al* [39], 2018	To compare the effects of combinations of gel, PR-FG, and nHA with the use of nHA alone	*In vivo* (animal model: Mature male Wistar albino rats)	Gel-nHA (4.29 wt% aqueous solution of gel) and PR-FG derived from rat PRP	Bilateral 5 mm osteotomies were performed on the radial diaphysis of 30 rats. Six groups were established: Empty defect (–C), autologous graft (+C), and defects filled with nHA, gel + nHA, PR-FG + nHA, and gel + PR-FG + nHA	All groups showed bone formation and remodeling. PR-FG + nHA achieved superior mechanical strength and healing compared to +C. Gel + PR-FG + nHA regenerated moderately
Kustermans and Mommaerts [25], 2017	To describe the modified Turkish Delight technique for dorsal augmentation using HA combined with Surgicel®	*In vivo* (women)	Hydroxyapatite-calcium carbonate matrix (ProOsteon® 200R), monolayer of oxidized cellulose (Surgicel®), and FS (Tissel®)	Four women (17–32 years old) with congenital defects were treated using hydroxyapatite-calcium carbonate particles wrapped in oxidized cellulose and fixed with 1–2 cm^3 FS, inserted endonasally	Stable, satisfactory outcomes with gradual mineralization were observed. At 4 months, HA granules remained visible; at 1 year, the material formed a homogeneous mass. There was no degradation at 2 years
Chen *et al*[26], 2013	To evaluate a biomaterial combining a biphasic calcium phosphate (HA/β-TCP) osteoconductive scaffold with allogeneic platelet FG	*In vivo* (humans)	Platelet gel, cryoprecipitate, and endogenous thrombin were prepared from PRP, cryoprecipitate, and fresh frozen plasma (FFP). HA/β–TCP (60%-40%), allogeneic platelet FG	Ten patients (20–52 years old) with orbital floor fractures (1–2 cm^2) were treated with PR-FG, prepared by mixing FFP, HA/β-TCP, and activated PRP	The material was easy to handle and mold, with no leakage. All patients showed successful defect restoration. Long-term bone formation likely replaced the biomaterial
Jang *et al*[38], 2014	To investigate the non-autologous Transplantation of hMSCs for regenerating osteochondral defects using a scaffold composed of PR-FG and HA	*In vivo* (animal model: White rabbits)	hMSCs, PR-FG and HA	Osteochondral defects (6 × 8 mm) were created in the femoropatellar groove of 28 rabbits. Five groups were established: Untreated, HA, HA + PR-FG, HA + PR-FG + undifferentiated, and HA + PR-FG + differentiated hMSCs	After 8 weeks, the HA + PR-FG + differentiated hMSCs group showed superior healing, better cartilage integration, and significantly higher histological scores
Filardo *et al* [27], 2014	To evaluate C-HA scaffolds in cadaveric knees under CPM, with and without loading, and assess the effect of FG addition	*Ex vivo* human cadaver	The osteochondral scaffold was a three-layered C-HA structure: (1) A cartilaginous layer made of type I collagen; and (2) An intermediate layer made of type I collagen (60%) + HA (40%); and a subchondral bone layer made of a mineralized blend of type I collagen (30%) and HA (70%). FG (Tisseel®)	Osteochondral defects were created in cadaveric knees. C-HA scaffolds were implanted using press-fit or FG. Two FG-fixed knees underwent loading and continuous passive motion	FG fixation improved outcomes (Drobnic: 4.3 *vs* 2.9; Bekkers: 5.0 *vs* 3.3). Knee loading did not compromise scaffold integrity
Martinčič *et al* [28], 2019	To evaluate patients with ACI grafts for graft-related or unrelated SAEs	*In vivo* (humans)	Classical periosteum-ACI, fibrin-collagen patch (Tachocomb®), collagen membrane (Chondrogide®), alginate-agarose hydrogel (Gel4Cell®), and three-layered C-HA biomimetic scaffold (Maioregen®)	Prospective 18-year study with 151 patients receiving ACI *via* various carriers: Periosteum, fibrin-collagen patch, FG, alginate-agarose hydrogel, or Maioregen®. Grafts were implanted through arthrotomy	Ten-year follow-up showed 86% graft survival. SAEs occurred in about 21%, but none led to definitive failure. Female patients had a 2.8 × higher risk of failure, particularly after cartilage surgery
Mazzone *et al* [31], 2018	To describe the outcomes of using a synthetic bone substitute combined with PRF	*In vivo* (humans)	A biphasic resorbable biomaterial composed of 50% HA and 50% PLGA (ReOss®) and an autologous PRF	Fifteen patients with cysts, trauma, or atrophy in the jaws, mandible, or zygomatic bone received grafts covered with a PRF membrane	Wound dehiscence occurred in four cases but healed without affecting regeneration. At 3–6 months, all patients showed satisfactory healing and mature bone formation

Taufik *et al* [32], 2022	To examine the potential use of bovine HA xenograft and PRF in the treatment of bone defects	*In vivo* (humans)	Bovine HA and PRF	Three patients (2 women and 1 man) with delayed or non-union fractures (humerus, femur, tibia) were treated with internal fixation, bovine HA, and PRF	All showed good to excellent bone restoration, full joint function, and no pain. HA + PRF accelerated healing
Studies with HA + β-TCP as main components					
Cassaro *et al* [37], 2019	To evaluate BCP and FB, combined or not with MSCs	*In vivo* (animal model: Male Wistar rats)	BCP composed of 60% HA and 40% β-TCP (Graftys® BCP, Graftys Sarls, France), FB, and MSCs	Femoral osteotomy (5 × 2 mm) in 80 rats. Five groups were established: Empty defect, BCP, FB + BCP, FB + MSCs, and FB + BCP + MSCs	FB was biocompatible and served as a scaffold. FB + MSCs showed greater bone matrix formation, even without prior osteogenic differentiation
Della Coletta *et al*[36], 2021	To evaluate the effects of PBM on GBR in rat Calvarial defects filled with BCP combined with FB	*In vivo* (animal model: Male Wistar rats)	BCP composed of 70% HA and 30% β-TCP (GenPhos XP®, Baumer SA), FBP, and resorbable bovine cortical bone membrane (GenDerm®, Baumer SA) (ROG)	Parietal osteotomies were performed in 5 mm in 30 rats. Groups included BMG (BCP), BFMG (BCP + FB), and BFMLG (BCP + FB + PBM); all defects were covered with a membrane	All groups showed bone formation, with BFMLG presenting the greatest increase. PBM enhanced and accelerated regeneration when combined with BCP and FB
Nair *et al*[43], 2020	To investigate the use of β-TCP associated with hMSCs combined with FG	*In vitro*	β-TCP, HA nanopowder, and hMSCs from the iliac bone	Twenty β-TCP scaffolds. Group A was seeded with osteogenic hMSCs + FG, and Group B (control) included β-TCP + FG only	Group A showed superior bone regeneration, increased angiogenesis, improved cell infiltration, and preserved mechanical strength
Guastaldi *et al* [35], 2022	To evaluate a biomaterial made of ACP, octacalcium phosphate, and HA	*In vitro* and *in vivo* (animal model: Male white rabbits)	ECP, FS (Center for the Study of Venoms and Venomous Animals), (DBB, Bio-Oss®), and β-TCP (Cerasorb®)	Parietal osteotomies (10 mm) were performed in 45 rabbits. Groups included: ECP, ECP + FS, coagulum, autograft, DBB, and β-TCP. All defects were covered with a collagen membrane	DBB and β-TCP combined with ECP showed increased BV/TV over time. ECP particles decreased in size, and giant cells were frequent. ECP had lower RUNX-2 but higher ALP levels than the other groups
Süloğlu *et al* [44], 2019	To compare the synthetic biphasic ceramic Ceraform® (CR) coated with FG or FN, seeded with osteogenically induced ADMCs	*In vitro*	CR, composed of 65% HA and 35% β-TCP; ADMCs; FG (Tisseel®); and bovine plasma-derived FN	ADMCs were cultured in OIM and seeded on CR scaffolds coated with FG (CR-FG) or FN. FG allowed cell embedding *via* clot formation	Both coatings induced osteogenic markers. CR-FG showed better cell survival, remodeling, and protein expression, including type 1 collagen and BMP-2
Nacopoulos *et al*[23], 2014	To compare the healing properties of PRF and its combination with a graft composed of HA and β-TCP	*In vivo* (animal model: New Zealand white rabbits)	Autologous PRF and HA/β-TCP (60% HA and 40% β-TCP)	Bone defects (4 × 8 mm) were created in femoral condyles of 15 rabbits. Each animal received PRF in one limb and PRF + synthetic graft in the other	The PRF + G group showed a statistically significant higher mean bone healing density, as well as greater cortical and subcortical bone formation
Studies with Fibrin as the main component					
Goto *et al*[34], 2016	To evaluate the combined use of an Atelocollagen sheet and FG for sellar reconstruction	*In vivo* (animal model: Female Wistar rats)	FG, atelocollagen sheet, PGA sheet, and autologous fat tissue	A bilateral 5 mm osteotomy was performed on the parietal bones of eight rats. Experimental groups: FG (Control group), atelocollagen + FG (CLG Group), PGA + FG (PGA Group), and autologous fat tissue + FG (Fat Group)	At 5 weeks, atelocollagen and PGA remained, while FG and fat were absorbed by week 2. Inflammation was lower around atelocollagen than around PGA
Mordenfeld *et al*[29], 2013	To evaluate graft healing and volumetric changes after lateral augmentation with two different materials: DPBB and AB	*In vivo* (humans)	DPBB (Bio-Oss®), monocortical AB block, and FG (Tisseel®)	Split-mouth RCT with 13 patients (6 men and 7 women). Jaws were augmented using 60: 40 or 90: 10 DPBB: AB grafts, both with FG and collagen membranes	The 60 40 group showed greater ridge gain and less graft resorption than the 90 10 group. New bone formation was similar, but soft tissue predominated near the periosteum in both groups
Bojan *et al*[30], 2022	To evaluate the feasibility of bonding freshly harvested human trabecular bone	*Ex vivo*	Phosphoserine-modified cement (OsStic®) and FG (Tisseel®)	Thirteen femoral heads were obtained from arthroplasty patients (8 men and 5 women). Bone cores were	The FG group achieved a peak force of 5.4 ± 1.6 N. The bone adhesive bonded effectively to wet,

	with OsStic® compared to FG			reattached using a bone adhesive (n = 10) or FG (control group)	fatty, osteoporotic bone
Witek *et al* [41], 2020	To evaluate the effect of the leukocyte- and Platelet-rich fibrin (L-PRF)/PLGA composite graft on bone regeneration	*In vivo* (animal model: Female sheep)	PLGA: 85/15 ratio of dl-lactide/glycolide; porous scaffolds; and L-PRF	Submandibular defects (0.40 cm³) were created bilaterally in six sheep. Groups included no L-PRF (control) and PLGA/L-PRF blocks (experimental)	Both groups showed bone formation, with significantly higher bone occupancy in the L-PRF group (38.3% *vs* 28%)
Studies with β-TCP as the main component					
Tee *et al*[40], 2016	To evaluate cell- and growth factor-based reconstruction of mandibular defects and compare scaffold materials and sealing methods	*In vivo* (animal model: Female domestic pigs)	β-TCP, BM-MSCs and PLGA	Mandibular defects (5 cm³) were created in six pigs. The groups were: A (β-TCP), B (β-TCP + BM-MSCs), and C (β-TCP + BM-MSCs + BMP-2/VEGF microspheres). Groups B and C were sealed with FS or PLGA membranes	Groups B and C showed greater regeneration, density, and remodeling than Group A. β-TCP degradation was delayed by membrane sealing and was not macrophage- or osteoclast-dependent
Cakir *et al*[42], 2019	To evaluate the effect of the MPM, composed of a synthetic graft and platelet concentrates, on bone regeneration	*In vivo* (animal model: Male sheep)	MPM, β-TCP, and PRF	Five tibial bone defects were created in six sheep. The groups included: Empty control, MPM, β-TCP, PRF + β-TCP, and autograft	At 3 and 6 weeks, autograft had the most frequent bone formation. MPM showed better healing and bone formation than β-TCP. All groups showed reduced graft remnants over time

ADMC: Adipose-derived mesenchymal cells (s); CR: Alternative synthetic biphasic ceramic Ceraform®; ACP: Amorphous calcium phosphate; AB: Autogenous bone; ACI: Autologous chondrocyte implantation; β-TCP: Beta-tricalcium phosphate; BCP: Biphasic bioceramic; BM-MSCs: Bone marrow-derived mesenchymal stem cells; BMP-2: Bone morphogenetic protein-2; BV/TV: Bone volume as a percentage of total volume; C-HA: Collagen-hydroxyapatite; Col-I: Collagen type I; CPM: Continuous passive motion; DBB: Deproteinized bovine bone; DPBB: Deproteinized bovine bone particles; ECP: Experimental calcium phosphate; FN: Fibronectin; FB: Fibrin biopolymer; FG: Fibrin glue; FS: Fibrin sealant; FFP: Fresh frozen plasma; GBR: Guided bone regeneration; HMSCs: Human mesenchymal stem cells; HA: Hydroxyapatite; L-PRF: Leukocyte- and platelet-rich fibrin; MPM: Mineralized plasma matrix; Nha: nanohydroxyapatite; PBM: Photobiomodulation; PRF: Platelet-rich fibrin; PR-FG: Platelet-rich fibrin glue; PRP: Platelet-rich plasma; PLGA: Poly (D,L-lactide-co-glycolide); PGA: Polyglycolic acid; SAE: Serious adverse events.

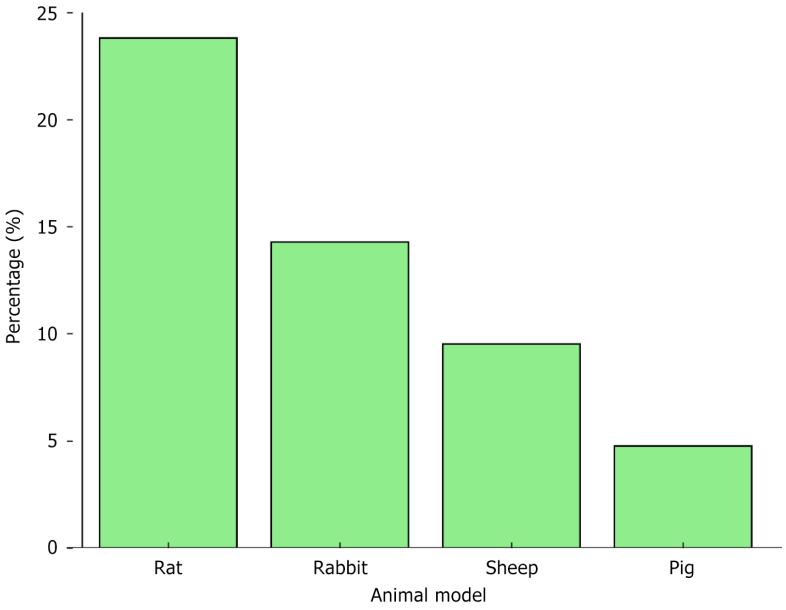

Figure 4 Proportion of types of animal models used in the studies evaluated.

The consistency of results across preclinical and clinical models supports the potential of combining synthetic biomaterials with fibrin-based biopolymers as a promising strategy for bone regeneration, offering biological support, mechanical integrity, and enhanced healing in both critical-size defects and clinical reconstructions.

Comparative performance of biomaterial-fibrin combinations

A systematic comparison of the included studies reveals notable differences in the regenerative potential of various

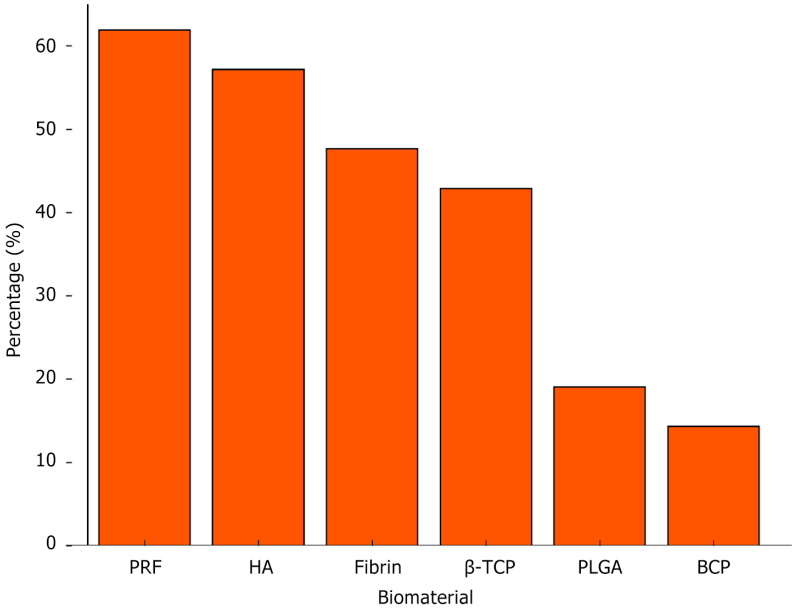

Figure 5 Percentages of each biomaterial used in the studies evaluated. PRF: Platelet-rich fibrin; HA: Hydroxyapatite; β-TCP: β-tricalcium phosphate; PLGA: Poly (D,L-lactide-co-glycolide); BCP: Biphasic bioceramic.

biomaterial-fibrin combinations. Composites containing HA and β-TCP consistently demonstrated superior osteoconductivity and mechanical integrity, particularly when enriched with FS or PRF. For instance, β-TCP + FS scaffolds yielded robust bone formation and vascularization in both small and large animal models, while HA + PRF formulations improved cellular infiltration and early tissue maturation. In contrast, fibrin alone, without a structural scaffold, exhibited limited capacity to support the regeneration of critical-size defects, despite its favorable biological activity. When combined with MSCs, both HA- and β-TCP-based scaffolds enhanced osteoinductive responses, with β-TCP showing slightly faster resorption and remodeling rates. Commercial formulations, such as HA/β-TCP coated with fibronectin or FG, promoted a higher expression of osteogenic markers, while composite scaffolds that incorporated collagen or polymeric matrices provided better flexibility and handling during surgery, although in some cases at the expense of long-term mechanical stability. These comparisons suggest that although all fibrin-based strategies contribute positively to bone regeneration, synthetic ceramics combined with fibrin and bioactive agents (*e.g.*, MSCs or growth factors) may offer the most promising outcomes in terms of integration, remodeling, and clinical applicability (Table 1).

DISCUSSION

This literature update analyzes advances in regenerative medicine on the use of biomaterials for bone repair. We review various applications for different types of bone defects, HA- and β-TCP-based composites and their interactions with fibrin, PRP, and L-PRF derivatives. We also examine the use of MSCs in bone repair to assess their combination and effects.

The physicochemical properties of biomaterials for bone substitutes are crucial for successful bone healing. To promote the differentiation of MSCs into osteoblasts, biomaterials must be biodegradable, non-immunogenic, non-allergenic, non-mutagenic, and porous[44]. Calcium phosphate-based ceramics are examples of synthetic biomaterials with high biocompatibility and tissue tolerance[44].

As explained by Song *et al*[45] and Wu *et al*[10], biocompatibility is vital for biomaterials to ensure cell survival and viability during interactions with polymers. Biomaterials must biodegrade within specific time frames: About one month for soft tissues and six to twelve months for hard tissues such as bone. Biodegradability allows the host to reabsorb the material after implantation in regenerated tissues or organoids, facilitating interaction between artificial and biological environments. In bone tissue, the resorption time is longer due to the calcification process, which enables the biomaterial to provide prolonged mechanical support, ensuring implant acceptance and enhancing host cell interaction with the graft.

Guastaldi *et al*[35] showed that amorphous calcium phosphate favors the *in vitro* growth and differentiation of osteoblastic cells, while octacalcium phosphate stimulates this cell lineage, thus promoting bone formation. During HA formation, octacalcium phosphate increases osteoblastic activity, and HA is associated with significant bone formation in bone defects, with a faster graft particle resorption rate than other substitutes. A biomaterial with combined Calcium phosphate phases may further enhance bone formation properties[46-48].

We observed that 52% of the studies combined HA with other components, such as β-TCP[23,26,36,44], to form cement or bone matrices. Other components, such as collagen[27], PRF[23,31,32], and PLGA[31], have been used to create biomimetic structures, gels, or 3D composites. HA's nanoparticle form has also been applied[39,43]. Overall, results show positive effects on bone regeneration, particularly with these combinations. HA and its injectable form have been used

since 1996 in orthopedic surgery, otorhinolaryngology, plastic surgery, and neurosurgery. HA injectable hardens within 5 minutes after injection under drying conditions, making it suitable for covering bone defects[49].

Due to its brittleness, weak mechanical properties, and low flexural strength, HA is unsuitable for isolated applications in skeletal parts under significant mechanical stress. Moreover, the difficulty in forming 3D HA structures limits its use in complex bone regeneration. Consequently, research has focused on developing HA-based composite materials that incorporate both natural and synthetic polymers. In this context, 3D porous hybrid scaffolds are more advantageous than conventional powders or granules for healing bone defects. Therefore, single-component scaffolds are inadequate as bone substitutes, and hybrid scaffolds are needed to better support cellular activities[8,9,11,12].

Goto *et al*[34] assessed atelocollagen sheets for bone regeneration and found inadequate absorption, which resulted in insufficient closure of the skull fenestrated area within five weeks. This result was attributed to the weak trabecular structure and slow revascularization of the skull cortical bone. Mizuno *et al*[50] corroborated these findings, observing that combining atelocollagen sheets with FS offered pressure resistance, stability, adhesive strength, minimal inflammation, and greater tissue affinity. Moreover, the tissue-like structure facilitated surgical handling and helped prevent cerebrospinal fluid leakage during sphenoid reconstruction[50].

Taufik *et al*[32] observed a lack of fracture union in early treatment but noted significant improvements in patient quality of life after using biomaterials. Mazzone *et al*[31] and Mordenfeld *et al*[29] also reported favorable functional outcomes after facial trauma and in edentulous jaw applications. Moreover, Martinčič *et al*[28] observed improved graft survival in patients undergoing autologous chondrocyte implantation.

The presence of HA in biomaterials (resembling the inorganic portion of bone) and its macropores of varying sizes aid in cell migration and deposition, creating a microenvironment conducive to cellular differentiation, growth, and neovascularization. From a physiological standpoint, its biocompatibility and osteoconductive properties trigger a protective inflammatory response at the injury site, promoting immunogenic changes and interactions between osteogenic and inflammatory cells to initiate tissue remodeling[36,51-57].

The combination of bone substitutes with fibrin-derived composites such as sealants, adhesives, and biopolymers—known as tissue adhesives— forms a stable scaffold that facilitates graft placement at the defect sites. Research shows that combining these biomaterials yields positive results in tissue regeneration[33,36,37,57-62].

Since the 2000s, PRF has been refined and is now popular in oral and maxillofacial surgery due to customized studies and protocols[63]. Bone formation and repair are achieved in environments that promote the proliferation of osteogenic cells through MSCs[64,65]. Incorporating autogenous properties into the β-TCP structure with MSCs and growth factors offers a promising alternative to autologous bone grafts for maxillofacial skeletal repair[43].

PRF can be used alone or with various biomaterials[66-68], as demonstrated in the studies reviewed here[23,31,32]. It is absorbable and remodels slowly, maintaining strength and stability, as opposed to natural blood clots. When combined with growth factors, the fibrin present in PRF presumably stimulates cell migration and microvessel formation; consequently, it accelerates bone regeneration. Further *in vivo* studies are needed to address challenges related to the interaction between MSCs, growth factors, and the fibrin matrix. This is crucial for advancing our understanding of tissue regeneration and ensuring the safety and efficacy of clinical therapies[31,32,43].

Kim *et al*[58] found that the porosity of the 3D structure formed by fibrin derivatives and biomaterial granules decreases as fibrinogen concentration increases. This occurs because the formation of a fibrin layer fills the spaces between the granules, thereby reducing porosity. In contrast, compressive strength increases with increasing fibrinogen concentrations, indicating a close relationship between compressive strength and porosity. The degree of fibrin fiber formation, along with the thickness and branching of the fibrin layer, may have influenced the compressive strength of the scaffolds[13,69].

Nair *et al*[43] concluded that the fibrin matrix is an ideal scaffold for transplanted MSCs in bone defect regeneration. They found that the bone appearance significantly improved when using β-TCP scaffolds ingrained with osteogenic stem cells and FG compared to FG alone. Moreover, they observed a significant improvement in overall mean density scores after eight weeks (all P-values < 0.05). These results align with those of Tanaka *et al*[64], who noted complete β-TCP resorption (with 75% porosity) and bone replacement in high tibial osteotomies. After four weeks, scaffolds with MSCs and growth factors exhibited osteoblastic borders, larger vascular spaces, and randomly arranged channels and osteocytes. Successful bone regeneration rates were achieved using MSCs + β-TCP + FG scaffolds, through minimally invasive autogenous bone generation approaches[66].

Cakir *et al*[42] found that the use of MPM, made by combining synthetic graft material with platelet concentrates (PRF + β-TCP), showed bone formation values similar to those of autogenous grafts—a positive outcome. However, MPM is not yet considered a definitive alternative to autogenous grafts.

The combination of FG and biomaterial granules creates a stable scaffold for placement at bone defect sites, as demonstrated in many studies[33,36,37,57,59-61]. This stability is crucial for bone regeneration[70], as stronger scaffolds correlate with better outcomes.

A common approach for addressing bone volume deficiencies is using homogeneous or heterogeneous bone grafts. Although these materials are effective, each has limitations that clinicians must consider to reduce adverse effects. Ideally, the selected material should exhibit low comorbidity, minimal side effects, and low cost[41,71-73].

Synthetic scaffolds, when combined with compatible biomaterials, create a low-toxicity, highly available framework. Moreover, they can be enriched with readily accessible autologous and regenerative additives, making them an attractive option for graft materials[74].

Professionals in regenerative medicine must stay updated on available biomaterials. Failure in the initial treatment of bone trauma can lead to bone loss, delayed healing, or non-union of fractures. Effectively managing these defects is critical to optimizing clinical outcomes and minimizing complications[1,2] that impact quality of life and financial health.

Future directions and research challenges

Despite the encouraging results reported in preclinical and clinical studies, several challenges remain in the application of fibrin-based biomaterials for bone regeneration. A major issue is the lack of standardization in the preparation of fibrin derivatives, such as PRF and FG, which leads to variability in fibrin architecture, growth factor concentration, and biomechanical properties. Future studies should focus on optimizing fibrin formulations—adjusting fibrinogen concentration, cross-linking density, and scaffold porosity, to improve performance and reproducibility.

Another critical area of investigation involves the immune response to fibrin and its interaction with synthetic biomaterials. Although fibrin is generally biocompatible, residual thrombin or xenogeneic components may trigger localized inflammation or fibrosis. Therefore, investigating the host-material interface at the molecular level will be essential to safely translate these technologies.

Advancements in 3D bioprinting and tissue engineering open new avenues for fabricating customized scaffolds that integrate fibrin matrices with stem cells or bioactive molecules in spatially controlled patterns. Moreover, long-term clinical trials with standardized outcome measures are required to assess the durability and cost-effectiveness of these approaches, particularly compared to autologous bone grafts.

Ultimately, integrating fibrin-based biomaterials into personalized regenerative strategies, driven by translational and interdisciplinary research, represents a promising path for addressing complex bone defects in orthopedic and maxillofacial surgery.

CONCLUSION

This literature update provides a comprehensive overview of the use of synthetic biomaterials combined with fibrin derivatives in regenerative medicine. Recent research shows increased use of bone substitutes—notably HA—and tissue adhesives such as FG or FS, yielding promising results. These advances have stimulated the development of 3D composites. The variety of studies and combinations of biomaterials highlights the need for improvement in their *ex vivo*, *in vitro*, and *in vivo* applications. Using bone substitutes as scaffolds for stabilizing and repairing bone defects emphasizes the importance of ongoing research to enhance methods within regenerative medicine. The combinations of biomaterials emerge as optimizers in the bone regeneration process and clinical applications.

FOOTNOTES

Author contributions: Pagani BT, Rosso MPO, and Buchaim RL contributed to conceptualization, original draft preparation, writing, review, editing, and visualization of the study; Pagani BT, Trazzi BFM, and Cunha MR contributed to conceptualization; Rosso MPO contributed to validation, research, and data curation; Rosso MPO and Buchaim RL contributed to the methodology and formal analysis; Moscatel MBM, Trazzi BFM, Cunha MR, Issa JPM and Buchaim DV contributed to the methodology, validation, and formal analysis; Moscatel MBM, Trazzi BFM, and Buchaim DV contributed to data curation and visualization; Cunha MR and Issa JPM contributed to validation and formal analysis; Rosso MPO participated in formal analysis, investigation, data curation, original draft preparation, writing, review, editing, and visualization; Buchaim RL contributed to writing, review, editing, and supervision.

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