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Recent Advances and Modifications in Bone Cements

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Abstract: The current review describe the state of the art of the modification of bone cement formulations, mainly biomimetic functionalized scaffolds, ion doped materials, the potential of decellularized extracellular matrix scaffolds and 3D printing scafoolds, and the reasons for the development of modifications.

Keywords: : *bone cement, biomimetic functionalized scaffolds, ion doped materials,* 3D printing scafoolds

1- Biomimetic Functionalized scaffolds:

Bone tissue may be subjected to trauma or other degenerative diseases during lifetime. The regeneration of impaired bone tissue is still a largely unmet clinical need, particularly when it comes to the treatment of critical size and load-bearing bone defects. Material scientists have been expending efforts to find effective technological solutions, based on the use of scaffolds, to develop materials and devices that exhibit high biomimetic character. Biomimetics is the ability of a scaffold to reproduce and mimic both the compositional and three-dimensional structural features of the host natural bone tissues and recreate its features in synthetic scaffolds., i.e., capable of exhibiting bioactivityy instructing cells by virtue of their chemical and structural similarity with the target tissue. Biomimetics have great promises and is a potentially fruitful direction of injectable bone repair material (16).

1.1 Ion doped materials:

In general, bone tissue is poorly vascularized, treating bone diseases and defects, with general drug administration, is a challenge. The issue becomes more severe when this vascularization is disrupted by trauma or during a surgical process. The mentioned problems are the main reason to encourage scientist to utilize implants containing biological agents and compensate for the shortage. **Several trace inorganic ions** have been discovered to be conducive to bone tissue regeneration. Recently, research has focused on improving the properties of CPC by doping in calcium phosphates, hydroxyapatite (HA), or another natural or polymeric material, with various trace elements essential for bone metabolisms, such as magnesium (Mg), zinc (Zn), strontium (Sr) and silicon (Si), copper which would effectively mimic the mineralization process of natural bone, further promote the biological performance of CPCs by improving bone metabolism and hence promote osteoinduction and osteointegration. It has been widely investigated and proved to be beneficial to the osteogenic differentiation of osteoblastic cells. The introduction of these trace elements into calcium phosphate-based ceramics or cements could stimulate the responses of bone repair-related cells and influence the physicochemical properties (such as strength and degradation). Thus, the repairing effect of bone defects could be enhanced if the osteogenic capacity of CPC is enhanced(2).

Among the different bioactive metal ions tested, strontium has been extensively investigated in the context of bone repair materials due to its structural and physicochemical similarity to calcium, promoting bone regeneration and inhibiting bone resorption.

A recent approach to advance the properties of CPCs is the combination of CaP containing cements with **bioactive glasses (BGs),** BG is characterized for its ability to support bone growth by chemically bonding to bone, and release of silica ions from BG surface, which is followed by the formation of an amorphous calcium phosphate precipitation. Precipitated amorphous calcium phosphate leads to the formation of a hydroxyapatite (HAp) layer on the surface of the material, which further activates cell migration to trigger new bone formation. The desirable properties of bioglass include relatively easy handling and adaptability to the defect site, good biocompatibility, osteoconductivity, antimicrobial activity, and a porous structure promoting vascularization(16).

They have been successfully used in periodontal surgery to stimulate bone regeneration. However, BAG can be brittle and possess low mechanical strength and poor fracture resistance. Thus, their use in dentistry is limited to low stress bearing area or in combination with other grafting materials. Bioglass materials have been successfully used in periodontal osseous defects and preserve alveolar bone following tooth extractions in orthodontic patients.

1.2 The Potential of decellularized extracellular matrix scaffolds:

The field of acellular biomaterials is progressing and is becoming a practical alternative to cell-based therapies. Previously, acellular materials only were regarded as fillers for the tissue defects, but now are able to be engineered into scaffolds that can interact with surrounding cells and tissues to alter the traditional recovery processes from disease or trauma or bone defect(16).

Another biomimicry target is the extracellular matrix (ECM), a complex network of polysaccharides and proteins secreted and regulated by cells that provides biochemical signals for the modulation of cell activities and as a bridge for connecting cells and materials. Bone ECM has both inorganic and organic constituents. The inorganic part, consisting of calcium phosphate, mainly in the form of hydroxyapatite (HA), is the source of bone strength, while the organic part, composed mostly of type I collagen, provides the tissue and cell with flexibility and adhesion, respectively.

Decellularized bone refers to biomaterials formed by human or animal organs/tissues with the removal of immunogenic cellular components via decellularized technologies, it is frequently used as a special scaffold material in bone tissue engineering, due to its ability to eliminate cellular components and antigenicity while its osteogenic and biomechanical properties as well as its physiological are similar to the bone matrix.

dECM scaffolds mainly consist of extracellular matrix (ECM) is a three-dimensional (3D) framework containing extracellular macromolecules such as collagen, elastin, fibronectin, laminin proteins, Meanwhile, the physicochemical signals and biological performance of dECM can be remained after decellularization, which provides a substrate for mechanical supporting and a biological 3D carrier for subsequent cell seeding , thus mimic an optimal non-immune environment with native three-dimensional structures and various bioactive components.

A recent study prepared decellularized extracellular matrix (dECM) deposited on a biphasic calcium phosphate (BCP) scaffold. Rat derived bone marrow messencymal stem cells RBMSCs were chosen as a source of ECM (MSCs can create ECM that mimics various tissues depending on culture conditions), isolated from femur and were cultured on porous BCP scaffolds under osteogenic condition to generate bone-like ECM on the surface of scaffold for 3 weeks, these scaffolds were decellularized by physical or chemical method. decellularized ECM derived from RBMSCs was evaluated whether it could improve the attachment and proliferation of newly seeded cells compared to those directly grown on bare BCP scaffold alone. The results indicated that the BCP scaffold with ECM was effective in promoting the bioactivity of scaffolds, showed increased osteoblastic differentiation as well as offering a stable microenvironment for osteogenesis (16,17).

2. 3D printing scaffold

Tissue engineers need to mimic the micro/nano-architecture of natural bone to investigate the means of stimulating effective tissue growth, cell actions such as migration, adhesion, proliferation, as well as differentiation could be regulated, further promoting bone regeneration.

Although injectability is one of the advantages of CPCs, designing of prefabricated biomimetic CaP ceramic scaffolds are often prepared for two reasons: (1) To ensure a complete setting reaction because only fully set CPCs demonstrate excellent tissue responses, when fail to set, they cause inflammatory reactions. Therefore, manufacturing prefabricated CPCs ensures complete setting prior to in vivo prefabricated (2) To facilitate the creation of interconnected macroporous structures into CPCs, that stimulates cell differentiation into osteoblasts and to stimulate cell chemotaxis and new bone matrix deposition. Self-setting CPC scaffolds without any modification are microporous but not macroporous and have limited pore interconnections. Variations in surface roughness, fiber alignment, especially interconnected pore structures, could be prepared by 3D printing technology that is able to produce sophisticated architectures with 3D features. Recently research has aimed to develop three-dimensional (3D) printing, has rapidly developed to allow the fabrication of pre-set 3D-printed CPC scaffolds(16).

Recent research has aimed to develop 3D prefabricated pre-set CPC scaffolds. 3D printing is an additive manufacturing process in which geometrical data are used to produce 3D structures by depositing (incremental addition) of materials layer by layer, they are favored to meet the specific needs of each patient defect and can accurately shape internal structures and external contour.

These printers utilize inkjet cartridges that are identical to those found in common desktop printers. 3D artificial bone tissue can be easily created using biological ink, these ink cartridges can be opened, cleaned, and refilled with the binder solution or bioactive inks, which exists in the form of a viscous fluid.

The benefits for clinical applications include easy adaptation and fixation, reduced surgical time, favorable esthetic results, and minimal waste products. For CPC scaffolds**, binder jetting** is the most employed 3D printing technique. Binder jetting operates using ceramic powders and polymeric binders. The powders form the final ceramic structure, while the binder acts as temporary material to hold each layer together before sinterization.

One or several print heads spray a binder solution, from inkjets (for example, an aqueous solution) precisely onto a bed layer of CPC powder phase which is most often a CaP, such as hydroxyapatite or tricalcium phosphate (TCP), α-TCP is most used than β-TCP, which is more thermodynamically unstable (and thus more

soluble) than b-TCP. For HA or TCP powder mixed with the binder used in the 3D printing process to form a 3D object (referred to as the "green part", green strength which is not suitable for end-use and are then subjected to a post-process such as sintering or infiltration to achieve desirable mechanical properties), the binding solution is usually a polymer in solvent liquid (which is pyrolyzed during sintering after printing) , or an aqueous solution, CaP powders such as TCP typically require aqueous binding solutions, such as dilute phosphoric acid (in a concentration range of 5–30 wt.%). The acidic binder initiates a dissolution-precipitation reaction, which yields brushite. The acidic binder solutions applied to CaP powders, locally joins and unify adjacent powder particles together to fuse the particles and hardens the wetted areas and enable low temperature binding of the particles in a dissolution-precipitation reaction.

The process repeats by spreading another layer of powder and ejecting binders according to design by the computer. As the build progresses, the layers of the print are bonded together, resulting in a box of powder with binder arranged in the 3D shape. This continues until the complete 3D structure is formed with desired geometry. Once the printing step is complete, some binder jet technologies require a post-cure to dry the binder, the binder may be then removed by post-processing to cure or set the binder if needed, such as high-temperature sintering or by chemical dissolution. Eventual removal of the binder will weaken mechanical stability; however, the structural drying and sintering process will help rebuild its integrity(17–19) .

After curing, the green parts have enough strength to be handled and moved to the densification furnace. At this critical step of powder-based 3D printing, the removal of the loose powder inside the pores of the printed scaffold after printing is done by a process known as depowdering, where the printed part(s) may be removed from the powder bed . Depowdering is especially challenging when the pores and pore interconnections are small and found in the innermost parts of the scaffolds with large dimensions (17–19) .

Bone tissue engineering scaffolds require interconnected 3D pore structures that permit cell infiltration as well as allowing nutrient access and waste removal. The printability of the material is related to many parameters such as particle size and size distribution, morphology and surface area of the powder, roughness and flowability of the powders, the solubility/wettability/ reactivity of the powder with the binder, and binder drop size. A study investigating beta-tricalcium phosphate powder suggested that 3D printing was not feasible with particles either too small (with a mean particle size of 7 μm) or too large (with a mean particle size of 51 μm), while mean particle sizes in the range of 20–35 μm resulted in good printing accuracy and considered optimal. Small particles tend to agglomerate under the influence of van der Waals forces. Very fine or porous particles exhibit low flowability and high surface roughness. Therefore, these factors greatly affect the smoothness and homogeneity of the powder bed. However, although large particles have better flowability, the powder flows easily but does not pack sufficiently, they tend to yield layer displacements due to low powder bed stability causing interlayer instability that compromises binding and geometrical accuracy, because the resolution is at least twice the particle size (17,19).

Main advantages of binder jetting are the ability to print pure CaP scaffolds, simultaneous printing of bioinks (drugs or growth factors) in ink cartridges, the shaping process occurs at room temperature and atmosphere, avoiding issues related to oxidation, residual stress, and phase changes, making the powder around the parts in the build box (the area where the powder bed is ready for printing) highly recyclable and is great for

larger, porous ceramic structures. While drawbacks include the designed pores are limited to ~ 500 μm, brittle and limited mechanical properties, inability to directly print cells, (19).

Organic/ inorganic scaffolds by 3D printing:

3D printing has become a widely used technique to fabricate composite scaffolds in regenerative medicine. One of the main problems associated with the use of biodegradable polymers in the development of biomimetic scaffolds, such as PLA, PLGA, and PCL is their degradation problems that could affect overall osteointegration process. Highly viscous nature of polymers can lead to inhomogeneous infiltration, inappropriate pore interconnectivity, as well as a significant reduction in the overall porosity which may hinder vascularization of the resulting composite material and affect the final mechanical performance. The incorporation of natural polymers, as collagen results in an ideal strategy in the development of bioactive organic/inorganic composite scaffolds. Further introduction of polyethylene glycol (PEG) has been addressed to increase hydrophilicity and the resulting cell adhesion, proliferation, and differentiation on the scaffold surface. Even though these polymeric components do not reproduce the biological features of natural polymers, such as collagen, their use can help in modulating the rheologic properties of bio-inks yielding scaffolds with complex shape and geometry.

References :

1. Liu D, Cui C, Chen W, Shi J, Li B, Chen S. Biodegradable Cements for Bone Regeneration. J Funct Biomater. 2023;14(3):134.

2. Zhao R, Yang R, Cooper PR, Khurshid Z, Shavandi A, Ratnayake J. Bone grafts and substitutes in dentistry: A review of current trends and developments. Molecules. 2021;26(10):1–27.

3. Ginebra MP. Cements as bone repair materials [Internet]. Bone Repair Biomaterials. Woodhead Publishing Limited; 2009. 271–308 p. Available from: http://dx.doi.org/10.1533/9781845696610.2.271

4. Yousefi AM. A review of calcium phosphate cements and acrylic bone cements as injectable materials for bone repair and implant fixation. J Appl Biomater Funct Mater. 2019;17(4).

5. Shah M. The clinical outcome of bone cement in dental implant insertion – A systematic review. J Dent Implant. 2020;10(2):59.

6. Jeong J, Kim JH, Shim JH, Hwang NS, Heo CY. bioactive calcium phosphate materials and applications in bone regeneration.pdf. 2019;1–11.

7. Alsahafi RA, Mitwalli HA, Balhaddad AA, Weir MD, Xu HHK, Melo MAS. Regenerating

Craniofacial Dental Defects With Calcium Phosphate Cement Scaffolds: Current Status and Innovative Scope Review. Front Dent Med. 2021;2(August):1–16.

8. Al-Sanabani JS, Madfa AA, Al-Sanabani FA. Application of calcium phosphate materials in dentistry. Int J Biomater. 2013;2013.

9. Tang G, Liu Z, Liu Y, Yu J, Wang X, Tan Z, et al. Recent Trends in the Development of Bone Regenerative Biomaterials. Front Cell Dev Biol. 2021;9(May):1–18.

10. Moussa H, El Hadad A, Sarrigiannidis S, Saad A, Wang M, Taqi D, et al. High toughness resorbable brushite-gypsum fiber-reinforced cements. Mater Sci Eng C. 2021;127(May).

11. Wang XH, Jia SJ, Hao DJ. Advances in the modification of injectable calcium-phosphate-based bone cements for clinical application. Chin Med J (Engl). 2020;133(21):2610–2.

12. Kheradmand Z, Rabiei M, Noori Tahneh A, Shirali E, Abedi M, Dashtipour B, et al. Targeted drug delivery by bone cements. J Compos Compd. 2022;4(10):61–70.

13. Paxton NC, Wong CS, Desselle MR, Allenby MC, Woodruff MA. Bone morphogenetic protein–assisted bone regeneration and applications in biofabrication [Internet]. Biomaterials for Organ and Tissue Regeneration: New Technologies and Future Prospects. LTD; 2020. 363–391 p. Available from: http://dx.doi.org/10.1016/B978-0-08-102906-0.00016-7

14. Sohier J, Daculsi G, Sourice S, De Groot K, Layrolle P. Porous beta tricalcium phosphate scaffolds used as a BMP-2 delivery system for bone tissue engineering. J Biomed Mater Res - Part A. 2010;92(3):1105–14.

15. Kang HJ, Park SS, Tripathi G, Lee BT. Injectable demineralized bone matrix particles and their hydrogel bone grafts loaded with β-tricalcium phosphate powder and granules: A comparative study. Mater Today Bio [Internet]. 2022;16(September):100422. Available from: https://doi.org/10.1016/j.mtbio.2022.100422

16. Pupilli F, Ruffini A, Dapporto M, Tavoni M, Tampieri A, Sprio S. Design Strategies and Biomimetic Approaches for Calcium Phosphate Scaffolds in Bone Tissue Regeneration. Biomimetics. 2022;7(3).

17. Xu HHK, Wang P, Wang L, Bao C, Chen Q, Weir MD, et al. Calcium phosphate cements for bone engineering and their biological properties. Bone Res [Internet]. 2017;5(July):1–19. Available from: http://dx.doi.org/10.1038/boneres.2017.56

18. Jiang S, Wang M, He J. A review of biomimetic scaffolds for bone regeneration: Toward a cell-free strategy. Bioeng Transl Med. 2021;6(2):1–36.