Scaffolds as Bone-Targeted Drug Delivery: Current Insights

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1.Introduction:

The bone is an essential organ in the human body that serves multiple functions, such as supporting and protecting other organs, generating blood corpuscles, and regulating hormones. A variety of disorders affecting the skeletal system are classified under the category of bone diseases, which can result in restricted mobility and increased risk of mortality. Bone diseases are treated by oral as well as intravenous administration of high doses of drugs so as to attain effective drug concentrations in the bone tissue. Such elevated levels of drugs in the systemic circulation can lead to additional adverse effects in various other organs and tissues (1). To address these side effects, researchers are currently investigating the use of nanotechnology as a possible approach to achieve bone targeted drug release and improve the process of bone regeneration. Organic and inorganic bone scaffolds, cements, nanoparticles (NPs), and hydrogels have been found to offer more benefits than drawbacks compared to other types of nano-systems, and as a result, they are the subject of numerous studies (2). Scaffolds are biocompatible templates, which act as a platform to support the attachment and growth of cells. They are commonly used for tissue regeneration and surgical restoration (3). Scaffolds are being explored as an efficient technique for the treatment of osteoporosis and osteomyelitis. Scaffold combinations for tissue regeneration is as an emergent and potentially effective strategy to treat osteomyelitis, both to enhance reaeration of bone tissue and to eliminate infections (4).

An ideal scaffold should exhibit biocompatibility, without initiating any immunological response. It should have optimum porosity, that is comparable to the human bone tissue. The scaffold should which allow vascular ingrowth, cellular transportation and possess the desired mechanical properties along with biodegradability in vivo (5). Currently, there has been a growing interest in utilizing scaffolds as a promising mode of delivering targeted therapies to the bone tissue to treat skeletal diseases. This involves the delivery of molecules like growth factors that aid and accelerate the process of bone regeneration, as well as small molecule drugs that can cure localized bone related diseases. The integration of bone tissue engineering with advanced nanotechnologies has proven effective for delivering therapeutic molecules to the bone (6).

2.Biomaterials constituting scaffolds:

2.1 Organic Scaffolds:

Synthetic polymers exhibit biodegradable and biomechanical properties, making them the right fit as biomaterials for bone scaffolds. The most extensively researched synthetic polymers for bone scaffolds are polylactic-acid, polycaprolactone, polyglycolic-acid, poly e-caprolactone, polypropylene, polyethylene, as well as polymethyl methacrylate (7). Additionally, natural polymers are being explored for the regeneration of bone tissue owing to their resemblance to the extracellular matrix present in the body. Natural polymers can be divided into two categories based on their chemistry: proteins (such as collagen, elastin, keratin) and polysaccharides (like chitosan, dextran, and pectin) (8). Further, Lipid nanoparticles (LNPs) are being explored since they are more promising than inorganic nanoparticles, being less toxic and highly biocompatible. LNPs are consistent nano-vehicles consisting of solid or liquid lipids that can form a uniform structure with a core-shell or homogeneous composition. There are different types of LNPs, such as lipid drug conjugate carriers, nanostructured lipid carriers, among others (9). Figure 1 summarises the biomaterials for organic bone scaffolds.

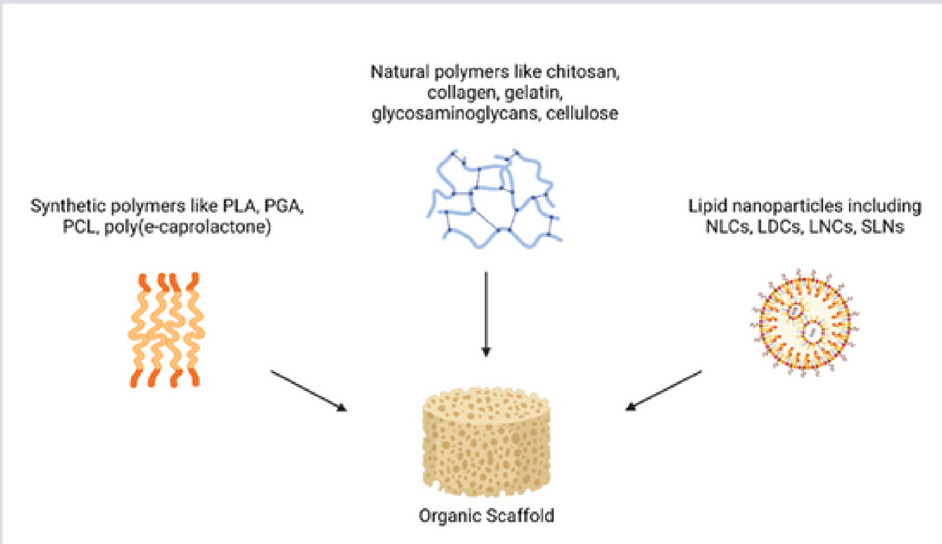

Figure 1: Biomaterials for organic bone scaffolds

2.2 Inorganic Scaffolds

Inorganicscaffolds can be classified into metallic and ceramic.

2.2.1 Metallic scaffolds:

Mesoporous silica nanoparticles based multifunctional scaffolds deliver drugs specifically to their intended target site and are designed to release the drugs in a controlled manner, which increases their cellular uptake and effectiveness while minimizing premature release before reaching the target site (10). Additionally, Gold nanoparticles are suitable for various uses such as controlled delivery, chemotherapeutic applications, medical imaging, and diagnosis, due to their biocompatibility, low toxicity, small size, and the capability to be coated with a range of medicinal agents (11).

2.2.2 Ceramic scaffolds:

These are derived from calcium phosphate (CaP) and are explored as potential substrates for bone tissue engineering (BTE) due to their similarity in chemical composition to the inorganic bone tissue. The most widely investigated CaP scaffolds include hydroxyapatite (HA), beta-tricalcium phosphate (b-TCP), and a combination of both called biphasic calcium phosphate. Composite scaffolds have also shown potential action in controlled drug release, owing to their porous nature and adhesive properties (12). Figure 2 summarises the biomaterials for inorganic bone scaffolds.

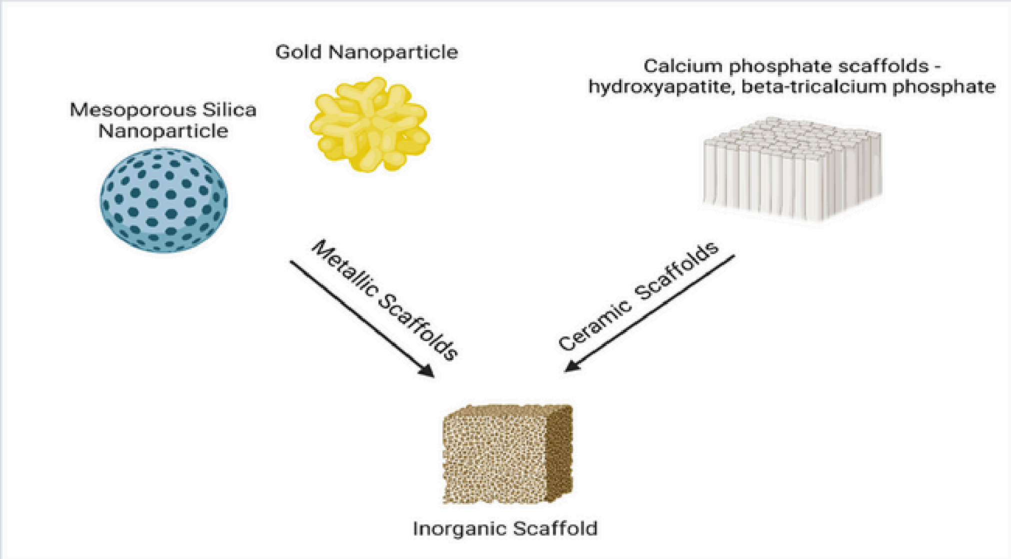

Figure 2: Biomaterials for inorganic bone scaffolds

3. Clinical Applications of Scaffolds in Drug Delivery:

3.1 Osteomyelitis and Orthopaedic Infections

Approximately 80% of the osteomyelitis cases can be attributed to Staphylococcus aureus. Standard treatment involves surgical debridement, dead space removal, and i.v. administration of antibiotics for 4-6 weeks. Local antibiotic delivery combined with a biodegradable polymeric scaffold for the regeneration of bone tissue has been explored as a new strategy to overcome disadvantages associated with systemic treatment and treat osteomyelitis more effectively. Localised antibiotic therapy is advantageous as it increases the antibiotic concentration at the area of infection, while minimizing systemic levels of antibiotics and avoiding adverse side effects. Biofilms in Staphylococcal infections of bone and ODRIs can decrease the effectiveness of systemic antibiotics, but local antibiotic carriers can overcome this resistance. Antibiotic-loaded carriers made of inert materials, such as PMMA, are commonly used for osteomyelitis and ODRIs treatment, and PLGA-based drug delivery systems have shown promising results due to their simple preparation, sustained release, injectable design, and in-situ gelling properties (13).

3.2 Osteoarthritis

Osteoarthritis leads to painful symptoms and signs of cartilage loss, and present-day therapies only alleviate pain without slowing disease progression. NPs can aid in local delivery of anti-inflammatory chemokines, thus increasing drug retention in local tissues. Cationic polymeric hydrogel and copolymer NPs have been reported to raise the retention time of dextran and IL-1 receptor antagonist, respectively, maintaining cartilage composition and conformation (14).

3.3 Tumor Bone Metastasis

Frequently occurring tumors, including those of the lung, breast and prostate gland, often metastasize to the skeletal tissue, causing bone pain as well as fragility. Treatment options include surgery, radiation therapy, systemic approaches, and bone-targeted drug delivery systems. Bisphosphonates are commonly utilised to treat cancer bone metastases and are often delivered through NP drug delivery systems. Targeting bone tissue biomarkers with nanoparticles, drugs, and genetic material may signify a promising strategy for treating and preventing bone metastases (15).

3.4 Osteonecrosis

Osteonecrosis can lead to hip and knee osteoarthritis due to vascular crisis causing bone weakness and collapse. Current surgical treatments are inadequate, and new methods such as necrotic bone regeneration are needed. Stem cells from bone marrow have been introduced in medical practice, and PDLLA and PLGA are promising delivery methods for bioactive molecules such as PDGF and simvastatin, which can improve cellular viability, decrease inflammation, promote cell recruitment, and facilitate osteogenic differentiation and maturation (16).

3.5 Osteosarcoma and Other Musculoskeletal Malignancies

Osteosarcoma and soft tissue sarcomas are primary bone malignancies that are managed with surgery, chemotherapy, and radiotherapy. However, the efficacy of these treatments is limited due to their systemic and organ toxicity. New treatment methods, such as molecular targeted therapy and nanoparticle-based drug delivery, may show potential for improving survival rates. Encapsulation of drugs like doxorubicin in PEGylated PLGA nanoparticles has shown enhanced efficacy in vitro and in vivo (17).

4. New strategies in bone delivery:

Numerous drug treatments have been researched to determine their effectiveness in improving bone tissue treatment. Growth factors, especially BMP-2 and BMP-7, are being extensively studied owing to their capability to promote the conversion of mesenchymal stem cells into osteoblasts. Additionally, bisphosphonates have shown potential in targeting bone for delivery of antibiotics or chemotherapy agents, and nucleotides like siRNA and miRNA have been studied for genetically rearranging cells to enhance regeneration of bone tissue. Other approaches including small molecules like statins, prostaglandins, steroids, and Wnt/beta-catenin agonists are also being researched for their potential in promoting bone tissue reaeration (18).

Growth factors for bone healing have attracted significant attention due to their ability to stimulate the proliferation and differentiation of target cells. BMP-2 and BMP-7 are two extensively researched growth factors. Nanoparticles have been developed for controlled delivery of BMP-2 and BMP-7 to bone, including organic polymers and hydrogels. PTH is an FDA-approved treatment for osteoporosis, and recent studies have shown its potential for fracture healing. Local application of PTH to fracture sites is being studied, and an RGD-modified PEG hydrogel bound to hrPTH 1-34 was shown to cause bone formation in canines of dental implants. Further studies are needed to determine the optimal timing of PTH degradation when stored in such carriers for translation to clinical practice (19,20).

Bioprinted bone scaffolds fabricated with suitable biolinks are being studied extensively for their application in treating bone defects including fractures, osteosarcoma, osteonecrosis, and tumor removal among others. Biolinks are composed of cells that may or may not containbiological components but possess optimum biocompatibility, biodegradability as well as bioactivity. Additionally, it must have the required viscosity for 3D printing, mechanical strength to withstand load and exhibit proper integrity of the bioprinted bone scaffold. Core/shell bioprinting technologies are being employed for developing hybrid scaffolds with robust designs, having the required porosity and pore geometry. Hydrogels being used for bioprinted bone scaffolds include collagen, chitosan, gelatin, and alginate among others. Bioprinting technologies being utilised include microextrusion, Inkjet and LAB. Cells being utilised include MCSs, Mesenchymal stromal cells, DPSCs, MC3T3-E1, SaOS-2 and hTMSCs among others (21).

3D bioprinted pseudo-bone drug delivery scaffolds have been developed with the aid of computer aided design software and have shown enhanced contact adhesion in a fractured bone, inducing the formation of a pseudo-bone matrix at the damaged site. Further investigations are being carried out in this domain (22, 23).

5. Conclusion:

Skeletal disorders such as fractures, orthopaedic infections, osteoarthritis, osteonecrosis, and bone tumor affect numerous people all around the world, often needing bone grafts. Research and development in material science has allowed bone scaffolds to be used for healing and repair of bone tissue and nanotechnology has the potential of exhibiting targeted delivery at the site of injured bone, eliminating adverse effects. However, more extensive research is required to understand the long-term effects of such implants along with their clinical applications.

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