Strategies and Drug Delivery Systems Used in Bone Targeting: An Overview

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1. Introduction:

The bone, a living tissue in vertebrates, is composed of 60% inorganic minerals such as hydroxyapatite Ca10(PO4)6(OH)2, 30% organic matrix including collagens, proteoglycans and lipids, and 10% of cells and blood vessels (1,2). It provides a rigid framework known as the skeleton. Based on the proportion of the above constituents it is thus classified into two types; cortical is a compact and dense outer layer, while the spongy, honeycomb structured inner layer is known as trabecullar or cancellous. Although bone mainly functions to protect the vital organs and support movements, it also acts as a storage of minerals and a major site of erythropoiesis (3). The highly specified tissue is constantly being metabolized and remodelled throughout life to maintain a healthy skeletal structure to execute these functions. Bone metabolism involves multiple bone cells as key regulators, including osteocytes, osteoblasts, and osteoclasts, which either on their own or in interaction keep the balance between bone catabolism and anabolism (4,5).The process initiates with the stimulation of osteocytes via a mechanosensory stimulation to elicit bone remodelling, recruiting osteoclasts to the old or damaged bone surface, thereby promoting bone resorption (the dominant event in the second phase). The mesenchymal stem cells and bone progenitor cells are recruited to the site at the same time, followed by MSCs differentiating into osteoblasts in the third phase to mediate the bone formation for a sustained time, and finally end with the mineralization of the organic matrix called osteoid to form new bones (6). The schematic representation of the bone remodelling cycle is given in Figure 1. However, when cells or cytokines in any of these four phases are altered, it may result in abnormalities in the bone structures, resulting in alteration of its flexibility and strength, finally culminating into bone metabolic diseases (7, 8, 9). A clinical survey in the year 2020 revealed that approximately 1.5 million Americans suffer from Osteoporosis mediated fragile fractures. Statistics of the cross-sectional studies conducted in the year 2022 amongst postmenopausal women in the state of Punjab itself, revealed the prevalence of approximately 30% osteoporosis and 44% osteopenia respectively (10). Thus, these observations have flagged an alarming signal in the entire country.

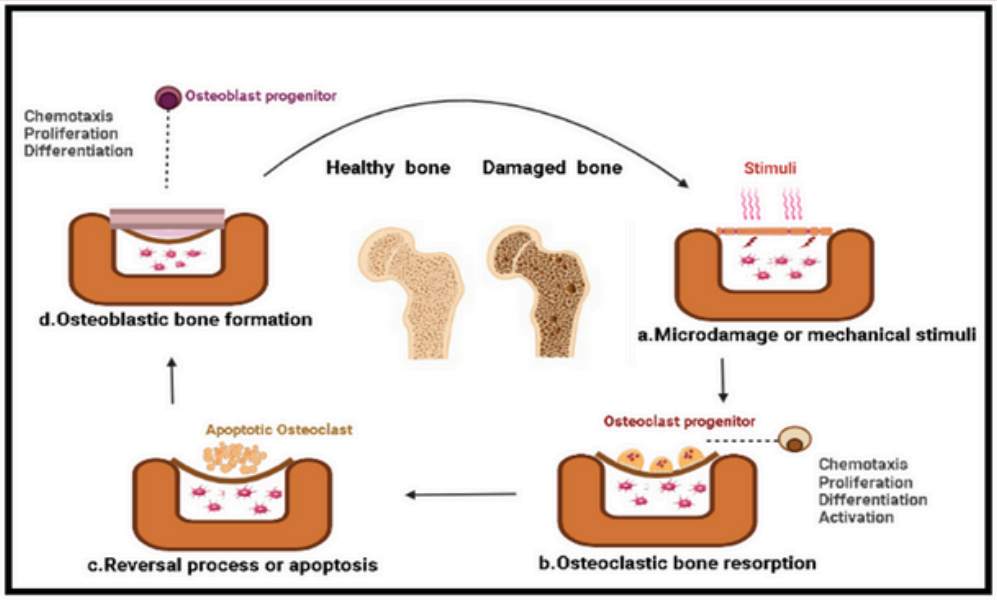

Figure: 1 Schematic Representation of Bone Remodeling Cycle.

Several bone metabolic disorders are briefly described below:

1.Osteoporosis: A condition with reduced bone mass and mineral density resulting in decreased bone strength, abnormal bone tissue microstructure as well as increased fragility and risk of fractures. It may be a primary (Age-related, Post menopause) or secondary disorder (smoking, excessive alcohol intake, type I diabetes mellitus, hyperthyroidism, chronic liver disease, and malnutrition) (11). T-score generally reveals a value below -2.5.

2.Osteopenia: Disorder with a decreased bone density below normal exhibiting a T score in the range of -1 and -2.5.

3.Osteoarthritis: A chronic arthropathy characterized by degenerative destruction of articular cartilage, local inflammation, subchondral bone sclerosis, and osteophytes, commonly diagnosed in the elderly (12,13).

4.Osteomyelitis: it is described as a condition characterized by an inflammation of the fatty tissue within the bone and/or fungal or bacterial infection in the bones.

5.Bone Cancer: Osteosarcoma and Ewing Sarcoma are the typical primary bone cancers caused due to abnormal growth of cells. This malignant tumour growth is generally observed in kids and adolescents.

6.Bone Metastasis: This is a secondary derived bone cancer due to metastasis of the cancerous cells from the other organs.

7.Paget's disease: A chronic condition affecting the bone remodelling process wherein the process of rebuilding of bones takes place at a faster rate. This results in an unusual bone structure causing the bones to become soft or large and increased susceptibility to fractures and bending.

8.Osteomalacia: The condition is characterized by incomplete mineralization of bone, resulting in an inability to harden while in the initial stages of bone formation.

9.Autoimmune diseases: Bone diseases are secondary complications in various autoimmune conditions like Type I Diabetes mellitus, Systemic lupus erythematosus, Rheumatoid arthritis, Celiac diseases.

Considering the various bone disorders and the significant impact of these diseases on the quality of life, patient suffering, disruption of routine activities, pain and discomfort, hospitalization and financial burden incurred, several treatment options are designed. The administration of drug in conventional dosage forms are unable to achieve the required therapeutic dose at the site of action, thereby providing inadequate benefits while producing additional side effects at the non-target site. Inspite of the large doses administered, the therapeutic effect did not balance their side effects. An example is an anti-osteoporotic drug used in post-menopausal women exposed patients to adverse effects like endometriosis, cancer risks and intrauterine haemorrhage (14). To cater to this drug loss as well as avoid or minimize the undesired effects, bone targeting approaches were suggested. They not only exhibited increased dose at the therapeutic site but also reduced the toxicity associated at the non-target site thereby providing better patient compliance while treating them in a rationalized and cost-effective optimized dosage regimen.

2. Strategies for Bone Targeting:

Two broad strategic approaches have been employed. First been the systemic targeting by employing targeting ligands with high affinity to hydroxyapatite, a bone tissue component, thereby delivering the drug to the bone for deposition to the lesion. This promising approach has been validated, experimented and worked out well using bone seeking targeting ligands such as bisphosphonates, tetracyclines, acidic oligopeptides and peptide sequences- aptamers as revealed in literature. Systemic targeting can be clinically applicable to systemic bone related disorders like osteoporosis and osteoarthritis. However due to the complexity and diversity of the bone disorders, systemic targeting might not be suitable for all of them, such as localized injury (critical fractures). Hence the second strategy designed is local targeting using local delivery of the therapeutics by surgical implantation, injection at the targeted bone site, or more specifically employing a microenvironment approach. The latter approach can accommodate weak acidic, abnormal enzyme and redox levels, localized heat and swelling in the diseased bone's microenvironment. They thus provide a more precise and sensitive response, thereby minimizing the probability of dose dumping and adverse effects (15, 16, 17). The approaches have been summarized in figure 2 given below.

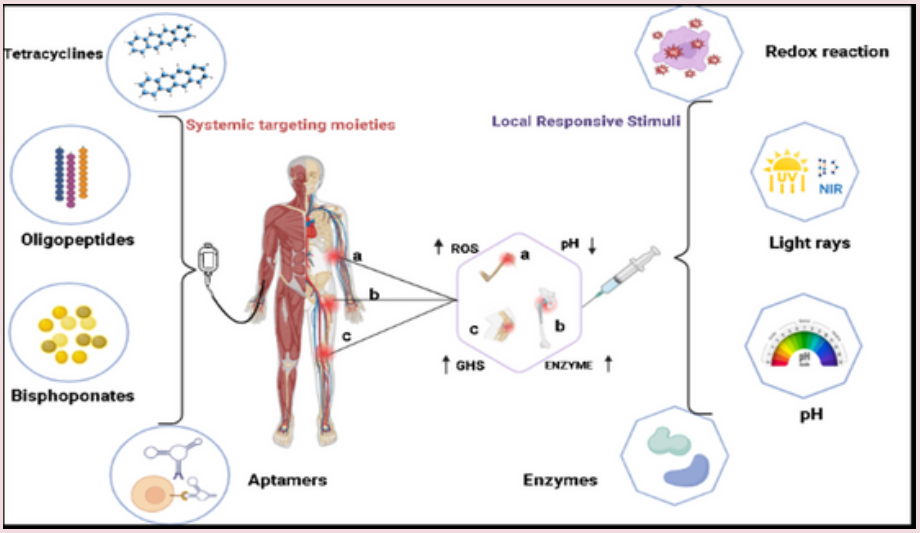

Figure 2: Strategic approaches used in Bone targeting

3. Drug Delivery Systems in Bone targeting:

Suitable drug carriers provide an excellent delivery of the therapeutic moieties to the target site. Thus, advantageously exploiting the binding of drug-ligand complexes to endogenous receptors at the therapeutic site and enhanced permeation and retention effect at the local site have benefited the novel drug delivery systems in controlling the progression of the disease as well as in treating the same. Several drug carriers have been employed successfully such as particulate systems (liposomes, dendrimers, nanoparticles, microspheres), hydrogels and matrix based. Figure 3 provides a concise list of the delivery systems used in bone targeting but is not limited to the same. Alencastre et al. 2016, summarized several drug carriers employed in the bone targeting of drugs in Table 1

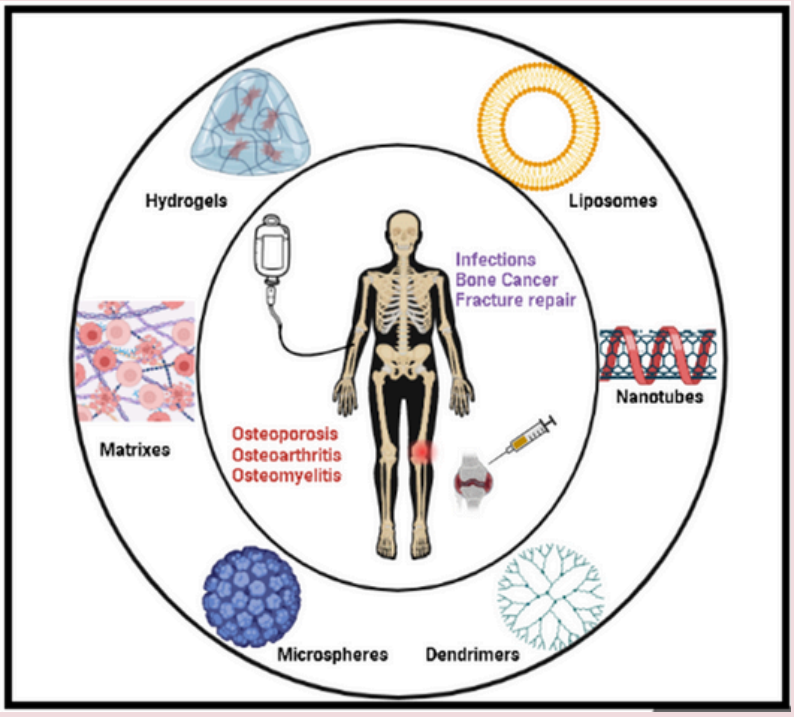

Figure 3: Drug Delivery systems employed in Bone targeting.

4. Conclusion:

Bone, a majorly mineralized tissue, exhibits an important support structure of our body. An extensive literature review has helped explain the mechanistic approach in bone targeting satisfactorily. Targeting of the therapeutics to the bones enables specific accumulation of the drugs in the diseased skeleton or the target cells. It not only helps to improve the pharmacokinetics of the drug but also enhances its therapeutic efficiency. It is thus understood that bone-related diseases need a systematic delivery of therapeutics in order to target the local site. The current review highlights the common prevailing bone disorders, strategies employed and drug delivery systems to provide rational selection and designing the same to suit the individualized medical needs of the patient in bone metabolic diseases.

Table 1 Drug carriers used in drug delivery to Bone (18).

	Therapeutic agent	Delivery	Therapeutic indication	Model of study
Inorganic				
MS and MS/apatite nanoparticles	OPG	Implant	Bone regeneration	*In vitro;* Simulated body fluid
CaP nanocapsules	Sim	Injection	Osteoporosis	*In vivo*; Ovariectomised mouse
HAp	Pur	Implant	Fracture	*In vivo*; Foetal chick femur
CaP cement	Alen	Implant	Osteoporosis	*In vitro*
Nanodiamonds	BMP-2; bFGF	Injection	Bone formation	*In vitro*, Osteoblast progenitor cells
CaP	Zol	Injection	Osteoporosis	*In vivo*, Ovariectomised rat and sheep
CaS	Sim	Implant	Fracture	*In vivo*, Rat tibia osteotomy
CaP granules (Tetrabone®)	Helioxanthin agonist	Implant	Fracture	*In vivo*, Rat Femur bone defect
LDH nanocarriers	MTX	-	Osteosarcoma	*In vitro*, Saos-2 cell culture
Ti	BMP-2	Implant	Fracture	*In vivo*, Rat tibial defect
Organic				
Collagen	Ros	Implant	Fracture	*In vivo*, Critical-size rabbit bone defect
Collagen sponge-Teraplug®	N-acetyl cysteine	Implant	Fracture	*In vivo*, Critical-size rat femur bone defect
Gelatine hydrogels	rhBMP-2	Implant	Bone formation	*In vivo*, mouse subcutaneous
PLGA	FTY720	Implant	Allograft implants	*In vivo*, Critical-size rat tibia defect
PLGA/PLLA nanofibrous scaffolds	Dox	Implant	Periodontitis and RA	*In vitro*, antibacterial assays
PLA-Nanospheres	BMP-2	-	Fracture	*In vitro*, microculture tetrazolium test
Polyurethane scaffolds	Los	Implant	Fracture	*In vivo*, critical-sized rat femur bone defect
Organic-Inorganic				
PLGA – MS membranes (SBA15)	rhBMP-2	Implant	Bone tissue engineering	*In vitro*, human bone marrow-derived mesenchymal stem cells
B-TCaP / Collagen	FGF-2	Injectable	Fracture	*In vivo*, rabbit tibia segmental defect
CaP/Gelatine microparticles	TGF-ss 1	Injectable	Fracture	*In vivo*, Rabbit femoral bone defect
HAp plasma-coated Ti alloy cylinders	Zol	Implant	Implant fixation in osteoporotic bone	*In vivo* Ovariectomized sheep
PLGA/HAp microspheres	Sim	-	Osteonecrosis bone defects	*In vivo*, mouse model of gap fracture bridging with a graft of necrotic bone
3D apatite-coated CH/CS scaffold	BMP-2, ASCs	Implant	Bone defects	*In vivo*, rat critical-sized mandibular defect model.

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