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A Narrative review on the basic science and Clinical implication on Bone grafts

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Abstract

Bone is a specialized connective tissue, consists of cells, fibres & intercellular matrix. Bone at the tissue level undergoes remodeling: it is continuously being resorbed and rebuilt (or formed). A negative balance between bone resorption and formation, frequently due to excessive resorption is the basis of many bone diseases. Resorption is carried out by osteoclasts, which are specialized multinucleated cells of hemopoietic origin. Bone resorption takes place at a specialized area of the osteoclast cell membrane called "ruffled border," which comprises a sealed lysosomal compartment where the acidic pH solubilizes the mineral and the proteolytic enzymes digest the matrix. Calcitonin and bisphosphonate have been shown to act directly on osteoclasts whereas other hormones and agents probably act on the osteoblasts or cells of the osteoblast lineage. Whenever there is a breach in the continuity of bone, it undergoes stepwise healing process and if the bone is missing or it could not heal then the bone grafting needs to be done. There are three types of procedures for bone grafting; Autograft, Allograft, and Synthetic bonegraft. Growth factors also play roles in bone grafts and they consist of either human growth factors or morphogens (BMPs in conjunction with a carrier medium, such as collagen). As the bone grafting is commonly used to augment bone healing and repair that is why the present review has been conducted to bridge the knowledge of basic science and clinical implication of various bone constituents with its function, bone healing process, various grafts and its advantage and disadvantage.

Key Words: Cortical bone, Trabecular bone, Autograft, Allograft, Hematopoiesis

Introduction

Bone is a living connective tissue. As bone is connective tissue, it consists of cells, fibers and intercellular matrix. It is subject to disease and repairable itself. It consists of dense white fibers embedded in hard calcium salt matrix. The cells of bone are osteoprogenitor cells, osteoblasts,

osteoclasts, osteocytes and bone lining cells. Bone lining cells do not take part in bone formation or resorption. Bone lining cells only helps in transport of substances. The ground substance of matrix is made up of proteoglycans and glycosaminoglycans such as hyaluronic acid, keratin sulphate, and chondroitin sulphate. The ground substance of matrix also contains some adhesive substances like osteocalcin, osteonectin. Resilience of the bone is due to fibrous tissue. The calcium salts make it hard & tough to resist compression forces. Bone is present in two forms; Compact and cancellous. Compact bone is dense and forms the shafts of the long bones covered by periosteum. Outer layer of periosteum is fibrous and inner layer is cellular. Cancellous bone is a network of bony plates and trabeculae with marrow spaces in between. The function of bone tissue is both supportive and locomotive by providing attachment sites for muscles, tendons and ligaments.^[1,2] In addition, bones permit motor capability, protect vital organs, facilitate breathing, play a role in homeostasis, and produce a variety of cells in the marrow critical for survival.^[3] Bone tissue is unique in that it can regenerate restoring to a fully-functional, pre-injury state as it is metabolically active with enormous bone cells (osteocytes) and extracellular matrix.^[4,5] Under the right conditions, bone tissue undergoes a process of mineralization, formed by collagen matrix and hardened by deposited calcium. It is hard and many of its functions depend on that characteristic hardness.^[6] The adult human skeleton is composed of 206 bones. At birth, there are approximately 270 bones, with the final adult count decreasing as a portion of these bones fuse during phases of skeletal growth and maturation. During life bone is constantly remodeling with most of the adult skeleton being replaced about every 10 years.^[6] Up to 80% bones are cortical while the rest are cancellous in nature.^[7] There are several growth factors responsible for bone growth such as morphogenetic protein (BMPs), transforming growth factor beta (TGF-B), insulin like growth factor I & II (IGF I, IGF II), platelet derived growth factor (PDGF), basic fibroblast growth factor (b FGF) and acidic fibroblast growth factor (a FGF). Whenever bone get fractured or breached, Stem cells of various origins, particularly endothelial progenitor cells (EPCs), have potential to enhance bone repair and regeneration. Endothelial progenitor cells are resident of bone marrow and move to ischemic sites to initiate vasculogenesis which is important for bone repair^[8]. Bone substitutes are being increasingly used especially in oncologic surgery, traumatology, revision prosthetic surgery and spine surgery^[9].

Types of Bone:

(a) On the basis of density

- Compact (cortical) bone: makes up 80% of the total bone in the body and is much stronger than trabecular bone. It is very resistant to bending, torsion, and compression and is much denser with a minimal role in metabolism. It is seen mostly in the shaft of long bones like the femur and the tibia as well as in the outer shell of trabecular bone
- Cancellous (trabecular or spongy) bone: makes up only 20% of the total bone but has ten times the surface/volume ratio of cortical bone. It responds eight times faster to changes in load making it far more dynamic. It occurs in areas that more subject to compression such as the vertebral body, pelvis, and the metaphysis.^[10]

(b) On the basis of shapes

- I. Long bones: These are mostly compacted bone with little marrow and include most of the bones in the limbs. These bones tend to support weight and help movement. Examples: Femur, tibia, fibula, humerus.
- II. Short bones: Only a thin layer of compact bone, these include bones of the wrist and ankle.
- III. Flat bones: Usually bones those are thin and curved. They consist of two outer layers of compact bone and an inner layer of spongy bone. Flat bones include most of the bones of the skull and the sternum or breastbone. They tend to have a protective role. examples- sternum, ribs
- IV. Sesamoid bones: These are embedded in tendons, such as the patella or kneecap. They protect tendons from wear and stress.
- V. Irregular bones: As their name implies, these are bones that do not fit into the first four categories and are an unusual shape. They include the bones of the spine and pelvis. They are often protecting organs or tissues.

Gross Anatomy: A long bone has 2 parts, the diaphysis and the epiphysis. Those bones that undergo endochondral ossification also have a physis (growth plate).

- I. The diaphysis is the tubular shaft that runs between the proximal and distal ends of the bone. The hollow region in the diaphysis is called the medullary cavity, which is filled with yellow marrow. The walls of the diaphysis are composed of dense and hard compact bone.^[11]
- II. The physes (singular: physis) or growth plates are found in bones that undergo endochondral ossification (the process by which the embryonic cartilaginous model of most bones contributes to longitudinal growth and is gradually replaced by bone).^[12]
- III. The epiphysis, the part or process of a bone that ossifies separately and later becomes ankylosed to the main part of the bone. The epiphysis contributes to a joint, compared with an apophysis which is a site of tendon or ligament attachment. Once the growth plate has fused, the epiphysis and metaphysis are joined.

Bone Composition: Bone is composed of cells and the extracellular matrix (ECM), which has both organic and inorganic substances. Osteoblasts synthesize bone ECM. The ECM consists of: Type I collagen mixed with a matrix of calcium phosphate crystal (which is up to 70 % of the dry weight) & Proteoglycans and glycoproteins, which are less abundant, but vital for the organization of collagen fibers, mineralization and resorption of bone. Chondroitin sulfate accounts for 67-97 % of the bone glycosaminoglycans.^[13]

Bone cells: Bone cells make up about 10% of total bone volume. Bones are not a static tissue but need to be constantly maintained and remodeled. There are three main cell types involved in this process. Osteoblasts are responsible for making new bone and repairing older bone. Osteoblasts produce a protein mixture called osteoid, which is mineralized and becomes bone. Another function is to manufacture hormones, including prostaglandins. Osteocytes are inactive osteoblasts that have become trapped in the bone that they have created. They maintain connections to other osteocytes and osteoblasts. They are important for communication within bone tissue. Osteoclasts are large cells with more than one nucleus, which break down bone. They release enzymes and acids to dissolve minerals in bone and

digest them in a process called resorption. Osteoclasts help remodel injured bones and create pathways for nerves and blood vessels to travel through ^[14].

Extracellular Matrix: Bones are, in reality, living cells embedded in a mineral-based organic matrix. This extracellular matrix consists of Organic components, being mostly type I collagen & Inorganic components, including hydroxyapatite and other salts, such as calcium and phosphate. Collagen gives bone its tensile strength, namely the resistance to being pulled apart. Hydroxyapatite gives the bones compressive strength or resistance to being compressed ^[14].

Bone marrow & Hematopoiesis:

Bone marrow is found in almost all bones where cancellous bone is present. Bone marrow is responsible for hematopoiesis, or the production of red blood cells, white blood cells, and platelets. ^[15] It makes around 2 million red blood cells every second, as well as producing platelets, and white blood cells. Also, defective and old red blood cells are destroyed in bone marrow. ^{[16][17]}

Healing of a Bone Fracture

Whenever there is fracture or breach in the continuity of bone the fracture site is filled with the blood as a result of blood vessels in the bone, periosteum, and surrounding tissues are torn. A simple fracture dealing with small or medium sized bones in young adults may take six to eight weeks to heal. A fracture dealing with longer bones, larger bones, weight-bearing bones, and bones of elderly could be a longer healing process. **First Stage of Bone Repair; Hematoma Formation** When a bone breaks, blood vessels in the bone, periosteum, and surrounding tissues are torn and hemorrhage. As a result, a hematoma (or mass of clotted blood) forms at the fractured site. Bone cells die because they are not getting the nutrition they need. The tissue at the site becomes swollen, painful, and inflamed. **Second Stage of Bone Repair; Fibro cartilaginous Callus Formation** Within a few days, capillaries grow into the hematoma. Phagocytic cells invade the area and begin cleaning up

the debris. Fibroblasts and osteoblasts invade fracture site and begin reconstructing bone. Fibroblasts produce collagen fibers that span the break and connect the broken bone ends. Osteoblasts begin forming spongy bone and this all helps to form the mass of repair tissue otherwise known as the fibro cartilaginous callus and this splints the broken bone. **Third Stage of Bone Repair;** Bony Callus Formation Within a week, new bone trabeculae begin to appear in the fibro cartilaginous callus and gradually convert it to a bony (hard) callus of spongy bone. Bony callus formation continues until a firm union is formed about two months later. **Fourth Stage of Bone Repair;** Bone remodeling begins during the formation of the bony callus and continues for several months after the bony callus is remodeled. The excess material is removed and compact bone is laid down to reconstruct the shaft walls. The final structure of the remodeled areas resembles that of the original unbroken bony region.

Bone healing and bone implants:

Bone is living connective tissue which constantly remodeling. It has the potential to regenerate with restorations of its biological and mechanical properties ^[18]. Regeneration of bone is a complex process in clinical conditions such as large bone defects caused by trauma, infections, tumor resection and skeletal abnormalities like avascular necrosis, osteoporosis, & certain diseases, disorders and trauma result in damage to the skeletal system. The fractures and defects in the skeletal system can lead to an increase in mortality ^[19]. Though bone is living connective tissue which constantly remodeling and has the potential to regenerate sometime need for an implant when bone fails to regenerate, producing bone defects ^[20]. There are different strategies to augment impaired regeneration. The current strategies for healing bone defects are numerous and varied. For proper alignment and healing clinical intervention is required to treat fractures and defects. If the incorrect material is chosen, the implants themselves can lead to bone fractures or defects. The surface of an implant determines its ability to integrate into the surrounding tissue. Effect of surface energy, composition, roughness and topography plays important role in biological response to the implant ^[21]. The fibrin structure and cellular content of a peri-implant clot can greatly affect osteo conduction and bone formation on implant surfaces ^[22].

Bone grafting

Bone grafting is a surgical procedure that replaces missing bone with its material from patient's own body or from another individual. This surgical procedure promotes body's natural bone-making process by applying substances to gaps in weak, broken or deficient bones for added support and stimulating tissue growth to bridge gaps and restore bone strength and rigidity. This procedure may be necessary if bones don't heal correctly after a fracture and leads to:

- **Delayed union:** Bone healing (fusion) that occurs more slowly than expected
- **Malunion:** Bones that heal in an abnormal position.
- **Nonunion:** When bone fusion does not occur.

Other reasons for a bone graft include:

- Bone diseases like osteonecrosis and cancer.
- Bone infection (osteomyelitis).
- Congenital anomalies, such as uneven limbs or an abnormally small chin.
- Jaw reinforcement (dental bone graft) before receiving a tooth implant.
- Joint replacement surgery, which may require bone growth to secure an artificial joint.
- Spinal fusion.
- Trauma, including bad fractures that shatter bones.

Methods of Bone grafting

- **Autograft:** An autograft uses a sample of same individual's bone tissue. The tissue typically comes from the top of your hip bone (iliac crest). The surgeon makes an incision to obtain the bone tissue. Autogenous cancellous bone graft provides an osteoconductive, osteoinductive, and osteogenic substrate for filling bone voids and augmenting fracture-healing. The proximal part of the tibia, distal end of the radius, distal aspect of the tibia, and greater trochanter are alternative donor sites that are particularly useful for bone-grafting in the ipsilateral extremity.

- **Allograft:** This method uses bone tissue from another person (donor). Public health services have strict regulations on how tissues are handled and the bone tissue is cleaned and processed (sterilized) to ensure the safety of the recipient. This type of graft is common in spinal fusion surgery. It provides a framework around which healthy bone tissue can grow.
- **Bone marrow aspirate:** Marrow is the spongy substance inside bones. It contains stem and progenitor cells that can help bone fractures heal. Using a needle, the surgeon gets a bone marrow sample from the hip bone (iliac crest). This bone marrow aspirate is used alone or mixed with other bone grafts to enhance bone healing for allograft procedures.
- **Synthetic bone graft:** This type of graft uses artificially produced materials made from a variety of porous substances. Flexible hydrogel-hydroxyapatite (HA) composite which has a mineral to organic matrix ratio, approximating that of human bone. Artificial bone can be created from ceramics such as calcium phosphates (e.g., HA and tricalcium phosphate), bioglass, and calcium sulphate are biologically active depending on solubility in physiological environment ^[23].

Advantage & Disadvantage ^[24-26]

S.N.	Bone Graft technique	Advantage	Disadvantage
1	Autograft	• Biocompatible, Osteoinductive, Osteoconductive • No risk of disease transmission. • Low chance of infection • Bone-growing cells are in the graft, which increases the likelihood of	• Need for additional surgery to procure the tissue • Donor site morbidity and post operative pain • Limited amount of tissue can be procured • Increase risk of fracture at donor site

		successful bone healing.	
2	Allograft	• No additional procedure is necessary to harvest bone tissue. • Low risk of spreading disease because bone tissue is sanitized. • Does not take tissue from other bones.	• Chance of rejection • Chance of disease transmission • Higher cost • potentially shorter recovery
3	Synthetic bone graft	• Sterile, free of germs. • Available in unlimited quantities, so it can repair large sections of bone. • Many options exist, making it easier to meet a wide range of medical needs.	• Brittle properties • Variable rates of resorption

Autograft Vs Allograft

The autograft take shorter time to union compared to allograft and exhibits a trend towards earlier union when compared to allograft/autograft combined. Furthermore, the autograft cohort has the lowest rate of surgical revisions compared to allograft/autograft combined. The overall new-onset postoperative infection rate is lower in the autograft group, compared to the allograft cohort ^[27]. Allogenic bone can serve as excellent material for prophylactic or primary bone grafting in difficult to heal fractures as it potentiates bone healing and bridges bone gaps. However in established cases of delayed and non unions which require grafts with good osteogenic potential, use of allogenic grafts along with adjuvants like bone marrow and autologous bone graft is more beneficial ^[28].

Growth Factor in Bone healing

Growth factor enhanced grafts are produced using recombinant DNA technology. They consist of either human growth factors or morphogens (BMPs in conjunction with a carrier medium, such as collagen). The factors and proteins that exist in bone are responsible for regulating cellular activity. Growth factors bind to receptors on cell surfaces and stimulate intracellular environment to act. Generally, this activity translates to a protein kinase that induces a series of events resulting in transcription of messenger ribonucleic acid (mRNA) and ultimately into the formation of a protein to be used intracellularly or extracellularly. The combination and simultaneous activity of many factors results in controlled production and resorption of bone. These factors, residing in extracellular matrix of bone, include TGF-beta, insulin like growth factors I and II, PDGF, FGF, and BMPs ^[29].

Risks of bone grafting

- Blood loss.
- Infection.
- Problems with bone healing.
- Chronic pain.
- Fractures.
- Hardware failure, meaning plates and screws fail to hold the graft in place.
- Scarring

Conclusions:

As bone substitutes are being increasingly used, understanding the type, architecture and constituents of bone is very important and this review had aligned the effective management strategies; the knowledge of recent advancement of various factors such as growth factors, type of bone, type of graft to be used, healing factors, risk factors in healing bone defects, skeletal abnormalities, acceptance of grafts leads to improved outcome & enhancement of quality of life by achieving proper treatment.

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References:

1. Borzini P, Mazzucco L. Tissue regeneration and in loco administration of platelet derivatives: clinical outcome, heterogeneous products, and heterogeneity of the effector mechanisms. *Transfusion*. 2005 Nov;45(11):1759-67.
2. Rodrigues MT, Reis RL, Gomes ME. Engineering tendon and ligament tissues: present developments towards successful clinical products. *Journal of tissue engineering and regenerative medicine*. 2013 Sep;7(9):673-86.
3. DiGirolamo DJ, Kiel DP, Esser KA. Bone and skeletal muscle: neighbors with close ties. *Journal of bone and mineral research*. 2013 Jul;28(7):1509-18.
4. Salhotra A, Shah HN, Levi B, Longaker MT. Mechanisms of bone development and repair. *Nature reviews Molecular cell biology*. 2020 Nov;21(11):696-711.
5. El Sayed SA, Nezwek TA, Varacallo M. Physiology, bone.
6. Dorozhkin SV. Calcium orthophosphates. *Journal of materials science*. 2007 Feb; 42(4) :1061-95.
7. Vico L, Collet P, Guignandon A, Lafage-Proust MH, Thomas T, Rehailia M, Alexandre C. Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. *The Lancet*. 2000 May 6;355(9215):1607-11.
8. Zaidi N, Nixon AJ. Stem cell therapy in bone repair and regeneration. *Annals of the New York Academy of Sciences*. 2007 Nov;1117(1):62-72.

9. Bhatt RA, Rozental TD. Bone graft substitutes. *Hand clinics*. 2012 Nov 1;28(4):457-68.
10. Carpenter SR, Ludwig D, Brock WA. Management of eutrophication for lakes subject to potentially irreversible change. *Ecological applications*. 1999 Aug;9(3):751-71.
11. Resnick DL, Kransdorf MJ. Bone and joint imaging. Elsevier Health Sciences; 2004 Nov 23.
12. Reno PL. Ossification of the mammalian metatarsal: Proliferation and differentiation in the presence/absence of a defined growth plate. Kent State University; 2006.
13. Palmer LC, Newcomb CJ, Kaltz SR, Spoerke ED, Stupp SI. Biomimetic systems for hydroxyapatite mineralization inspired by bone and enamel. *Chemical reviews*. 2008 Nov 12;108(11):4754-83.
14. Kini U, Nandeesh BN. Physiology of bone formation, remodeling, and metabolism. Radionuclide and hybrid bone imaging. 2012:29-57.
15. Kini U, Nandeesh BN. Physiology of bone formation, remodeling, and metabolism. Radionuclide and hybrid bone imaging. 2012:29-57.
16. Vogler 3rd JB, Murphy WA. Bone marrow imaging. *Radiology*. 1988 Sep;168(3):679-93.
17. Dhaliwal G, Cornett PA, Tierney Jr LM. Hemolytic anemia. *American family physician*. 2004 Jun 1;69(11):2599-607.
18. Giannoudis PV, Einhorn TA, Marsh D. Fracture healing: the diamond concept. *injury*. 2007 Sep 1;38:S3-6.
19. Lee EJ, Jain M, Alimperti S. Bone microvasculature: stimulus for tissue function and regeneration. *Tissue Engineering Part B: Reviews*. 2021 Aug 1;27(4):313-29.
20. Hollinger JO, Kleinschmidt JC. The critical size defect as an experimental model to test bone repair materials. *Journal of Craniofacial Surgery*. 1990 Jan 1;1(1):60-8.
21. k.Kieswetteret.all “The Role of Implant surface characteristics in the Healing of Bone”,SAGE Journals, Vol 7, issue 4. [http:// doi.org/10.1177/10454411960070040301](http://doi.org/10.1177/10454411960070040301).

22. Tissue Engineering Part B: Reviews VOL. 20, NO. 6 | Review Articles normal Formation of Blood Clot on Biomaterial Implants Influences Bone Healing Hoi Ting Shiu, Ben Goss, Cameron Lutton, Ross Crawford, and Yin Xiao Published Online: 17 Jul 2014 <https://doi.org/10.1089/ten.teb.2013.0709>)
23. Kumar P, Vinitha B, Fathima G. Bone grafts in dentistry. J Pharm Bioallied Sci. 2013 Jun;5(Suppl 1):S125-7. doi: 10.4103/0975-7406.113312. PMID: 23946565; PMCID: PMC3722694.
24. <https://www.medicalnewstoday.com/articles/allograft-vs-autograft#allograft-vs-autograft>
25. Myeroff C, Archdeacon M. Autogenous bone graft: donor sites and techniques. JBJS. 2011 Dec 7;93(23):2227-36.
26. Sohn, HS., Oh, JK. Review of bone graft and bone substitutes with an emphasis on fracture surgeries. Biomater Res **23**, 9 (2019). <https://doi.org/10.1186/s40824-019-0157-y>
27. Flierl MA, Smith WR, Mauffrey C, Irgit K, Williams AE, Ross E, Peacher G, Hak DJ, Stahel PF. Outcomes and complication rates of different bone grafting modalities in long bone fracture nonunions: a retrospective cohort study in 182 patients. Journal of orthopaedic surgery and research. 2013 Dec;8(1):1-0.
28. Lakhwani OP, Jindal M, Agarwal S, Keerty G. Efficacy of Allogenic Bone Graft Per Se and when Augmented with Various Adjuvants in Fracture Healing. Orthopedics and Rheumatology Open Access Journals. 2018;11(4):73-80.
29. Valdes MA, Thakur NA, Namdari S, Ciombor DM, Palumbo M. Recombinant bone morphogenic protein-2 in orthopaedic surgery: A review. Arch Orthop Trauma Surg. 2009;129:1651–7