ADVANCES IN BONE FRACTURE MANAGEMENT: A COMPREHENSIVE REVIEW OF TREATMENT STRATEGIES AND INNOVATIONS

[1]Aysha Afeefa A, [2]Dr. R. Nethaji, [3]Dr. Vimal KR

[1]Primary author, [2]Professor and head, [3]Associate professor
Department of Pharmaceutics
Devaki Amma Memorial College of Pharmacy
Near Calicut University, Chelembra- 673634

***Abstract*- Many implants like biodegradable offer a promising approach to enhance bone healing by providing controlled drug release directly to the site of injury.Compared with non-degradable materials, biodegradable biomaterials play an increasingly important role in the repairing of severe bone defects, and have attracted extensive attention from researchers. Twelve publications on pure Mg, Mg alloys and Zn alloys were finally included and reviewed after extraction from a collected database of 2122 publications.Imagine a tiny implant that not only supports the broken bone but also serves as a localized drug delivery system. This means that therapeutic agents, carefully selected to aid in bone healing, infection prevention, and inflammation reduction, are released directly at the site of injury over a controlled period.**

***Key Words*: human bone, bone fracture, biodegradable implants, drug loading**

INTRODUCTION:

The study on "Advances in bone fracture management: A comprehensive review of treatment strategies and innovations" aims to provide context and rationale for the research topic. It starts by acknowledging the significant impact that bone fractures have on individuals' well-being, emphasizing the importance of effective treatment methods to minimize complications and promote speedy recovery.

Traditional treatments, such as casting or surgical fixation, have been the go-to approaches for managing bone fractures. However, these methods have limitations. Casting, for instance, can lead to muscle atrophy and joint stiffness due to immobilization, while surgical fixation involves invasive procedures that might carry risks of infection, complications, and a prolonged recovery period.

The limitations of conventional treatments have fuelled the exploration of novel strategies to enhance bone healing. This is where biodegradable implants come into play. These implants are designed to provide structural support to the fractured bone during the initial stages ofhealing. Unlike permanent implants, which may require a second surgery for removal, biodegradable implants gradually degrade over time, eliminating the need for a second procedure.

One of the key innovations is the integration of drug delivery within these biodegradable implants[1]. By loading the implants with therapeutic agents, such as antibiotics or growth factors, researchers aim to address common complications associated with bone fractures, such as infection and delayed healing. The localized and controlled release of drugs directly to the site of injury can help prevent infections and reduce inflammation, thereby promoting a more favourable environment for bone regeneration.

This approach capitalizes on the controlled degradation of the implant to coincide with the healing progression of the bone[2]. As the bone heals and gains strength, the implant's need for structural support diminishes, and its gradual degradation aligns with the bone's recovery. This not only eliminates the need for implant removal but also offers the advantage of targeted drug delivery precisely when it is most needed.

In conclusion, the introduction serves to establish the significance of the research topic by highlighting the limitations of existing treatments and the potential benefits of biodegradable implants loaded with drugs. It sets the stage for further exploration into the mechanisms, benefits, challenges, and implications of this innovative approach in the context of bone fracture management.

HUMAN BONE:

Bone has a hierarchical structure that provides it with the strength necessary for functional loading and specific toughening mechanisms to resist fracture[4]. They provide structural support, protect vital organs, facilitate movement, and serve as a reservoir for minerals like calcium and phosphate.Bones are rigid, hard, and dense connective tissues that make up the human skeletal system[5]. Bone fractures create five problems that must be resolved: bleeding, risk of infection, hypoxia, disproportionate strain, and inability to bear weight [6]. Bones are remarkable structures that undergo constant change throughout a person's life.

Each bone in the body is a complex living organ, composed of both organic and inorganic components:

1. Organic Components: These include cells and a protein matrix called collagen. Collagen gives bones their flexibility and strength, allowing them to withstand bending and twisting forces.

2. Inorganic Components: These mainly consist of minerals, primarily calcium and phosphate, which make bones hard and resistant to compression. These minerals give bones their density and durability[12].

The human skeleton is made up of more than 200 individual bones of various shapes and sizes, categorized into five main types:

1. Long Bones: These bones are longer than they are wide and have a shaft (diaphysis) and two ends (epiphyses). Examples include the femur (thigh bone) and humerus (upper arm bone).

2. Short Bones: These bones are roughly cube-shaped and provide stability and support. The bones of the wrist (carpals) and ankle (tarsals) are examples of short bones.
3. Flat Bones: These bones are thin and flat, providing protection for internal organs and serving as attachment points for muscles. Examples include the skull, scapula (shoulder blade), and ribs.
4. Irregular Bones: These bones have complex shapes that don't fit into the other categories. The vertebrae (bones of the spine) and facial bones are examples of irregular bones.
5. Sesamoid Bones: These are small, round bones found within tendons. The patella (kneecap) is an example of a sesamoid bone.
Bones perform several essential functions in the body:
1. Support: Bones provide the structural framework that supports the body's shape and posture.
2. Protection: Bones protect vital organs. For instance, the skull protects the brain, and the ribcage shields the heart and lungs.
3. Movement: Muscles attach to bones, allowing them to generate movement when contracted. Joints enable bones to move in various ways.
4. Storage: Bones store essential minerals, especially calcium and phosphate, which the body can release when needed for functions like muscle contraction and nerve signaling.
5. Blood Cell Formation: Bone marrow, found within certain bones, is responsible for producing blood cells (hematopoiesis), including red blood cells, white blood cells, and platelets.
Overall, bones are vital structures that give the body its shape, provide protection for organs, facilitate movement, store minerals, and contribute to the production of blood cells. Their complex composition and arrangement make them a crucial component of the human body's overall function and health.

STRUCTURE OF BONE:
Certainly, let's delve into the structure of bones. Bones are complex organs with a hierarchical structure that combines various layers and components to provide strength, flexibility, and support to the body. The structural organization of bone can be described at different levels:
1. Macroscopic Level:
- Diaphysis: Also known as the shaft, the diaphysis is the elongated central part of a long bone. It is primarily composed of compact bone, which provides strength and stability.
- Epiphyses: These are the rounded ends of long bones. They consist of spongy or cancellous bone covered by a thin layer of compact bone. The epiphyses contribute to articulation with other bones in joints.
2. Microscopic Level:
Bones have a microscopic structure that consists of various types of bone tissue and cells:
- Compact Bone: This dense outer layer of bone forms a solid shell around the medullary cavity (inner space). Compact bone is made up of units called osteons, or Haversian systems, which contain concentric layers of bone matrix (lamellae) surrounding central canals (Haversian canals). Blood vessels and nerves pass through these canals[8].
- Spongy (Cancellous) Bone: Found in the interior of bones and the epiphyses of long bones, spongy bone consists of trabeculae (small, interconnected columns) that create a lattice-like structure. Spaces between trabeculae are filled with red or yellow bone marrow.
- Bone Marrow: The medullary cavity and spaces within the spongy bone contain bone marrow. Red bone marrow is responsible for producing blood cells, while yellow bone marrow consists mainly of fat cells[13].
3. Cellular Level:
- Osteoblasts: These cells are responsible for bone formation. They secrete collagen and other organic components, which form the bone matrix.
- Osteoclasts: Osteoclasts are specialized cells that break down bone tissue during a process called bone resorption. This helps regulate bone shape, calcium release, and mineral balance.
- Osteocytes: These are mature bone cells embedded within the bone matrix. Osteocytes help maintain bone tissue by sensing mechanical stress and orchestrating the process of bone remodeling.
- Bone Matrix: The bone matrix is made up of collagen fibers and mineral salts, primarily calcium and phosphate. Collagen provides flexibility and tensile strength, while mineral salts give bones their hardness and resistance to compression[15].
4. Periosteum and Endosteum:
- Periosteum: The periosteum is a fibrous membrane covering the outer surface of bones. It contains blood vessels, nerves, and connective tissue that nourish and support bone growth and repair.
- Endosteum: The endosteum is a thin layer of connective tissue lining the medullary cavity and covering the trabeculae within spongy bone. It contains osteoblasts and osteoclasts involved in bone remodeling[12].
In summary, the structure of bones is characterized by their macroscopic and microscopic composition. Long bones consist of diaphyses and epiphyses, while the microstructure comprises compact and spongy bone, bone marrow, and a network of cells. This hierarchical arrangement of bone tissue and components contributes to their remarkable strength, flexibility, and ability to adapt to mechanical stress over a person's lifetime[16].

BONE FRACTURE:
Bone fractures occur when the force applied to a bone is greater than its ability to withstand that force. This can result from various causes such as falls, car accidents, sports injuries, or even from simple activities if the bone is weakened by conditions like osteoporosis. The severity and type of fracture depend on factors like the force applied, the angle of impact, and the bone's strength[7].

Causes and Types:
Closed Fracture: In a closed fracture, the bone breaks but does not puncture the skin. This type of fracture is less likely to cause infection compared to open fractures.
Open Fracture: Also known as compound fractures, these occur when the broken bone pierces through the skin. Open fractures are more prone to infection due to exposure to external contaminants.
Greenstick Fracture: Common in children whose bones are more flexible, a greenstick fracture occurs when the bone bends and breaks partially, similar to how a green twig snap.
Comminuted Fracture: In this type, the bone shatters into multiple fragments. It can be more challenging to treat due to the increased risk of bone pieces not healing properly[17].
Hairline Fracture: A hairline fracture is a small crack in the bone's surface. It's often difficult to detect and might only show up on imaging tests like X-rays.
Displaced Fracture: Displaced fractures occur when the broken bone ends are out of alignment. This type often requires realignment for proper healing.
Non-displaced Fracture:In a non-displaced fracture, the broken bone ends remain in alignment. These fractures are generally less severe and might require less invasive treatment[14].

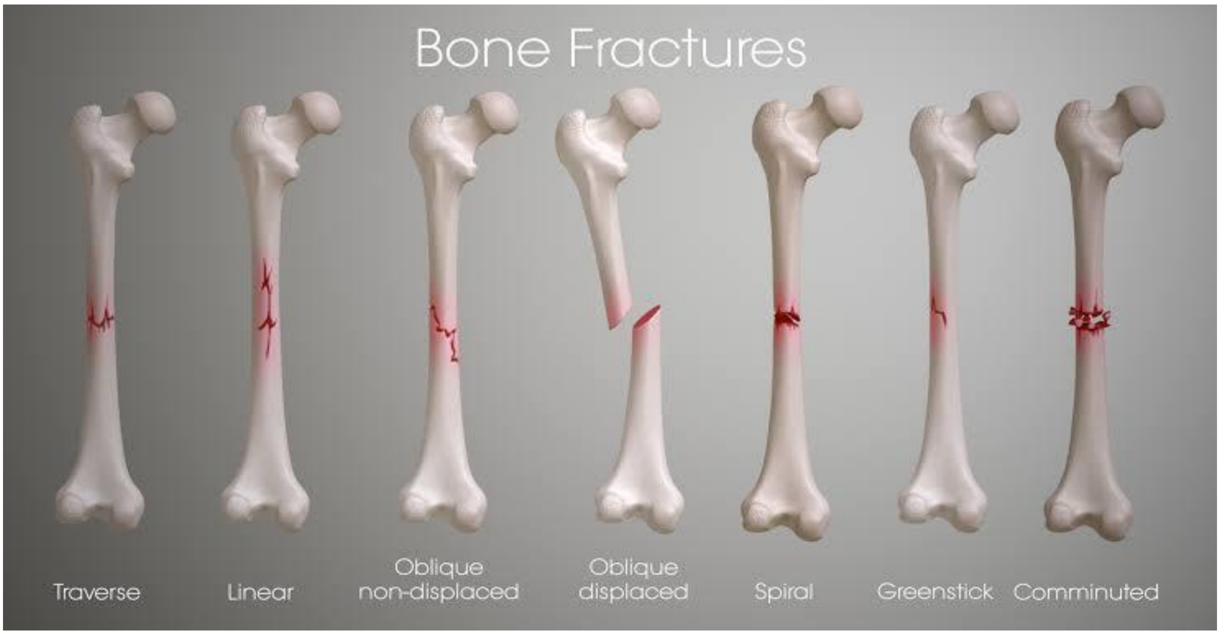

Figure 1: Types of Bone Fractures

Symptoms and Diagnosis:
The symptoms of a fracture can vary but typically include pain, swelling, bruising, and difficulty moving the affected area. In some cases, a noticeable "cracking" sound might be heard at the time of injury. A doctor diagnoses a fracture through a physical examination, medical history, and imaging tests such as X-rays, which can show the location and extent of the fracture[18].

TREATMENT OF BONE FRACTURE:
The repair of long bones has not been optimized by Mother Nature[3].The treatment of bone fractures varies based on factors such as the type of fracture, its location, the patient's age and overall health, and the presence of any associated complications[9]. The primary goals of fracture treatment are to promote proper bone healing, alleviate pain, restore function, and minimize the risk of complications. Here's an elaborate explanation of the different approaches to treating bone fractures:
1. Immobilization:
For stable fractures, a cast made of plaster or fiberglass is applied around the injured area to immobilize and protect the bone as it heals. Casts can be customized to fit the specific shape of the body part, providing stability and support.
Splints are used to immobilize and temporarily stabilize the bone before a cast is applied or in cases where swelling might require flexibility[10].
2. Surgery:
In more complex fractures, surgery may be necessary to realign the bone fragments accurately. Internal fixation devices such as screws, plates, rods, or wires are used to hold the bone in place while it heals. This approach is common for fractures that are displaced, comminuted, or involve joints[20].
In certain cases, external fixation devices are used. These devices are placed outside the body and are attached to pins that are inserted into the bone. They provide stability and allow for proper alignment during the healing process.
3. Traction:
Traction involves applying a pulling force to the affected limb to realign the broken bone ends. This approach is sometimes used before surgery to correct alignment or as a temporary measure to manage fractures in children[11].
4. Medication:

Over-the-counter or prescription pain relievers are often prescribed to manage pain associated with fractures. In open fractures, where the bone punctures the skin, antibiotics might be prescribed to prevent or manage infection. For individuals at risk of blood clots due to immobilization, blood thinners might be prescribed[19].

5. Physical Therapy:

Once the fracture begins to heal, physical therapy might be recommended to restore strength, flexibility, and function to the affected area. Physical therapists can guide patients through exercises and activities to prevent muscle atrophy and regain mobility. Regular follow-up appointments with a healthcare provider are essential to monitor the healing progress, address any complications, and make adjustments to the treatment plan if necessary[21].

For more severe fractures or fractures involving joints, a more comprehensive rehabilitation program may be required. This could include ongoing physical therapy, specialized exercises, and gradual return to normal activities.

It's important to note that the treatment approach will be tailored to each individual's specific circumstances. Factors such as age, overall health, lifestyle, and the type of fracture play a significant role in determining the most appropriate course of action. Effective fracture treatment requires a collaborative effort between the patient, orthopaedic specialist, and healthcare team to achieve the best possible outcome in terms of healing, function, and quality of life.

NOVEL THERAPY FOR BONE FRACTURE:

Types of biodegradable materials for bone fracture:

Several biodegradable materials can be used for bone fracture treatment to create implants that provide initial stability and support during healing, gradually degrade, and stimulate bone regeneration. Here are some examples of biodegradable materials that have been investigated for this purpose:

1. Biodegradable Polymers:

Poly (lactic acid) (PLA): PLA is a biocompatible and biodegradable polymer that has been widely studied for medical applications. It degrades into lactic acid, a naturally occurring compound in the body, which is then metabolized.

Poly (glycolic acid) (PGA): PGA is another polymer that can degrade into glycolic acid. It's known for its strength and is often used in combination with other polymers to create composite materials[24].

Poly (lactic-co-glycolic acid) (PLGA): PLGA is a copolymer of PLA and PGA, offering a balance between the degradation rates of the two individual polymers. It's commonly used in medical devices due to its tunable degradation characteristics[23].

Polycaprolactone (PCL): PCL is a slow-degrading polymer that retains its mechanical strength for an extended period. It has been used in bone regeneration applications due to its long-lasting support.

2. Biodegradable Ceramics:

Calcium Phosphate: Calcium phosphate ceramics closely resemble the mineral composition of bone. They gradually degrade and release calcium and phosphate ions, promoting bone healing and regeneration.

Tricalcium Phosphate (TCP) and Hydroxyapatite (HA): Both TCP and HA are biocompatible ceramics that can be used as scaffolds for bone growth. They degrade at a controlled rate, supporting bone healing[25].

3. Biodegradable Metals:

Magnesium Alloys:

Magnesium alloys have gained significant attention as potential biodegradable implant materials. Magnesium is an essential mineral in the body and plays a role in bone health. Magnesium alloys can provide mechanical support to fractured bones while gradually corroding in the body's physiological environment. As the alloy degrades, magnesium ions are released, which can stimulate bone formation and healing. One challenge with magnesium alloys is controlling the degradation rate to match the bone healing timeline[22].

Zinc Alloys:

Zinc is another biocompatible metal that has been explored for biodegradable implants. Zinc alloys can gradually degrade and release zinc ions, which have been shown to support bone growth and tissue regeneration. These alloys can provide initial stability and eventually be absorbed by the body, eliminating the need for implant removal surgeries[29].

Iron Alloys:

Iron-based alloys, such as iron-manganese and iron-polymer composites, have been investigated for their potential as biodegradable implant materials. Iron is a biocompatible element, and these alloys can corrode in the body's environment, releasing iron ions. Some iron-based alloys are designed to degrade gradually and provide mechanical support during the critical healing period[30].

Zirconium Alloys:

Zirconium alloys are being explored as potential biodegradable implant materials due to their biocompatibility and corrosion properties. These alloys can gradually break down and release zirconium ions, which may have a positive impact on bone regeneration and healing.

Calcium-Based Alloys:

Calcium-based alloys, such as calcium phosphate and calcium magnesium alloys, have been studied for their ability to mimic the mineral composition of natural bone. These alloys can gradually degrade in the body, releasing calcium and other ions that support bone healing and tissue regeneration.

Combination Alloys:

Some research has focused on developing combination alloys that incorporate multiple elements to achieve specific degradation rates, mechanical properties, and biocompatibility profiles. These alloys are engineered to provide optimal support during the healing period while gradually degrading and being absorbed.

It's important to note that the selection of a biodegradable metal for bone fracture treatment depends on various factors, including the desired degradation rate, mechanical properties required for stabilization, and the potential biological effects of the released ions. Research in this field is ongoing, and scientists continue to explore new alloy compositions and designs to optimize the performance of biodegradable implants for bone fracture treatment.

4. Natural Biodegradable Materials:

Collagen: Collagen is a natural protein found in bone and other connective tissues. Collagen-based scaffolds can be used to support bone regeneration and provide a template for new bone growth[27].

Chitosan: Chitosan is derived from chitin, a natural polymer found in crustaceans. It has been studied for its potential to enhance bone healing and tissue regeneration[28].

These materials can be used alone or in combination to create implants or scaffolds that provide mechanical support while gradually degrading as the bone heals. The choice of material depends on factors such as the desired degradation rate, mechanical properties, biocompatibility, and the specific needs of the patient and fracture type. Researchers continue to explore and develop new biodegradable materials and formulations to optimize their use in bone fracture treatment.

How Biodegradable Implants Work:

1. Initial Support: Similar to traditional metal implants, biodegradable metal implants are used to stabilize fractured bones and maintain proper alignment during the healing process. They provide mechanical support and prevent movement that could hinder bone healing.
2. Gradual Degradation: What sets biodegradable implants apart is their ability to degrade naturally as the bone heals. These implants are made from materials that are compatible with the body and can be broken down by the body's natural processes.
3. Stimulation of Healing: As the biodegradable implant degrades, it releases metallic ions or other compounds that can stimulate bone growth and healing at the fracture site.
4. Elimination of Second Surgery: Since biodegradable implants degrade over time, they eliminate the need for a second surgery to remove the implant once the bone has healed. This reduces the risks, costs, and inconvenience associated with implant removal procedures[26].

Advantages of Biodegradable Implants:

1. Reduced Risk of Infection: The risk of infection is reduced because there's no need for a second surgery for implant removal, which can introduce the risk of infection.
2. Natural Healing: Biodegradable implants encourage natural bone healing processes by providing support during critical stages of bone regeneration.
3. Elimination of Stress Shielding: Traditional permanent metal implants can cause stress shielding, where the implant bears too much load, potentially leading to bone atrophy around the implant. Biodegradable implants avoid this issue as they degrade, allowing the bone to gradually bear more load[31].
4. Customization: Biodegradable implants can be designed and shaped to fit the unique contours of a patient's bone, enhancing their effectiveness[33].
5. Environmentally Friendly: Biodegradable implants reduce the long-term presence of foreign materials in the body and minimize the environmental impact associated with permanent implants[32].

Considerations:

While the concept of biodegradable implants is promising, challenges remain, such as finding the right combination of materials that balance strength, degradation rate, and biocompatibility. Additionally, the effectiveness of these implants in different fracture types and patient populations needs further research.

Drug loading in biodegradable implants:

It is a sophisticated treatment approach where biodegradable implants are designed to release specific drugs at the site of a bone fracture. This method combines the benefits of implant stability with controlled drug delivery, aiming to enhance the bone healing process and improve patient outcomes.

In the context of bone fracture treatment, the biodegradable implant is engineered to carry and release therapeutic drugs directly to the fracture site. The process of incorporating drugs into the implant is known as "drug loading." The drugs can include growth factors, pain relievers, anti-inflammatory agents, antimicrobial substances, or any other therapeutic compounds that can aid in the healing process[34].

Controlled Drug Delivery:

The goal of drug loading is to achieve controlled drug delivery, where the implanted device releases the drugs in a controlled and sustained manner over a specific period. This targeted drug release ensures that the therapeutic agents are delivered directly to the fracture site, optimizing their effectiveness while minimizing potential side effects on the rest of the body.

Enhanced Bone Healing:

By releasing specific drugs at the fracture site, the biodegradable implant can enhance the bone healing process by usinggrowth factors or drugs that promote osteogenesis (bone formation) can accelerate the regeneration of bone tissue, helping the fracture to heal faster.Anti-inflammatory drugs can help control inflammation at the fracture site, which can aid in reducing pain and promoting proper healing.

Antimicrobial agents can prevent or treat infections that might occur at the fracture site, minimizing the risk of complications. Pain-relieving drugs can provide localized pain relief, enhancing patient comfort during the healing process.

Patient-Specific Approach:

The drugs and their release profiles can be tailored to the specific needs of each patient and the type of fracture. This personalized approach allows healthcare professionals to optimize treatment outcomes based on individual circumstances.

CONCLUSION:

This comprehensive review sheds light on the potential paradigm shift brought about by biodegradable implants loaded with drugs in bone fracture treatment. In the world of fixing broken bones, combining dissolvable implants with special drugs is like a new superhero team-up. These implants give temporary support and then vanish, while the drugs they release work directly where the bone is hurt. This smart teamwork speeds up healing, reduces pain, and makes sure the treatment matches each patient's needs. Though this idea is super cool, it's not without challenges. Picking the right drugs, figuring out how much to release, and making sure everything works together isn't easy. But scientists are constantly improving this idea by using better materials and smarter technology.

In the end, the combination of dissolvable implants and drug delivery is like a new way to heal bones, making recovery quicker and better. It's a bit like a team of superheroes working together to make sure bones mend well and people feel better faster.

REFERENCES:

1. Shuai Wei, Jian-Xiong Ma, Lai Xu, Xiao-Song, Xin-Long Ma. "Biodegradable materials for bone defect repair." Military Medical Research, 7:54, Article number: 54 (2020).
2. Jiazhen Zhang, Zhizhong Shang, Yanbiao Jiang, Kui Zhang, Xinggang Li, Minglong Ma, Yongjun Li, Bin Ma. "Biodegradable metals for bone fracture repair in animal models: a systematic review." Regenerative Biomaterials, Volume 8, Issue 1, February 2021.
3. Per Aspenberg. "Drugs and fracture repair." Acta Orthopaedica, 76 (6), 741–748, 2005.
4. N.L. Fazzalari k. "Bone fracture and bone fracture repair." Osteoporosis International, 22, 2003–2006 (2011), 27 April 2011.
5. Einhorn TA. "The cell and molecular biology of fracture healing." Clinical Orthopaedics and Related Research, 335, S7–S21, October 1998.
6. Charles Sfeir, Lawrence Ho, Bruce A. Doll, Kodi Azari, Jeffrey O. Hollinger. "Fracture Repair, Bone Fracture, and Repair." In: Bone Fracture and Repair, pp. 21–44.
7. Courtney E. Baker, Stephanie N. Moore-Lotridge, Alexander A. Hysong, Samuel L. Posey, J. Patton Robinette, Deke M. Blum, Michael A. Benvenuti, Heather A. Cole, Satoru Egawa, Atushi Okawa, Mansanori Saito, Jason R. McCarthy, Jeffry S. Nyman, Masato Yuasa, Jonathan G. Schoenecker. "Bone Fracture Acute Phase Response—A Unifying Theory of Fracture Repair: Clinical and Scientific Implications." 16, pages 142–158, 2018.
8. Matthew J. Olszta, Xingguo Cheng, Sang Soo Jee, Rajendra Kumar, Yi-Yeoun Kim, Michael J. Kaufman, Elliot P. Douglas, Laurie B. Gower. "Bone structure and formation: A new perspective." Materials Science and Engineering: R: Reports, Volume 58, Issues 3–5, 28 November 2007, Pages 77-116.
9. Andreassen T T, Oxlund H. "Local anabolic effects of growth hormone on intact bone and healing fractures in rats." Calcified Tissue International, 73 (3), 258-264, 2003.
10. Muminagic, Sahib N. "History of Bone Fracture: Treatment and Immobilization." Materia Socio-Medica, Vol. 23, Iss. 2, (2011): 111.
11. A. Graham Apley, Pyrford, England. "Fractures of the lateral tibial condyle treated by skeletal traction and early mobilisation." Vol. 38 b, no. 3, August 1956.
12. Doty SB, Schofield BH. "Enzyme histochemistry of bone and cartilage cells." Prog in Histochem and Cytochem 8:1–38, 1976.
13. N.H. Hart, S. Nimphius, T. Rantalainen, A. Ireland, A. Siafarikas, R.U. Newton. "Mechanical basis of bone strength: influence of bone material, bone structure and muscle action." J Musculoskelet Neuronal Interact. 17 (3): 114–139, 2017.
14. Milte R, Crotty M. "Musculoskeletal health, frailty and functional decline." Best Pract Res Clin Rheumatol, 28 (3): 395–410, 2014.
15. Steve Weiner a 1, Wolfie Traub a, H.Daniel Wagner. "Lamellar Bone: Structure–Function Relations." Journal of Structural Biology, Volume 126, Issue 3, 30 June 1999, Pages 241-255.
16. H.D. Wagner, S. Weiner. "On the relationship between the microstructure of bone and its mechanical stiffness." J. Biomech., 25(12): 1311-1318, 1992.
17. Piermattie D, Flo G, Decamp C. "Handbook of small animal orthopedics and fracture repair." St. Louis: Saunders, 2006.
18. Amin Bigham-Sadegh, Ahmad Oryan. "Basic concepts regarding fracture healing and the current options and future directions in managing bone fractures." International Wound Journal, Volume 12, Issue 3, p. 238-247.
19. Tamara S. Ritsema, Gabor D. Kelen, Peter J. Pronovost, Julius Cuong Pham. "The National Trend in Quality of Emergency Department Pain Management for Long Bone Fractures." Academic Emergency Medicine, Volume 14, Issue 2, p. 163-169.
20. Britt Wildemann, Anita Ignatius, Frankie Leung, Lisa A. Taitsman, R. Malcolm Smith, Rodrigo Pesántez, Martin J. Stoddart, R. Geoff Richards, Jesse B. Jupiter. "Non-union bone fractures." Nature Reviews Disease Primers, volume 7, Article number: 57, 2021.
21. Young P. "A short history of the Chartered Society of Physiotherapy." Physiotherapy. 55(7): 271-278, 1969.

22. B.C. Wexler. "Pathophysiologic responses of spontaneously hypertensive rats to arterial magnesium–aluminum wire implants." Atherosclerosis, 35 (2), 257-261, 1980.
23. M.C. Meikle, Stelios Papaioannou, Trevor J. Ratledge, Paul M. Speight, Steven R. Watt-Smith, Peter A. Hill, John J. Reynolds. "Effect of poly dl-lactide-co-glycolide implants and xenogeneic bone matrix-derived growth factors on calvarial bone repair in the rabbit." Biomaterials, 15(7): 538-546, 1994.
24. D.K. Gilding, D.K Gliding. "Biodegradable polymers for use in surgery — polyglycolic/poly (lactic acid) homo — and copolymers1." Polymer, 20 (12), 1459-1464, 1979.
25. G. Dominique. "Biomechanics and Biomaterials in Orthopedics." Springer, Heidelberg, 2004, pp. 22-23.
26. Y.C. Xin, K.F. Huo, H. Tao, G.Y. Tang, P.K. Chu. "Acta Biomater." 4 (6): 2008-2015, 2008.
27. Wang J, Wang L, Zhou Z, Lai H, Xu P, Liao L, et al. "Biodegradable polymer membranes applied in guided bone/tissue regeneration: a review." Polymers (Basel), 8(4): 115, 2016.
28. Di Martino A, Sittinger M, Risbud MV. "Chitosan: a versatile biopolymer for orthopaedic tissue-engineering." Biomaterials, 26(30): 5983–90, 2005.
29. Kafri A, Ovadia S, Goldman J, Drelich J, Aghion E. "The Suitability of Zn–1.3%Fe Alloy as a Biodegradable Implant Material." Metals, 8: 153, 2018.
30. Asgari M, Hang R, Wang C, Yu Z, Li Z, Xiao Y. "Biodegradable Metallic Wires in Dental and Orthopedic Applications: A Review." Metals, 8: 212, 2018.
31. M.M. Avedesian, H. Baker. "Magnesium and Magnesium Alloys." ASM International, Materials Park, OH, 1999.
32. S. Housh, B. Mikucki, A. Stevenson. "Properties of Magnesium Alloys Properties and Selection: Nonferrous Alloys and Special-Purpose Materials." ASM Handbook, 2, pp. 1424-1432, 1992.
33. N.T. Kirkland, I. Kolbeinsson, T. Woodfield, G.J. Dias, M.P. Staiger. "Mater. Lett." 64, pp. 2572-2574, 2010.
34. E. Meng, T. Hoang. "Micro- and nano-fabricated implantable drug-delivery systems." Therapeutic Delivery, 3: 1457-1467, 2012.