EURASIAN EXPERIMENT JOURNAL OF PUBLIC HEALTH (EEJPH)

ISSN: 2992-4081 ©EEJPH Publications

Volume 7 Issue 2 2025

Engineering Approaches to Enhance Bone Healing

Tugonza Akiro F.

Faculty of Science and Technology Kampala International University Uganda

ABSTRACT

Bone healing is a complex biological process influenced by mechanical, cellular, and molecular factors. Despite the human skeleton's inherent regenerative ability, certain fractures or pathological conditions lead to impaired healing or non-union. Engineering approaches, including biomaterials, tissue engineering, and advanced 3D printing technologies, offer innovative solutions to enhance bone repair. This review examines the phases of bone healing, clinical challenges, and the integration of engineering strategies such as personalized medicine, bioactive scaffolds, and exosome therapies. The synergy of biological insights and engineering innovations holds the potential to revolutionize bone healing, addressing limitations in traditional treatment paradigms and enabling customized therapeutic solutions.

Keywords: Bone healing, tissue engineering, biomaterials, 3D printing, bioactive scaffolds.

INTRODUCTION

The human skeleton may be the best example of biological engineering as a result of its ideal structure and mechanical advantages. A pertinent subject in bone health is the recovery of lost bone functions, which may occur as a result of an accident or disease. In the realm of bone recovery, there are numerous difficulties in terms of the full return or equivalence of bone to its original state since its immune and neural systems have been compromised. Engineering may have a significant impact on bone healing. Using various techniques, the bone healing procedure might be advanced. Additionally, advancements in prototyping, such as 3D printing, may enable one to create new prostheses that can address specific loss-bearing needs in the immediate future. This paper concentrates on such cutting-edge engineering issues and presents an overview of the approaches that can make a difference in improving the healing process. In the field of medicine, there are a variety of clinical techniques available for the recovery of fractured bones. There are three distinct stages in the healing process: the inflammatory response, the main healing stage, and the bone mineral deposition phase. Clinical strategies have been developed to help the healing process, including fracture stability, functional assistance, blood supply, and mechanotransduction. Bone defects or nonunion can be difficult to heal in traumatic injuries. As a result, both fundamental and innovative ways to augment broken bones using engineering have taken shape. Bone and their healing procedures are the subjects of our attention since they are particularly challenging to heal. We have explained the prerequisites for bone integration. The condition of the microenvironment of a bone prosthesis is examined, as well as alternative therapies for promoting implant integration in radiation-treated bone, which can aid in revealing the knowledge that underscores the implant's data [1, 2].

Bone Healing Process

The healthy bone microenvironment is in constant remodeling and is thus primed for recovery from injury or fracture. In clinical care, fractures can be prompted to heal by applying mechanical stabilization of one sort or another. Understanding healing triggers and pathways has been increasing over the past decades, but fractures frequently need extended mechanical stabilization time. This opting for safe margins in treatment planning attests at least to the complexity of bone healing and likely also reflects the suboptimal use of insights gained so far. Although some patients do end up in non-union, the majority of patients do experience bone union, even with extended stabilization times. Thus, natural healing does work. The challenge is to understand how it works and accelerates the process. Within healing bone, distinct phases of inflammation, callus cartilage formation, bone formation, and remodeling can be distinguished. Different cells are active in different healing stages. At sites of primary bone healing, osteoclasts appear to be more involved in later stages of remodeling than in fracture line cartilage or hematoma, where hematoma biology inserts an additional level of complexity into natural healing. On longer time scales, bone union is achieved through gradual chondrocyte-to-osteoblast transdifferentiation, in concert with gradual endochondral ossification. This aspect may perhaps be considered more akin to developmental biology than to tissue regenerative biology as such. The mechanical environment during healing also influences cellular activities. For instance, it is known that global as well as local low-intensity pulsed ultrasound can accelerate some, but not all, stages of fracture healing. In conclusion, a complex interaction between mechanical and biological factors influences bone healing. The next sections will explore how this interplay between biology and mechanics is affected and what role an engineering approach can provide to help guide and support healing [3, 4].

Phases of Bone Healing

The healing of a bone fracture is divided into a sequence of processes that occur in a temporary order. During the first days following fracture formation, a hematoma is formed at the fracture site. The concomitant inflammatory immune response initiates the first phase, resulting in the invasion of non-bone cells. The hematoma undergoes gradual resorption and the callus formation phase starts. In this second phase, a meshwork of fibrous collagen and cartilaginous tissue is formed that loosely connects the bone fragments. The early soft callus is mainly composed of mesenchymal stem cells and chondrocytes, excreting collagen types I, II, IV, and X, and matrix glycoproteins. Starting in this early phase and continuing into the following hard callus phase, the process of resorption of bone fragments is conducted by the osteoclasts, directed by a progenitor module. Penetration of vasculature and nutrient supply from the callus to the bone shaft begins, which is crucial to provide the semi-differentiated cells in the fracture callus with oxygen and nutrients. The splint function and weight-bearing abilities of the fractured limb are gradually regained. The callus hardening due to the deposition of bone material is performed by a mineralization and remodeling module. The remodeling process demands approximately 40% of the healing period but can be extended when healing is impaired. This is initiated by the shifting of osteoblast-dominating regions to osteoclast-dominating regions, or a novel whole bone remodeling process is initiated from the bone centers and periosteal loci and is coupled to biological regeneration of bone, osteoblasts, and perfused vasculature with limited diffusive supply to the cells. The first option kinetically heals the fracture in a shorter time but may achieve mechanical stability below the physiological strength. The domineering cells of bone repair are osteoblasts and osteoclasts and their precursor cells. Osteoblasts originate from stromal bone marrow cells. In response to the fracture event, these will produce a blood clot providing a hematoma above the fracture as well as bone proteins to attract mesenchymal stem cells to the fracture site. The migration and differentiation of non-local progenitor cells in this fracture callus are of paramount importance to bridge the fracture gap. These parent cells may differentiate into osteoblasts and osteoclasts at bone surfaces. Blood supply to the fracture site is essential both for the anti-infection response and to provide nutrients to fuel resorption and new bone formation. Fractures with compromised blood delivery tend to have an impaired healing process. Kinetically, fracture healing is highly dependent on the blood supply. This is mainly due to the invasion of cells and diffusion of nutrients. Technology or methodologies to improve blood supply to the bone regeneration site can therefore be focused on the first phase and second phase [5, 6].

Challenges in Bone Healing

Whilst the bone-healing process is a highly orchestrated synergy of cellular responses, angiogenesis, and anti-inflammatory activity, there are a variety of challenges that may hinder the successful and efficient healing of bone defects and fractures. These difficulties can be further exacerbated in certain groups of patients, such as children and elderly patients, due to a reduction in mesenchymal stem cell number and differentiation potential, or those affected by congenital conditions and major traumatic injury. Similarly, certain types of fractures or associated health conditions, such as osteoarthritis, osteoporosis, and diabetes, are also known for their inhibitory effects on bone healing and regeneration. It is estimated that 5–20% of all fractures result in bone healing complications, involving delayed union or non-union of bone, which presents clinically as pain, instability, and decreased functional performance, subsequently delaying rehabilitation and return to work. The presence of hypertrophic non-unions, a rare form of non-union with increased cellularity and vascularity, has been associated with increased rates of recurrence and often requires prolonged surgical intervention to promote the regeneration of healthy bone [7, 8]. Bone is unique in its ability to regenerate itself with concomitant acquisition of mechanical competency, and yet, there remain patient groups and types of bone pathology where bone healing or regeneration is inefficient and hampered by several known, but poorly understood, risk factors. These challenges in themselves may necessitate either a single or combination of surgical and pharmacological interventions to ensure successful healing of bone. In this review, we critically discuss the various surgical and pharmacological strategies currently employed in clinical practice and give an overview of a more regenerative approach to enhance bone healing with a concurrent introduction to novel technologies that are still in the developmental stages [9, 10].

Non-Union and Delayed Union

Non-union is a major complication in the clinical management of fracture healing and can be defined as a fracture that has not shown clinical and radiological healing for a minimum of 6 months since the fracture occurred. Two types can be distinguished: hypertrophic non-union is characterized by a persistent callus—bone formed as a result of fracture repair, which is larger than the initial diameter of the bone. Atrophic non-union develops when the callus is not formed. Delayed union means a prolonged fracture repair, but eventually, it becomes non-union. Overall, non-union should be seen as a fracture repair system failure and not as a delayed time to healing by secondary intention, as occurs in some bone pathologies [11, 12]. The occurrence of non-union is considerably high in elderly patients due to osteoporosis, in severe acute injuries such as open fractures, and in severe traumas compromising the vascular supply of the bone. Risk factors that negatively influence the path to complete bone repair and finally lead to non-union include insufficient blood supply, mechanical instability of the fracture site, hormonal dysregulation of cells, nutritional status of patients, age, and drugs. Control of fracture stability is usually achieved by surgical stabilization of the bone with orthopedic hardware. Therapeutically, several methods have been developed to foster primary bone healing or lead to a successful clinical outcome. Biological methods using autografts, allografts, and a variety of bone graft substitutes, combined with cells and growth factors, are mainly focused on stimulating the host's bone repair capacity. Mechanical aids, such as plates and intramedullary nailing, help in achieving bone repair by providing optimal manipulation of the local mechanical environment to induce the 'sufficient' [13, 14].

Current Clinical Strategies

In current clinical practice, a spectrum of strategies is used to manage bone healing complications. There are both surgical and non-surgical methods. Timely interventions in broken bones could prevent an unsatisfactory outcome of fractures where healing does not meet clinical expectations, causing malunion, delayed union, and non-union. Several surgical interventions have emerged, with the Standard of Care being intramedullary nails and plates and screws that are the most widely used. In addition to these interventions, there is an emerging use of physical therapies, including extracorporeal shock wave therapy, low-intensity pulsed ultrasound, pulsed electromagnetic field, and medications such as anti-resorptive and bone anabolic drugs, among others [15, 16]. Despite these strategies currently available, there are limitations and drawbacks to these technologies, to which an engineering approach could potentially provide solutions. Bone grafts to date remain the Standard of Care where a bone defect cannot regenerate. There is a large clinical unmet need in the size of non-reconstructable bone defects where viable bone graft cannot be harvested from another site on the patient. In parallel, bone healing medications, while providing the biological signals promoting the healing cascade, have their limitations. The onus to affect the balance between safety and efficacy is often hard to achieve. Juxtaposed with bone grafts, the clinical unmet challenge here is the possibility of systemic effects beyond the targeting of the healing site in bone. These considerations show an inherent need for engineering to play a key role in the clinical management of broken bones. Engineering approaches involving bone healing solutions include the use of inorganic bone grafts, metal-based bone therapies, local drug delivery systems, and natural and synthetic bioactive scaffolds. Engineering technologies that rely on endogenous stem cell-based repair include cell-based therapies using polymers and ceramics, intelligent synthetic growth factors, extracellular matrix-based regenerative approaches in bone, exogenous stem cell-based therapies, and gene therapy [17, 18].

Bone Grafts

The current gold standard for enhancing bone healing is by using bone grafts. The clinical strategy originates from the additive effects of structural support provided by bone grafts and enhanced cellular activity due to the abundant repository of osteogenic, chondrogenic, and angiogenic factors extravasated from each bone component. A broad desideratum for bone grafts is paired with an ongoing pursuit of suitable bone graft substitutes. Bone grafts are currently classified into autografts, allografts, xenografts, and synthetic materials. Autografts are harvested from the patient's own body, possess all essential factors to promote bone growth, and induce the fewest adverse effects, but necessitate a second surgery, resulting in potential donor site morbidity. Allografts are obtained from the same species but different individuals, are more easily available, and do not require additional surgery, but carry the potential for immune rejection, disease transmission, and ethical issues. Xenografts are procured from another species and are osteoconductive, but have been documented to be less effective in the long-term treatment of bone defects. Different synthetic materials have been engineered to provide structural support, create bone-conductive surfaces, or act as carriers for osteogenic factors, some of which have made a successful crossing from bench to bedside. Grafts containing mesenchymal stem cells are also formulated, along with the engineering of the surface to achieve controlled drug or growth factor release, either directly off the implant or via carrier materials. This review aims to provide insight into a variety of currently available materials for cell differentiation, osseointegration, and only a portion of bioresorbable metal and other natural polymer-based materials and their potential to promote bone growth. Research and development of bone graft substitutes are an open field and growing at a fast pace. It behooves us to read the literature constantly to acquire the latest developments and advancements in the field [19, 20].

Engineering Approaches

Multiple engineering strategies can be explored to develop effective approaches that could enhance bone healing. Engineering aims to integrate technologies with the knowledge of biological processes to provide novel solutions to serious clinical health problems. Considering the biomechanical properties that play a crucial role in bone healing, the fabrication of bone constructs with matching mechanical properties has become an active field of research. Hence, researchers believe that several formidable concepts and techniques such as tissue engineering-based techniques, scaffold designing, stem cell-based therapies, exosome therapy, platelet-rich plasma therapy, and the latest 3D-printed techniques could lift the tempo of bone healing efficacy. For example, 3D patterning of engineered bone substitutes could lead to the formation of tissues with different mechanical properties compared to those of whole bone organization; therefore, ultimately better than its previous histological phases. One of the latest engineering theories is "personalized" approaches to bone healing. Personalized nurses always take into account the individual patient condition, prognostic, diagnostic, and treatment-referring parameters, which would answer more robustly the ongoing research efforts. All of these developments and actions ultimately lead to a more rapid resolution of clinical limitations encountered in current basic and clinical practice. Additionally, in the future, successful progress in bone repair may be expected to originate from synergies between the pioneering disciplines such as biomaterials, tissue engineering, and cell biology that have laid the foundation for these innovative treatment approaches. This might include, beyond refurbishing the biophysical interface for cell biology, the invocation of developments in fields like bio-inspired adaptive biomaterials, 3D printing, and gene editing, as well as a consideration of system-wide network-directed controls that ultimately unleash organ- or even body-wide participation of natural processes. To answer these questions, a more integrative approach that is free of discipline-based limitations and instead emphasizes the cross-linking of science may be able to contribute to achieving some of the expectations, as discussed in detail below. This review reflects on the current research trends in the engineering-based approaches towards bone healing, the new theories that are progressing successfully, and the limitations and areas of improvement within the bone treatment paradigms. Although valuable contributions have been shown by different research groups, additional research in different directions will be required in the future. This area should be continuously revisited, and more effort in resolving the limitations in the physical manifestations of the clinical system should be focused. The further focus on personalized, predominantly techno-medicinal efforts should lead to planned longitudinal evaluation of mechanisms of bone repair, whether drilling, nailing, or non-invasively affected patients after minor bone damage [21, 22].

Biomaterials for Bone Regeneration

In this paper, we particularly focus on the strategies based on the use of bioactive materials for the modulation of the environment around the injury site and to improve the osteointegration of implants. In the role of bioactive ceramic materials for bone applications, we provide a brief history of their use and their working principles as well as their main advantages. We also present an overview of the most common bioactive ceramics, silicate glass-ceramics as advanced materials to guide soft tissue repair in bone, as well as their combination with natural or synthetic polymers to form bioactive and degradable composites useful for bone tissue engineering. The translation of the most interesting solutions to selected clinical cases is finally described [23, 24]. New developments in this field also include the study of the mechanical behavior of biomaterials and their capacity to guide cell fate, thus controlling bone tissue formation while substituting or repairing bone defects. Sections are devoted to the novel applications of these materials as bioactive coatings for prosthetic implants and as delivery systems for drugs and growth factors, respectively. Histologically, these materials have been described to interact with the surrounding tissues once implanted in the body thanks to the formation of bone-like hydroxyapatite on their surface, often not defective for the very limited content of carbonate ions. Clinical data, based on radiographic analysis, showed a minimum of three years of follow-up, with no differences in bone resorption mechanisms observed between samples [25, 26].

CONCLUSION

Engineering approaches have ushered in a new era in bone healing, addressing gaps in traditional clinical strategies. By leveraging advancements in biomaterials, 3D printing, and regenerative medicine, researchers and clinicians can design targeted solutions for complex fractures and non-union cases. Personalized therapies tailored to the patient's unique biological and mechanical environment further promise enhanced outcomes. Future interdisciplinary efforts should focus on overcoming existing challenges, optimizing integration across biological and engineering domains, and accelerating the translation of emerging technologies into clinical practice. These advancements have the potential to significantly improve patient outcomes, restoring function and quality of life for those affected by challenging bone injuries.

REFERENCES

1. Du M, Chen J, Liu K, Xing H, Song C. Recent advances in biomedical engineering of nano-hydroxyapatite including dentistry, cancer treatment and bone repair. Composites Part B: Engineering. 2021 Jun 15;215:108790.
2. Zhu G, Zhang T, Chen M, Yao K, Huang X, Zhang B, Li Y, Liu J, Wang Y, Zhao Z. Bone physiological microenvironment and healing mechanism: Basis for future bone-tissue engineering scaffolds. Bioactive materials. 2021 Nov 1;6(11):4110-40. sciencedirect.com
3. Hu Y, Huang J, Chen C, Wang Y, Hao Z, Chen T, Wang J, Li J. Strategies of macrophages to maintain bone homeostasis and promote bone repair: a narrative review. Journal of Functional Biomaterials. 2022 Dec 29;14(1):18. mdpi.com
4. Li M, Chu X, Wang D, Jian L, Liu L, Yao M, Zhang D, Zheng Y, Liu X, Zhang Y, Peng F. Tuning the surface potential to reprogram immune microenvironment for bone regeneration. Biomaterials. 2022 Mar 1;282:121408.
5. 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. nih.gov
6. Duda GN, Geissler S, Checa S, Tsitsilonis S, Petersen A, Schmidt-Bleek K. The decisive early phase of bone regeneration. Nature Reviews Rheumatology. 2023 Feb;19(2):78-95. [HTML]
7. Kim T, See CW, Li X, Zhu D. Orthopedic implants and devices for bone fractures and defects: Past, present and perspective. Engineered Regeneration. 2020 Jan 1;1:6-18.
8. Palanisamy P, Alam M, Li S, Chow SK, Zheng YP. Low-intensity pulsed ultrasound stimulation for bone fractures healing: a review. Journal of Ultrasound in Medicine. 2022 Mar;41(3):547-63. wiley.com
9. Inchingolo F, Hazballa D, Inchingolo AD, Malcangi G, Marinelli G, Mancini A, Maggiore ME, Bordea IR, Scarano A, Farronato M, Tartaglia GM. Innovative concepts and recent breakthrough for engineered graft and constructs for bone regeneration: a literature systematic review. Materials. 2022 Jan 31;15(3):1120. mdpi.com
10. Tang G, Liu Z, Liu Y, Yu J, Wang X, Tan Z, Ye X. Recent trends in the development of bone regenerative biomaterials. Frontiers in Cell and Developmental biology. 2021 May 7;9:665813. frontiersin.org
11. Orji C, Ojo C, Onobun DE, Igbokwe K, Khaliq F, Ononye R. Fracture Non-Union in Osteoporotic Bones: Current Practice and Future Directions. Cureus. 2024 Sep 20;16(9):e69778. nih.gov

12. Phillips MR, Harrison A, Mehta S, Nolte PA, Bhandari M, Zura R. A scoping review of operative and non-invasive management in the treatment of non-unions. Injury. 2022 Dec 1;53(12):3872-8. [HTML]
13. Quan K, Xu Q, Zhu M, Liu X, Dai M. Analysis of risk factors for non-union after surgery for limb fractures: A case-control study of 669 subjects. Frontiers in Surgery. 2021 Dec 14;8:754150.
14. Gharu E, John B. Nonunion of Fractures: A Review of Epidemiology, Diagnosis, and Clinical Features in Recent Literature. Indian Journal of Orthopaedics. 2024 Sep 18:1-6.
15. Bhatti UF, Shah AA, Williams AM, Biesterveld BE, Okafor C, Ilahi ON, Alam HB. Delay in hip fracture repair in the elderly: a missed opportunity towards achieving better outcomes. Journal of Surgical Research. 2021 Oct 1;266:142-7. [HTML]
16. Nicolaides M, Vris A, Heidari N, Bates P, Pafitanis G. The effect of delayed surgical debridement in the management of open tibial fractures: a systematic review and meta-analysis. Diagnostics. 2021 Jun 2;11(6):1017.
17. Laubach M, Hildebrand F, Suresh S, Wagels M, Kobbe P, Gilbert F, Kneser U, Holzapfel BM, Hutmacher DW. The concept of scaffold-guided bone regeneration for the treatment of long bone defects: current clinical application and future perspective. Journal of Functional Biomaterials. 2023 Jun 27;14(7):341. mdpi.com
18. Lu J, Wang Z, Zhang H, Xu W, Zhang C, Yang Y, Zheng X, Xu J. Bone graft materials for alveolar bone defects in orthodontic tooth movement. Tissue Engineering Part B: Reviews. 2022 Feb 1;28(1):35-51. [HTML]
19. Sanz-Sánchez I, Sanz-Martín I, Ortiz-Vigón A, Molina A, Sanz M. Complications in bone-grafting procedures: classification and management. Periodontology 2000. 2022 Feb;88(1):86-102. ortizvigon.com
20. Rodham PL, Giannoudis VP, Kanakaris NK, Giannoudis PV. Biological aspects to enhance fracture healing. EFORT Open Reviews. 2023 May 1;8(5):264-82. bioscientifica.com
21. Niu Y, Wang Z, Shi Y, Dong L, Wang C. Modulating macrophage activities to promote endogenous bone regeneration: Biological mechanisms and engineering approaches. Bioactive materials. 2021 Jan 1;6(1):244-61.
22. Battafarano G, Rossi M, De Martino V, Marampon F, Borro L, Secinaro A, Del Fattore A. Strategies for bone regeneration: from graft to tissue engineering. International journal of molecular sciences. 2021 Jan 23;22(3):1128. mdpi.com
23. Asa'ad F, Pelanyte G, Philip J, Dahlin C, Larsson L. The role of epigenetic functionalization of implants and biomaterials in osseointegration and bone regeneration—A review. Molecules. 2020 Dec 12;25(24):5879.
24. Walter N, Stich T, Docheva D, Alt V, Rupp M. Evolution of implants and advancements for osseointegration: A narrative review. Injury. 2022 Nov 1;53:S69-73.
25. Li X, Lu L, Li J, Zhang X, Gao H. Mechanical properties and deformation mechanisms of gradient nanostructured metals and alloys. Nature Reviews Materials. 2020 Sep;5(9):706-23.
26. Johari N, Moroni L, Samadikuchaksaraei A. Tuning the conformation and mechanical properties of silk fibroin hydrogels. European Polymer Journal. 2020 Jul 5;134:109842.

CITE AS: Tugonza Akiro F. (2024). Engineering Approaches to Enhance Bone Healing. EURASIAN EXPERIMENT JOURNAL OF PUBLIC HEALTH, 7(2):55-60.