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*Article*

# The Annals of Biomedical Engineering on Critical Size Bone Defect: A Review

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*Abstract*— **Bone can heal on its own through the process known as bone remodelling. Nonetheless, a critical size bone defect will hinder the natural bone-healing process and may not allow for complete fracture healing. These requires surgical intervention by employing the use of bone tissue implants and in need of realignment and fixation for proper fracture healing. Traditional knowledge of bone injury and fracture healing must be comprehended thoroughly for a proper invention of bioengineered material or devices that could enhance the physiological process. Heretofore, engineered materials used to address critical size bone defects have encountered various challenges and improvement be it in bone grafting or choices of mechanical stabilization devices. To date, researchers have been mainly focussing on the alternative material for bone graft substitute albeit the selection of fixators to establish mechanical stabilization are as important. This review highlighted the challenges, improvement and advancement in mechanical stabilization devices and bone graft substitute with respect to the physiological process of bone fracture healing. Identifying these challenges would help assist the researcher in an expedition toward the recovery and restoration of critical size bone defects.**

*Keywords*— **critical size bone defect, bone remodelling, tissue engineering, bone graft**

## I. INTRODUCTION

The bone is a crucial rigid human organ that has an orderly and complex structure to supports its diverse mechanical, biological and chemical functions. A highly documented rates of bone vulnerability to trauma and fractures have attracted extensive researches in the fields of bone fracture healing. The interruption to the normal structure of bone could bring about significant morbidity as well as an economic burden on the healthcare system (1). Bone defects especially involving a critical sized deformity has been a great unresolved challenge in the healthcare practice (2). The correction of critical sized bone defects called for substantial surgical intervention. Current strategies for treatment of critical size bone defects include bone grafting and stabilization using internal metal plates. These strategies involve a slow healing with high infection risk and elicit considerable pain. In addition, the intervention sometimes does not provide an assurance of complete rectification of the defect. Therefore, a search for better alternatives continues to present a major challenge.

The application of biomedical engineering applies the interdisciplinary aspect of engineering and medical sciences contributed to the rapid advancement in providing a solution for bone fracture healing particularly in critical size bone defects (3). In the past few decades, there were various breakthroughs in biomedical engineering to facilitate the process of critical sized bone fracture healing from a conventional autologous bone grafting to a more radical approaches using allograft and synthetic bone graft substitute (4,5). Moreover, the materials used for stabilization to fix the bone graft implants also have undergone various advancement. Throughout the years, mechanical fixators for bone stabilization advanced from conventional metal plate to comprehensive biodegradable internal fixators. Although not all of these materials can be employed in all types of bones, it served as a potential area to be explored. Meanwhile, there are various bone graft substitute diversified from natural polymer, biomaterials, to recent 3D bio printed bone graft. As innumerable theory and mechanism of bone healing have been discerned by researcher. Hence, the evolution in biomedical engineering especially the application of bone tissue engineering has been progressively aimed at facilitating faster healing and restoring the function of bone and quality of life. Therefore, this paper aim at reviewing and pinpoint the annals of biomedical engineering

highlighting the challenges, improvement and advancement in mechanical stabilisation devices and bone graft substitutes.

## II. Bone Fracture

A fracture happens when a structural continuity of the bone is interrupted (6,7). The fracture is termed as a simple or closed fracture when overlying skin remains intact whereas open fracture ensues following a skin breach. Open fracture in most cases is vulnerable to contamination and infection hence prompt management is vital. The brittle property of bone causes the bone to be more prone to fracture. This could be due to various reason such as injury, repetitive stress and pathological fractures that occur as a result of an abnormal weakening by diverse processes (7).

### *A. Mechanism of bone fracture healing*

The complexity and well-regulated bone healing process are related to sequential events involving various cell and signalling molecules (8). However, events such as non-unions, malunion or delayed fracture healing could happen during the healing process even though the bone tissue possessed a powerful regenerative capability (9).

The mechanism of bone fracture healing can take place in two manners either by primary healing or secondary healing (10)(11). Primary healing is a process whereby there is a direct attempt by the bone to re-establish itself after an injury that mimics the process of normal bone remodelling. Meanwhile, secondary healing process prior to bone fractures involves responses in the periosteum and external soft tissues with the subsequent formation of a callus. The formation of a fracture callus differentiates the pattern of bone healing. Secondary healing involves a combination of intramembranous and endochondral ossification in which these two processes participate in the fracture repair sequence. The secondary healing process have three distinguished overlapping phases as shown in Figure 1 including inflammatory, reparative, and remodelling stages (11)(12).

#### *1) Inflammatory stage*

As shown in Figure 1, following a fracture, an inflammatory response is initiated whereby a hematoma assembles at the fracture site. This inflammatory process reaches its peak at the first 24 h of injury and remains there for one week. Vascular events most often govern the process in this stage. Neutrophils are the first recognized inflammatory cells within 24 h of fracture which attain to the hematoma. The platelets then released chemotactic factors within the hematoma built-up. A cascade of signals emerged from the necrotic tissue by releasing complementary factors, proinflammatory cytokines and stimulating integrin expression on fibrin to attract inflammatory cells to the fracture site (13).

The neutrophils then attract the secondary inflammatory cells such as monocytes or macrophages to the fracture site through secretion of inflammatory and chemokines such as interleukin-6 (IL-6) and C-C motif chemokine ligand 2 (CCL2) (1). The level of inflammatory factors includes tumour necrosis factor-a (TNF-a), interleukin-1 (IL-1), IL-6, interleukin (IL-11), and interleukin (IL-18) increased significantly in the first three days. These inflammatory molecules also attract polymorphonuclear leukocytes, lymphocytes, blood monocytes, and macrophage soon after the release of cytokines to the fracture site.

These cells then trigger the angiogenesis process and enhance the extracellular matrix synthesis (11)(1). Therefore, the formation of hematoma is deemed to be an elementary event for a proper outcome of fracture healing.

#### *2) Reparative stage*

Bone reabsorption occurs at the point of 1 to 2 mm of fracture margins with the coexisting loss of blood supply. It is this bone reabsorption that makes fracture lines radiographically distinct 5 to 10 days after an injury. Concurrently, the reparative stage begins with revascularization process resulting from normal disruption bone architecture (13). The angiogenesis process occurs externally across the fracture site (12). The activation of the platelets initiate the secretion of platelet-derived growth factors (PDGFs) and transforming growth factor-β1 (TGF-β1) (1).

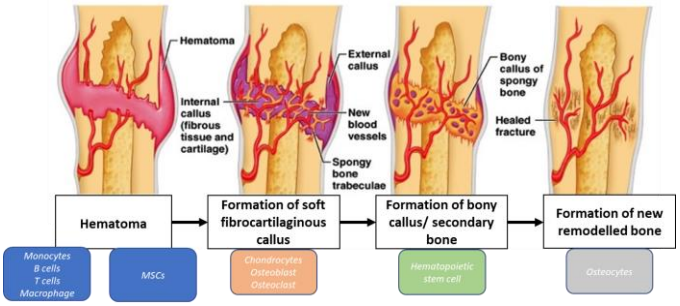


Figure 1: Illustration of a typical fracture healing process. Adapted from Wang *et al* 2017

These subsequently triggers proliferation and differentiation of bone mesenchymal stem cells (MSCs) (14).

The hematoma tissue is then replaced by the cartilaginous callus (15). The osteoprogenitor cells and bone MSCs adjacent to the fracture line differentiated mainly into chondrocytes and osteoblasts initiating the ossification process for the formation of new bone. Moreover, the osteoprogenitor cells release IL-11, IL-6, and IL-1, along with other factors to stimulate osteoclast formation (14). The soft callus eventually extends throughout the fracture gap connecting both fracture ends (11). This event takes place within the period of one week after the injury (16, 17).

A hard callus forms simultaneously with the soft callus in the subperiosteal area through intramembranous ossification. The chondrocytes develop into hypertrophic chondrocytes after the release of calcium which leads to endochondral ossification (18).

Furthermore, the differentiation of MSCs into osteoblast replaced the resorbed lacunae with new bone. These lead to the construction of woven bone with a trabecular structure. Hence, the cartilaginous callus is replaced by a hard callus in this process (19).

### 3) *Remodelling stage*

In the remodelling phase, the endochondral callus becomes completely ossified and remoulded into a secondary mature bone. The deposition of osteoblasts and osteoclasts leads to the reconstruction of the woven bone into the lamellar bone. This is accomplished via regulation of pro-inflammatory signals such as IL-1, IL-6, IL-11 and IL-12, TNF-a, and interferon-gamma (IFN-g) (20). The remodelling stage can last for many years to allow the bone to resemble its pre-fracture condition.

Thus, as beforehand mentioned, numerous types of cells and signalling pathway have been recognized to involve in the fracture repair process (21). Respective to the discovery of normal physiology of fracture repair, the contribution of biomedical engineering toward fracture healing is made in accordance with these scientific knowledges.

## III. Biomedical Engineering Invention In Bone Fracture Healing

A favourable outcome can be achieved in fracture healing with the comprehension of the conceptual framework of the diamond concept as in Figure 2 that described the prominent components of fracture healing (22). A number of particular applications have been discovered in biomedical engineering to complement and improve bone fracture healing response.

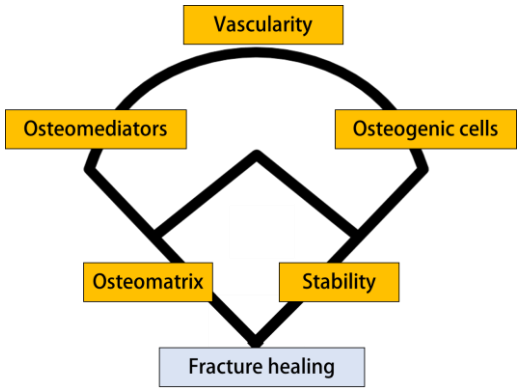


Figure 2: Diamond concept of fracture healing showing the important components of bone fracture healing.

### A. *Mechanical stabilization: Bone plating*

Fracture fixation is one of the many procedures performed to achieve mechanical stability in fracture healing (11). Different degrees of stability may be attained by using different fixation devices (23). Primary bone healing without the formation of callus effectuates toward absolute stability in bone fracture. Meanwhile supposing that the same fracture is fixed by the relative stability principle, bone healing could happen with callus formation. However, in reality, most fixations may involve components from both types of healing.

Bone plating is applied for internal fixation in which the implantation requires the tissue adjacent to the fracture to be opened (24). The fixation method aid in the biology of bone healing through mechanical transduction in which the method acts as mechanical stimuli. These stimuli play an important part in the physiological process of bone fracture healing that allows migration of bone cell precursors (25,26)

The mechanical aspect of the bone plate is further explained by Thakur *et al., 2015* in which bone the plate facilitates the load transfer and load-bearing property by transmitting forces from one end of the bone to the other (27). Furthermore, the bone plate could preserve the stability and offer protection to the fracture zone from overloading as well as providing maintenance to the mechanical alignment of the fracture fragments (28). These actions are beneficial to achieve a good outcome of bone fracture healing process.

The structure and materials used for the bone plate must be presented with a proper biomechanical environment suitable for bone healing requirements. The bone plate design can be categorized into two distinct patterns namely: conventional plates and locking plates (29).

#### 1) *Conventional bone plating*

Absolute stability of the fracture is established using a conventional bone plate as opposed to locked plating The conventional bone plating aim to restrain any relative movement between the fracture fragments hence promoting direct healing of the fracture gap without callus formation (30). The compression of the plate on the bone surface provides mechanical stability in the conventional plating. Moreover, the compression serves as a load transfer in a form of axial forces from the bone to the plate and back to the bone.

The conventional screws occupy the bicortical space in the bone to toggle within the plate. The eccentric lever arm created by the pull of the plate on the screw leads to the anchorage of the screw in the far cortex and toggle in the near cortex. This movement pulls the plate tight to the bone surface. The stability of the conventional plate is dependent on the friction at the bone–plate interface which is equivalent to the sum of the torques on each screw (31).

The conventional plate offers various advantages such as low incidence of mal-union, no requirement of external immobilization and supports a stable internal fixation, few drawbacks still persist (24). However, the process of primary healing itself is a slow enduring process. On top of that, some other drawbacks includes resulting from the use of conventional bone plate could lead to osteoporosis and secondary bone fracture where there are loss of bone mass at the subcortical bone (32). The compression of the plate onto the bone directly beneath the plate contributed toward bone necrosis and porosis which subsequently exposed the patient to risk of refracture after plate removal (33).

*2) Locking plate*

The biomechanical advancement leads to the introduction of limited-contact plate (LCP). This plate was invented attributed by the fact that excessive contact could hinder the flow of blood to the constructed site. Perren *et al., 2003* suggested that a redundant amount of contact between the bone plate and cortical bone obstructs blood flow resulting in necrosis of the cortical bone under the plate and that leads to local osteoporosis (34).

The biological internal fixation concept was proposed by Gerber *et al.,1990* in which it is an adaptation in reducing damage to the blood supply by retaining a complete reduction and absolute stability of fixation by avoiding excessive surgical approach (34–36). The development of the locking plate arises from the need of biological internal fixation.

In this method, the screw head engages with the plate hole and the load transfer from the bone to the plate is provided by the locking mechanism of the screw within the plate hole. The load is transferred and distributed evenly in a uniform manner over the length of the plate. The plates can be inserted through a minimal skin incision and then slid along the bone surface without creating a large open approach (29). With the minimally invasive application of anatomical locking plates, the blood supply to the periosteal region and the fracture area is largely preserved thus providing a biological environment for fracture healing. Thus allows for adequate osseous healing and decreased risk for infections, delayed union or non-union and secondary loss of reduction (37).

The absence of compression, resulted in flexible elastic fixation and stimulation of callus formulation which follow the secondary healing pathway. In locking plates, the strength of fixation is equal to the strength of all screw–bone interfaces rather than that of the single screw's axial stiffness or pull-out resistance (38). Therefore, a single screw is difficult to pull out unless several adjacent screws are also pulled out. This locking biomechanical principle increases the stability of the internal fixation, especially in osteoporotic bone, comminuted fractures, or highly unstable fractures (39). At the same time, the locking plate structure can avoid stress shielding below the plate and reduce the need for soft tissue dissection.

A study on osteoporotic comminuted radial diaphyseal fracture model revealed that the minimum contact locking plate (MC-LP) plating systems is significantly more stable than the limited contact dynamic compression plate (LC-DCP) system when tested in four-point bending and torsion. This is due to the fact is that in osteoporotic bone, there is a significant correlation between the pull-out strength and the cortical layer and its thickness. (40). Hence, progressive improvements have been made to address the issues in bone plating to facilitate fracture healing and reduce other possible adverse risk.

*B. Mechanical stabilization: Materials*

A part from the mechanical consideration, internal fracture fixation requires materials that are able to resist stress load to allow skeletal functions. Although metals are widely used material for this purpose, biomaterials such as polymers and ceramics have all been introduced for the same purpose. Currently, there is also an option for biodegradable internal fixation devices employing biodegradable polymers without requirement of secondary removal. These devices are currently used for in fixation in craniofacial and maxillofacial applications [41]. Given its highly opportunistic property, there are still unsettled debates over the scanty mechanical properties for other parts of the limbs [42].

Moreover, the use of polymer-based material has shown to be an alternative to metal. Polymer has a substantial fatigue resistance, high strength and flexibility [43]. The use of laminate composites of carbon fiber reinforced epoxy resin in a clinical trial indicates its viable potential as internal fixation devices. A recent study also considers the use of hybrid material for this purpose and positive findings were presented in fixating bone fractures [44].

*C. Bio- intervention: Bone tissue engineering*

The capability of bone to regenerate and a growing demand for an alternative approach necessitates the advancement of bone tissue engineering in the millennial world. This review constitutes the discussion bone graft, synthetic bone grafts substitute and various growth factor that aid in bone tissue reparation.

*1) Bone graft*

By definition, bone grafting is a surgical procedure involving the replacement of a defective or missing bone using the patient's bone structure, an artificial, synthetic, or natural substitute of the bone. The favourable environment for bone grafts generated through distinctive mechanisms accounting various osteogenic pathway which support *de novo* bone formation that potentiated by osteoblast precursors derived from the graft itself. Osteogenesis requires angiogenesis and differentiation of MSCs into osteoblasts. The osteoconductive property is characterized by the capacity of the graft to act as a scaffold for initiation of bone growth. Lastly, osteoinduction allows the graft to be able to recruit MSCs and induce its differentiation (45). Various growth factors and osteoinductive factors for example bone morphogenic proteins (BMPs) are required in this process (46).

**Autogenous bone graft**: Autograft comprises of cancellous; cortical or bone marrow aspirate from patients bone, which remains as the gold standard for bone grafts. Integration of an autograft into the host bone may accelerate bone healing (47).

The downside of autografts is the requirement of a second surgical procedure to obtain the harvested tissue such as from the patient's iliac crest (48). Other than that, an autogenous bone graft is a considerably cheaper option but may ensue adverse issues such as significant donor site

injury and morbidity, deformity, scarring and associated with surgical risks of bleeding, inflammation, infection, and chronic pain (49). However, the advantages of autologous bone graft includes fewer risk of disease transmission as well as less immunological rejection from the bone graft transplantation (50).

**Allogeneic bone graft:** Bone structure that is harvested and transplanted from one genetically different individual of the same species, it is known as allograft (51). Histocompatibility property is likely to be presented in a machined and tailored allogeneic. The allograft is derivable from variety forms, including cortical, cancellous and demineralized bone matrix (DBM).

In contrast to autografts, allografts are linked to the risk of immunoreactions, transmission of infections and manifest a lower success rate. The primary osteoinduction phase would be eradicated by an immune response and inflammatory cells due to the activation major histocompatibility complex (MHC) antigens and thus cause immunoreactions (52).

Cancellous allograft also exerts exquisite osteoconductive properties accustomed by its porosity which allow a speedy establishment into host bone in comparison to cortical allografts. Meanwhile, a DBM is a type of allograft derivative that produced through an acid extraction with preserved content of collagens, non-collagenous proteins and growth factor (53). An advance formulation of DBM has been discovered namely a cellular bone allografts (CBA) that is safe for foot and ankle arthrodesis (54).

*2) Bone graft substitutes: Biomaterials*

Bone is a combination of both organic and inorganic components. Substitute from ceramic, polymer or composite materials has been used to mimic the natural composition of bone with the aim to restore bone and improve bone regeneration (55). A noteworthy interest to the exploration of non-biological material as bone graft substitutes may be explained by the deficit supply compared to the demands, especially in developed countries. The aim of most bone graft substitute is to achieve ingrowth of bone from the surrounding tissue (56). However, these remain an issue in critical bone defects. Hence, biomaterials designed for bone regeneration are required to induce bone formation at the desired locations (55). Additionally, it is vital that these materials possess optimal physical properties, sufficient mechanical stability, with similar surface properties and bioresorbability (57).

***a) Natural biopolymer***

Natural polymers can be categorized into proteins (silk, collagen, gelatin, fibrinogen, elastin, keratin, actin, and myosin) or polysaccharides (cellulose, amylose, dextran, chitin, and glycosaminoglycan) (58). In order to gain necessary mechanical and biological properties of hard bone tissue,a combination of natural degradable polymers and inorganic bioactive particles were proven as one of the suitable candidates (56). A fabrication of natural polymer can either be derived from cells induced with suitable ECM or from decellularized bone tissue (58). Recently, the combination of chitosan with polysaccharides and proteins has been shown to induce osteochondral regeneration (59). Additionally, a natural polymer known as bacterial cellulose associated with osteogenic growth peptide (OGP(10–14) promoted a greater bone regeneration in vivo with a higher radiographic density of repaired bone (60). In another study, bacterial cellulose (BC) incorporated with Graphene oxide/hydroxyapatite (GOHA) composite showed good viability on osteoblast cells in vitro which may act as a potential osteoinductive material (58).

***b) Synthetic bioceramic: calcium phosphate (CaP) and calcium sulfate (CaS) compounds***

At present, resulting from extensive researches and innovations; calcium sulfate (CaS) and calcium phosphate (CaP) are some of the most commonly available synthetic bone graft substitutes (53,61).

CaS is a type of osteoconductive and biodegradable ceramics material constitutes of calcium sulphate hemihydrate ($CaSO_4$). This structure is generally prepared in a form of cement or pellet form that dissolves *in vivo* within 2 months attached to the graft. The compounds establish a readily competent filling component to bony voids similar to those in the metaphyseal bone defects after fracture reductions and post-traumatic fractures (62). Other than that, few studies have been conducted by augmenting injectable CaS in the treatment of tibial plateau fractures and calcaneus fractures using open reduction and internal fixation (ORIF) technique. These studies documented the use of the material as safe with high efficacy (63,64).

Next, osteoconductive feature exhibits by the CaP ceramics and cement are conducive to enhance bone fracture healing (53). CaP ceramics consisting of the chemical composition similar to the mineralized calcified tissues that is the calcium hydroxyapatites (Hap)(59). CaP ceramics are generally encompassed a similar primary mechanical property of cancellous bone in which it is brittle with weak tensile strength but resistant to compressive loads. After their implantation, the resistance ability may decrease by 30-40% (61,65). The formulation of CaP constitutes of the calcium dissolution with an aqueous solvent causing the cement to harden while the CaP crystals expand efficaciously (53). Some prospective clinical trials have been conducted proving significant result to the safety and efficacy of these material for bone graft. Readily available CaP cement injections aids in reinforcing the percutaneous pinning procedures in distal radius fractures treatment (66,67).

***c) Synthetic bioactive glass***

Bioglass, a shorter term for bioactive glass constitutes mainly of silicate with combination of other components such as silicon dioxide (SiO2), sodium oxide (Na2O), calcium oxide (CaO) and phosphorus pentoxide (P2O5), potassium oxide (K2O), magnesium oxide (MgO) and boric oxide (B2O) acting as the stabilizing compounds (65). A strong physical bonding is created between the bioglass and the host's bone caused by extraction and accumulation of silicon ions with the formation of

hydroxyapatite laminate the surface of bioglass (68). The hydroxyapatite layer will biologically replace by bone tissue gradually through a substitution process after the implantation (69). Currently, the use of bioglass is mostly utilized in the reconstruction of facial bone defects with the combination of growth factors (70,71).

***d) 3D bioprinted graft***

The most recent advancement that in tackling the issues of bone regeneration is known as 3D bioprinting techniques. These techniques employed the use of bioinks for production of 3D printed materials. Bioinks consist of cells and biomaterial building blocks tailored with specific ECM signalling's to produce 3D fabrication of accurately shaped bone constructs. Importantly, these techniques also allow production of constructs by employing patient imaging data for example from magnetic resonance imaging (MRI) or computer tomography (CT) (72). The ability to tailor the complex anatomical structure of an individual's bone construct may has a promising application in critical bone defects. A study by Kuss et al., 2017 on 3D bioprinted bone constructs composed of polycaprolactone/hydroxyapatite (PCL/HAp) and SVFC-laden hydrogel bioinks showed promising promotion of vascularization-related gene expression (73). Moreover, in a updated research, the use of 3D bioprinted construct by using silk-gelatin bioink was tested *in vitro* using custom made bone-marrow derived mesenchymal stem cell line (TVA-BMSC) and compared with *in vivo* endochondral ossification route. The study aims to highlights the imitation of the developmental biology in endochondral ossification route for progenitor cells differentiation. The results of the study indicated overall enhancement of progenitor stem cells osteogenic differentiation via various signally pathway and improved mineralization in 3D bioprinted constructs *in vitro* (74).

Lasty, research on engineered vascularized 3D bioprinted bone construct indicated an excellent bioactivity and vascularized bone forming potential using smart release nanocoating that is induced through a matrix metalloprotease 2 regulative mechanism using growth factors (75).

*D. Promotion of bone regeneration: Cell biology*

Biological properties are vital and in particular signalling molecules are required to recruit mesenchymal progenitor cells. These molecules are taken into consideration in development of bone substitute and promotion of its regeneration. As mentioned, bone fracture healing normally is coordinated by a sequence of physiological process by cytokine signalling sequences evoked by the intensified expression of various types of growth factors (GFs) including osteogenic, angiogenic and pro-inflammatory growth factors (76). GFs such as BMPs, fibroblast growth factors (FGFs), and other GFs have been discovered to exist during natural bone fracture healing through an *in vivo* study (77). The adoption of GFs on bone regeneration can be observed as an augmentation for osteoinductive purposes in the majority of bone graft substitutes and therapeutic strategies in treatment settings (51,78).

Osteogenic factor such as the bone morphogenic protein (BMPs) are considered as an important promoter of bone healing especially in large bone defects. Two prominent members of BMPs that are highly commercialized are BMP-2 and BMP-7 (79). Several studies reported that BMPs have significant influence in treatment of bone fracture by promoting cells differentiation and angiogenesis process. BMP-2 has important function in triggering an osteoblastic differentiation from MSCs (80). Whereas BMP-7 have the ability to influence the expression of important initiators of acute-phase reaction in angiogenesis process. Utilization of BMP-7 in bone graft transplantation produces a costimulatory effects on proinflammatory cytokines expression such as IL-6, TNF-α and IL-8 which urges an increased VEGF expression (81).

Few examples of clinical application of BMPs were observed. For instances, reported application in treatment of open tibia fractures and non-union condition (82). Besides that, BMPs also aid the formation of new bone in the disc spaces for spinal fusion procedures by promoting cells differentiation (83,84). In another randomized controlled trial for the treatment of open tibial fracture, compared to the control group, the patient treated with BMP-2 GFs shown to develop earlier formation of bone callus with decrease infection rate at wound closure site and less amount of pain after the operation (85). Moreover, the Food and Drug Administration and European Medicines Evaluation Agency (EMEA) has recognised the use of BMP-2 in anterior lumbar spinal fusion and open tibial fractures operations (86) and BMP-7 utilization as a component in the treatment of posterolateral lumbar spine fusion (87).

Although the function of FGFs is not clearly understood, it exhibits a fundamental role in angiogenesis and osteoclast formation (88) in addition to the effective mitogenic action that mediated by the FGFs/FGFRs signalling on MSCs (89).

A study by Bjorn *et al., 2010* demonstrated that FGFs associate directly with the healing of calvarium, especially to the parietal bone defect. Improvement and gradual restoration of missing bone manifested in the experimental mice treated with collagen scaffolds containing FGF9 and FGF18 was observed (90). A randomized controlled trial which involving patients with tibial shaft fracture showed a fast recovery of fracture healing after the patients were injected with rhFGF-2 contained gelatine hydrogel (91). Furthermore, the fracture in FGFs-treated patient portrayed a greater effect of fracture union compared to the placebo group. A study by Hurley *et al*., 2016 revealed that FGF-2 produced a curative outcome to the close fractures of tibia in transgenic mice (92). The study concluded that overexpression of FGF-2 aided in osteoprogenitor cells differentiation which eventually speeds up the healing process. Many studies are continuously still being performed to understand the roles of FGFs and FGFRs in bone healing.

## IV. Conclusion

Critical bone defects require quick and precise management to avoid any delayed union or non-union of the bones. Such undesirable effects could occur when treated inappropriately. Currently, the management of critical-size defects remains as one of the biggest challenges for bone-defect healing. However, iterative improvements to the technologies for bone-defect healing has led to a significant advancement of bone tissue engineering. Overall biomechanical environment in which implants would be positioned in is essential to address these challenges. These includes investigation of the suitable substitute for bone graft and also mechanical materials and properties for its support. The attained knowledge should be considered as a golden opportunity to address these challenges for better bone fracture healing. Future studies should explore further conventional technologies and biomaterials to create a better intervention for critical size bone defect.

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