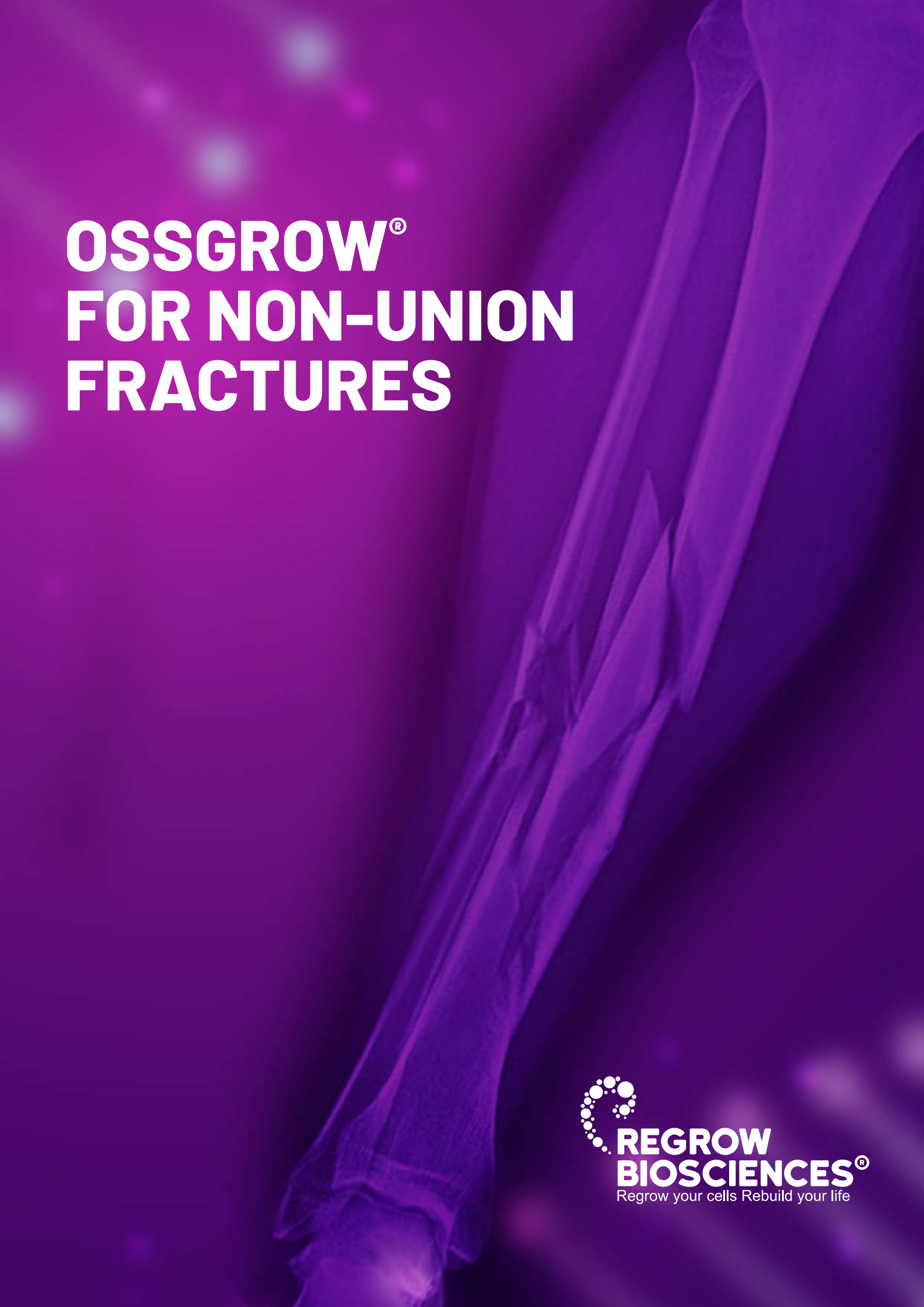
OSSGROW®
FOR NON-UNION FRACTURES



REGROW BIOSCIENCES®
Regrow your cells Rebuild your life

CONTENTS

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1.1 FRACTURE NON-UNION

According to the US FDA definition, a fracture ununited 9 months after injury or one in which there is a failure of progression towards union over the previous three months, can be classified as a non-union.[1]

Rather than relying on a specific time frame to define a non-union, it has been proposed that a more practical definition of non-union is a fracture that will not unite without further medical intervention.[1]

Non-union in clinical practice is commonly associated with long bone fractures of the forearm, humerus, tibia, clavicle and femur.

The main characteristics of a non-union are pain while weight bearing and persistent fracture lines on X-ray.

Skeletal bone has remarkable regeneration capacity. Bone healing after a fracture is a phenomenon arising from a complex interplay of mechanical and biological factors.

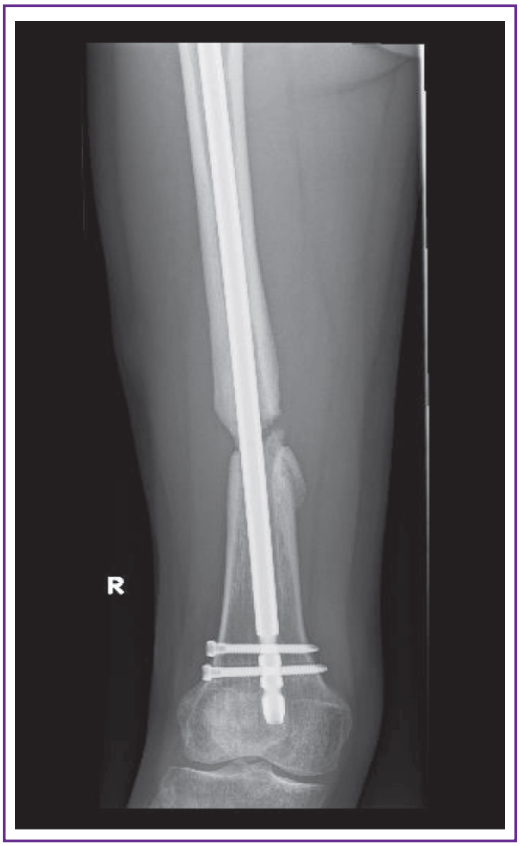


Figure 1: X-ray of a fracture non-union

1.2 BONE HEALING INVOLVES THREE MAJOR STEPS

Inflammation

Hematoma formation provides hemopoietic cells and immune cells that are capable of secreting growth factors and cytokines which recruit fibroblasts and mesenchymal cells to the fracture site and initiate granulation tissue formation, proliferation of osteoblasts and fibroblasts.

Repair

This stage involves primary callus formation and if the bone ends are not touching, then bridging soft callus forms. Endochondral ossification converts soft callus to hard callus. Cartilage production provides provisional stabilization.

Remodelling

During this step, terminal differentiation of chondrocytes and cartilaginous calcification occurs. Newly formed bone (woven bone) remodeling occurs via organized osteoblastic and osteoclastic activity.

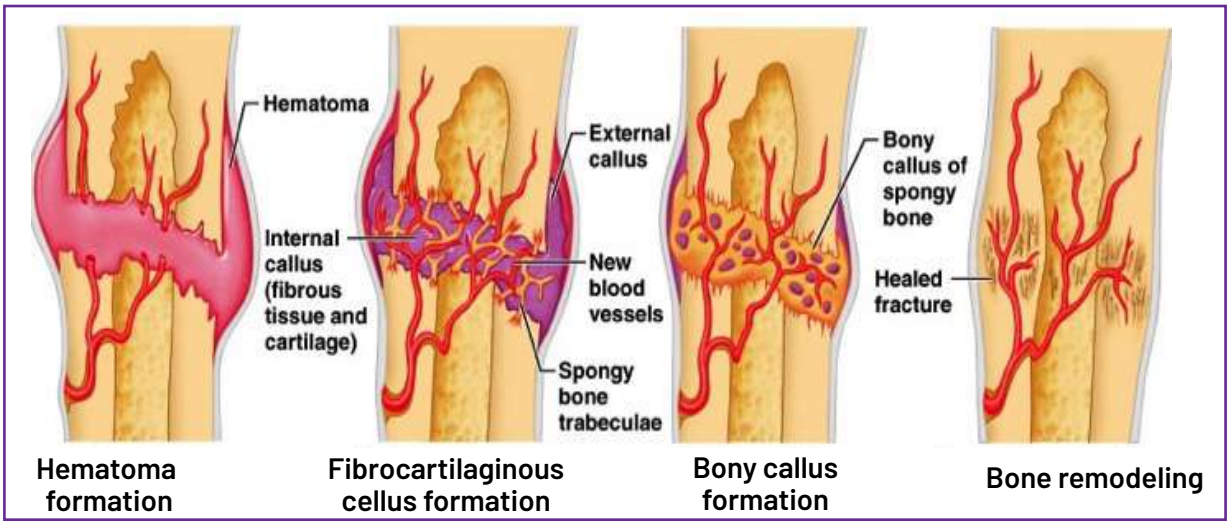


Figure 2: Process of bone healing

These steps are perfectly orchestrated to bring about consolidation of a fracture resulting in functionally repaired bones. Impairment of one or more of these factors can result in the failure of the bone to heal, a condition termed as 'non-union.' [2]

1.3 CLASSIFICATION OF NON-UNION[3]

Atrophic non-union

Atrophic non-unions are characterized by the lack of regenerative potential, which is often associated with insufficient blood supply of the fracture ends and the surrounding soft tissue or low-grade infections of the fracture site. Despite adequate mechanical fixation, bone regeneration fails in these cases and the fracture ends in atrophy due to inadequate biological local environment.

Hypertrophic non-union

Hypertrophic non-unions are characterized by vital, regenerating bone tissue with good blood perfusion of the fracture ends and the availability of necessary molecular mediators, progenitor cells, osteoconductive matrix and immunoregulatory cells, among others. However, hypertrophic non-unions fail to heal due to insufficient mechanical stabilization, and typically heal once the mechanical stability has improved.

Oligotrophic non-union

Poor callus formation is considered to have viable fracture fragments but has a combination of excess motion along with impaired biological potential for healing at the fracture site.

Understanding the biomechanical reasons for non-union

Healing of the fracture is a multifactorial (biological and mechanical) process. Successful fracture healing requires mechanical stability and a viable biologic microenvironment. If any of these factors are impaired, healing process is interrupted resulting in fracture nonunion.

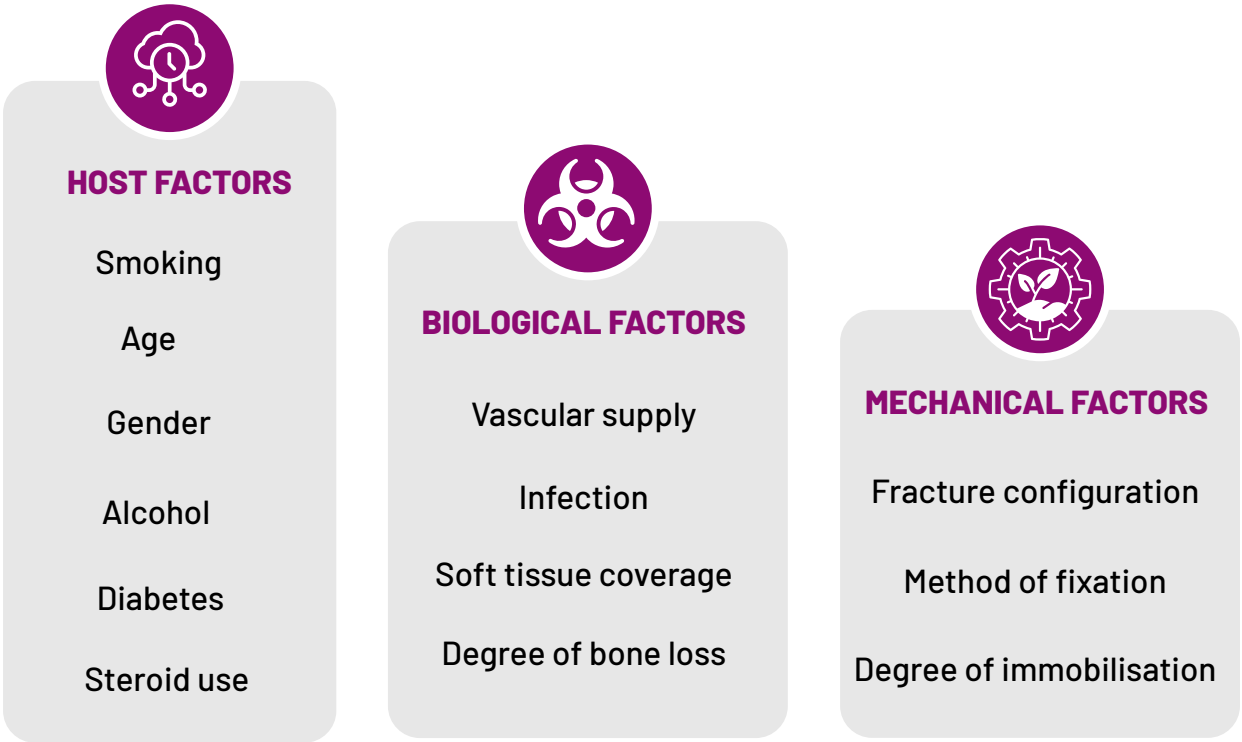
Mechanical factors relate to the stability of the fracture. Instability at the fracture site leading to excessive strain is the principal mechanical factor resulting in non-union.

Lack of viable biological environment at the site of fracture leads to poor regeneration of bone and results in nonunion. Biological factors refer to the local environment at the fracture, such as the presence of infection, the extent of bone loss, the vascularity of the bone and quality of the surrounding soft tissues and availability of molecular mediators, progenitor cells and matrix, immunoregulatory cells amongst others.

1.4 ETIOLOGY AND PREVALENCE OF NON-UNION

Etiology

Etiology of non-unions can arise from host factors, biological factors and mechanical factors shown below[11]



Etiology of non-unions classified by host, biological and mechanical factors (Adapted from Stewart SK. Malays Orthop J. 2019;13(2):1-10)

Prevalence

The best current overview is provided by a Scottish study evaluating the risk of non-union per fracture in a population of over 4 million adults. Here, the overall risk of suffering from a non-union was estimated to be 1.9%, i.e 800,000 adults.[4]

It has been estimated that 100,000 fractures go on to nonunion each year in the United States and the median cost of treating fracture non-unions has been estimated at $25,556 per open tibial fracture[5,6].

The lifetime risk of any fracture at the age of 50 years is 53% among women and 21% among men[6], and roughly 5% of the fractures result in non-union[7]

The rate of fracture non-union varies greatly in different anatomical locations of the fracture[8], with an average incidence rate of 4.93%[9] and as high as 10%[10] as it is associated with high economic and health burden and significant loss of working days.

The global fracture fixation devices market is expected to increase at a CAGR of 5.9% over the forecast period, reaching nearly **$11 Bn in 2023**[11].

1.5 CURRENT TREATMENT OPTIONS FOR FRACTURE NON-UNION

1. Nonsurgical therapy: Low-intensity pulsed ultrasound (LIPUS)

In some cases, a bone stimulator can be used to treat a non-union. A bone stimulator is a small device that delivers ultrasonic or pulsed electromagnetic waves to a bone to stimulate healing.

The stimulator is placed over the skin near the non-union for between 20 minutes and several hours each day. The stimulator must be used every day to be effective until the non-union heals.

2. Surgical therapy

Until now, the standard treatment for non-union fracture is surgical, it is usually stabilized during a surgical procedure. The stabilization can be done internally by using metal plates and screws attached to the bone or by placing a rod inside the canal of the bone (Figure 3).

A surgeon may also recommend external fixation of a non-union that uses a scaffold-like rigid frame outside the injured arm or leg to stabilize the fracture. The frame is attached to the bone with wires or pins. Generally hypertrophic non-unions will heal with application of rigid fixation (plate, an intramedullary nail, or an external fixator) (Figure 3).

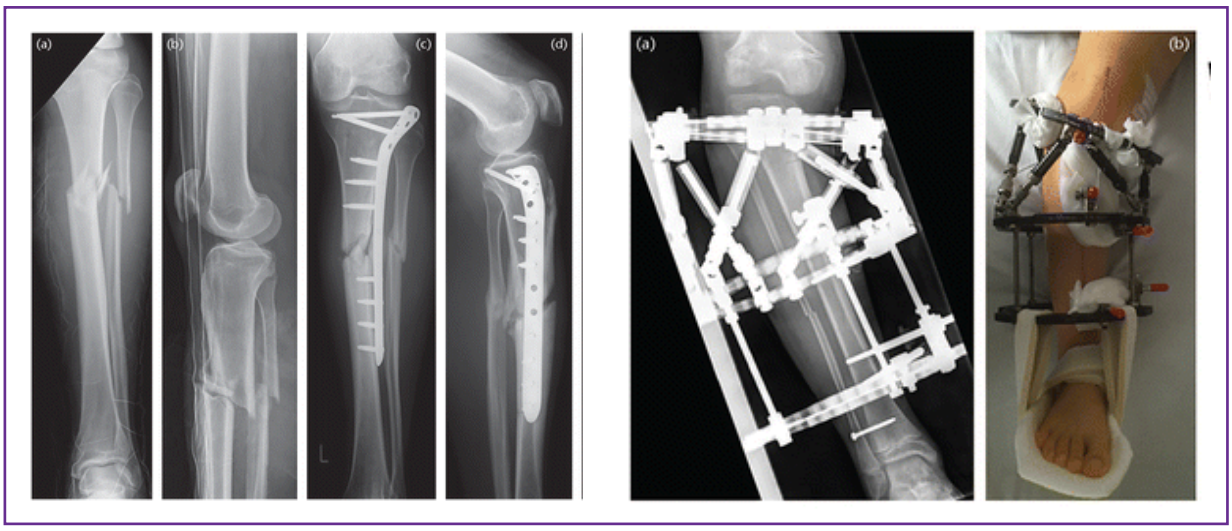


Figure 3 : Surgical fixation with intramedullary nails (left) and scaffold-like rigid frame (right). adapted from Hagen Schmal et al., EFORT Open Rev. 2020 Jan; 5(1): 46–57.

3. Grafting

The need for a graft depends on the applied treatment strategy in which the presence of a significant bone defect is decisive. A graft not only fills the gap but provides regenerative microenvironment making it a useful adjuvant mainly in atrophic non-union (Figure 4).

Harvest and transplantation of autogenous bone (autograft) from the iliac crest is still considered as "gold standard" in bone healing of non-unions as it provides a combination of osteogenic, osteoinductive and osteoconductive properties. However, autografts are only available in limited supply, and accompanied with high morbidity during harvest including wound infection and postoperative pain (Figure 4).

Allogenic bone grafts provide relatively safe alternative as autografts have limited availability and harvesting them is associated with longer operation time and donor site morbidity. Allografts are usually used as cancellous bone chips providing some degree of structural strength.

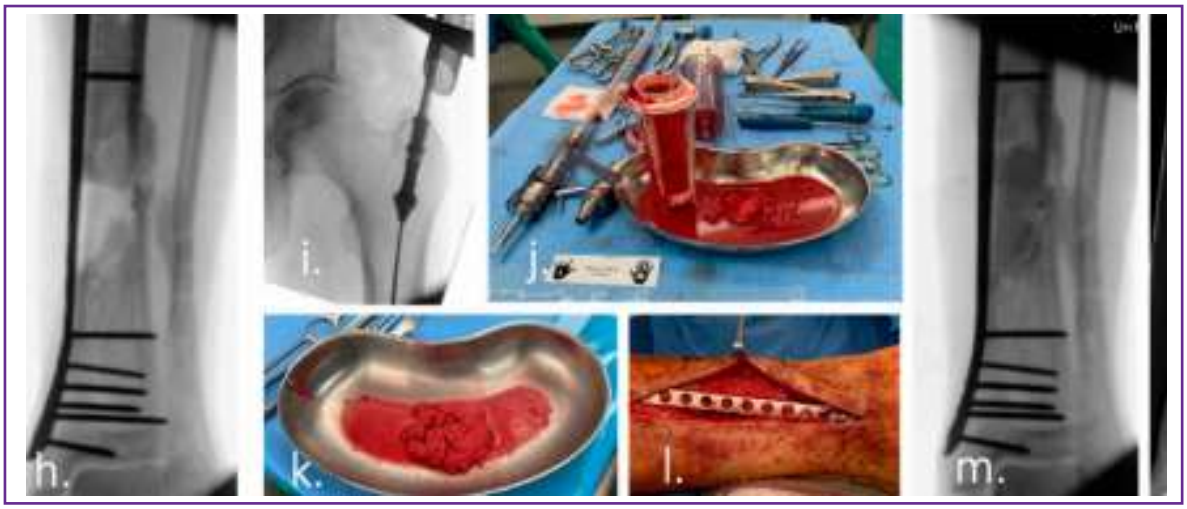


Figure 4: (h) Intraoperative radiograph after removal of cement spacer, 2 months after implantation. (i–k) Harvest of autologous bone graft (bone marrow, morselized bone) from the femur using the Reamer–irrigator–aspirator (RIA). (l,m) Picture and intraoperative radiograph after filling the bone defect with autologous bone (Adapted from Schlickewei CW et al,. Int J Mol Sci. 2019;20(22):5805.

1.6 LIMITATIONS OF EXISTING TREATMENT STRATEGIES AND NEED FOR NOVEL THERAPEUTICS

Although many cases of non-unions can be treated successfully using existing treatment strategies, they are often highly specialized and individual treatments are expensive, time-consuming, and a large economic burden on affected patients.

They have the following risks

- Atrophic non-union remains to be the most difficult to treat, even with autologous bone grafting approximately 10% of cases tend to have major complications and around 40% may suffer from minor complications.[12]
- Furthermore, availability of autografts is limited, and its harvesting procedure is associated with significant donor site morbidity, local hematoma and remodeling issues of the implanted bone.[12]
- On the other hand, allograft carries the risk for transmission of infectious disease, post-operative infection and re-fracture. The strength of synthetic scaffolds is varied in different individuals as various anatomical locations and clinical conditions may affect material degradation differently.[13]
- Allograft is hampered by bone tissue integration from the host and vascularization issues.[13]
- Therefore, it is essential to establish a more sustainable, novel therapeutic approach, which prevents impaired bone healing and facilitates bone regeneration when non-union has occurred.

2.1 ROLE OF ORTHOBIOLOGICS IN NON-UNION HEALING

- "Orthobiologics" refers to using biological substances in helping musculoskeletal injuries heal quicker. They are used to improve the healing of fractured bones and injured muscles, tendons and ligaments, and are derived from substances naturally found in the body.[15]
- Orthobiologics for bone healing implements the "diamond concept" that combines osteoconduction, osteoinduction and osteogenesis thus, appearing as a promising strategy to treat non-healing fractures, in particular, atrophic non-unions.[15]
- Among orthobiologic approaches for bone healing, cell-based therapies and bone marrow derivatives with or without bone grafts and biomaterials have been widely investigated in the recent years.[15]

2.2 CELL BASED THERAPIES FOR NON-UNION

- Stem cell therapy, as one of the methods used in bone repair, has been developed over the last two decades.[16]
- Mesenchymal stem cells (MSCs) play a crucial role in bone repair, and thus cell therapy can serve as an alternative to autologous bone grafting.[17]
- The involvement of MSCs in bone healing is critical particularly for difficult non-union fractures resulting from trauma, blood insufficiency and other conditions.[17]
- Bone marrow MSCs are currently the most appropriate cells for inducing bone repair as they have a strong osteogenic potential and are easily obtained by culturing iliac crest aspirates associated with limited morbidity for harvesting bone marrow.[17]
- Several MSC-based cell therapy modalities have been developed, i.e., with and without cell culturing, and with or without a matrix.
- The mononuclear cell fraction of the bone marrow, which contains the MSCs, can be used directly by percutaneous injection of aspirated bone marrow into the injury site or mononuclear cells may also be cultured in vitro to allow selection and expansion of an adherent fraction corresponding to MSCs. This increases the number of MSCs to millions of cells.[18]

2.3 'DIAMOND CONCEPT'

- The 'diamond concept', being a conceptual framework for successful bone repair response, gives equal importance to mechanical stability and biological environment (availability of molecular mediators, progenitor cells and matrix, immunoregulatory cells amongst others), thus, facilitating evolution of a physiological process leading to successful bone repair response (Figure 4).[14]
- Moreover, adequate bone vascularity and physiological state of the host are thought to be essential within this framework of fracture repair.[14]
- A deficit in the biological environment or the mechanical environment, or failure to appreciate the host comorbidities and lack of vascularity can all lead to impaired fracture healing response (non-union).[14]

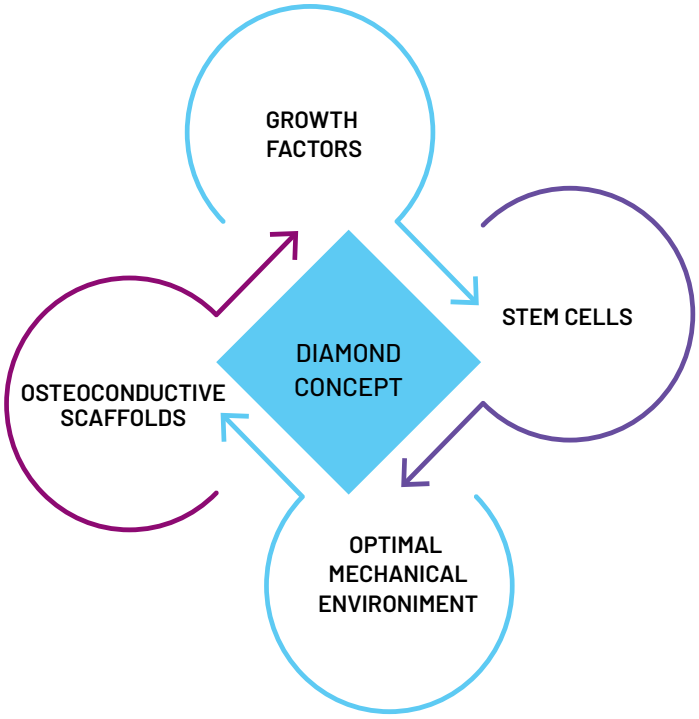


Figure 5: The diamond concept of fracture healing describes the three biological prerequisites (stem cells, growth factors and osteoconductive scaffolds) and optimal mechanical environment required for bone healing (Adapted from Stewart SK. Et al., Malays Orthop J. 2019 Jul; 13(2): 1–10.)

2.4 ADVANTAGES AND DISADVANTAGES WITH MSCs IN BONE HEALING PROCESS

MSCs are multipotent stromal cells present in most adult connective tissues. They are extensively studied due to their ability to differentiate into multiple cell types, and their advantages and disadvantages are listed in Table 2

Sr.No	ADVANTAGES OF BONE MARROW-DERIVED MSCs	DISADVANTAGES OF BONE MARROW-DERIVED MSCs
1.	Accessible source for cell harvesting	Risk of contamination with malignant cells if harvested from different donors
2.	Ease of preparation	Yield of MSCs is low and they have low proliferative capacity Number of cells required for bone healing is controversial
3.	High stability and affinity to differentiate into	Safety issue from regulatory standpoint– differentiation to other cell lineages and evidence to differentiation to bone in vivo remains controversial

Table 2: Advantages of bone marrow-derived MSCs (adapted from Oryan A et al., Cells Tissues Organs 2017;204:59-83)

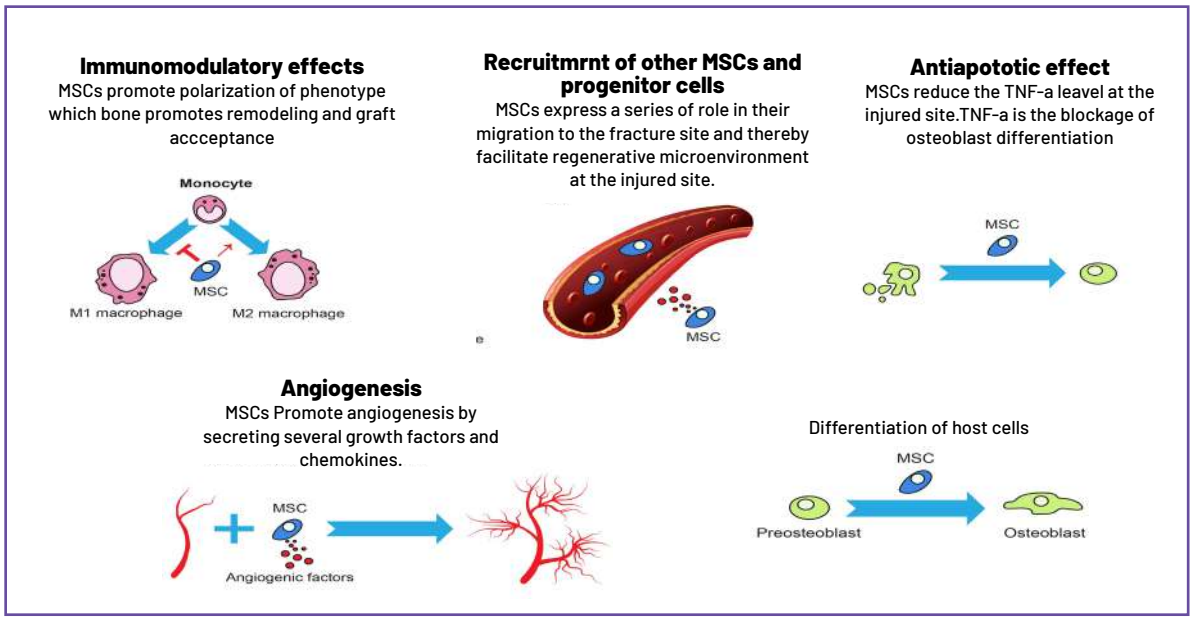


Figure 6: Mechanism of action of MSCs in bone regeneration and remodelling (Adapted from Oryan A et al., Cells Tissues Organs 2017;204:59-83)

3.1 USE OF AUTOLOGOUS CULTURED OSTEOBLASTS IN LONG BONE HEALING

A multi-center, randomized, clinical study to compare the effect and safety of autologous cultured osteoblast injection to treat fractures.

- Apart from stem cell therapy, using autologous cultured osteoblasts are gaining much prominence as their success rate in healing long bone fracture is significant.
- In a randomized controlled trial by Kim et al., non union patients injected with autologous cultured osteoblasts benefited with speed recovery and an absence of immune rejection was observed when autologous cultured osteoblasts were used.[19]

3.2 MECHANISM OF ACTION OF OSTEOBLASTS IN BONE MATURATION AND FORMATION

- Osteoblasts synthesize: collagen-I, osteocalcin, osteonectin.[20]
- Osteoblasts regulate mineralization of osteoid.[17]
- Bone mineral is a precipitate of calcium, phosphate, and water.[20]
- Osteoblasts control transport of Ca^{2+} on to osteoid surface, as well as deposition of phosphate (through osteoblast enzyme Alkaline Phosphatase).[20]
- Osteoblasts produce a range of different secretory molecules, including M-CSF, RANKL/OPG, WNT5A, and WNT[16], that promote or suppress osteoclast differentiation and development.[18]
- OPG secreted by osteoblasts binds to RANKL on osteoclast thereby inhibit osteoclast activation and bone resorption.[18]

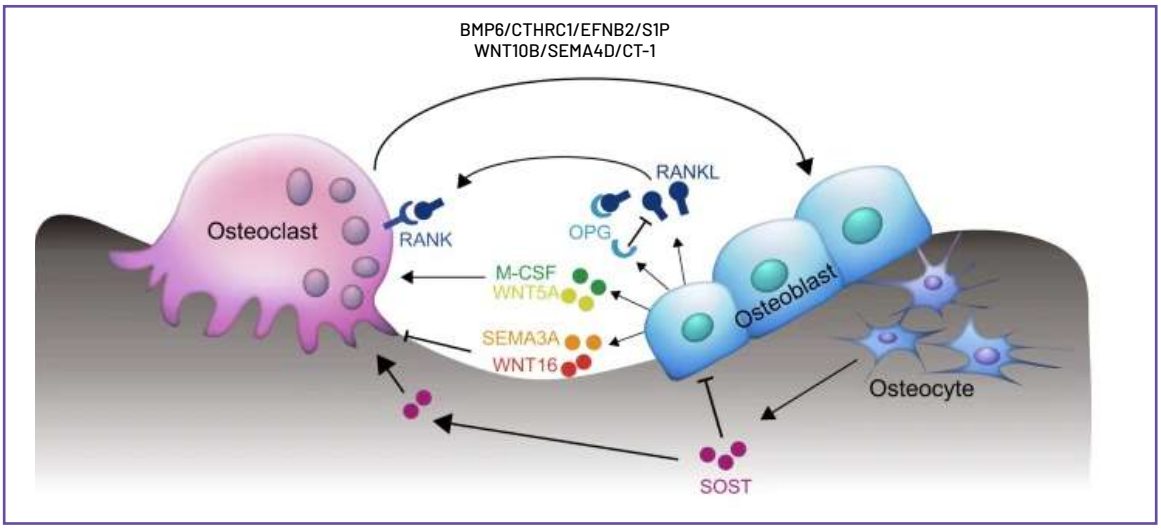
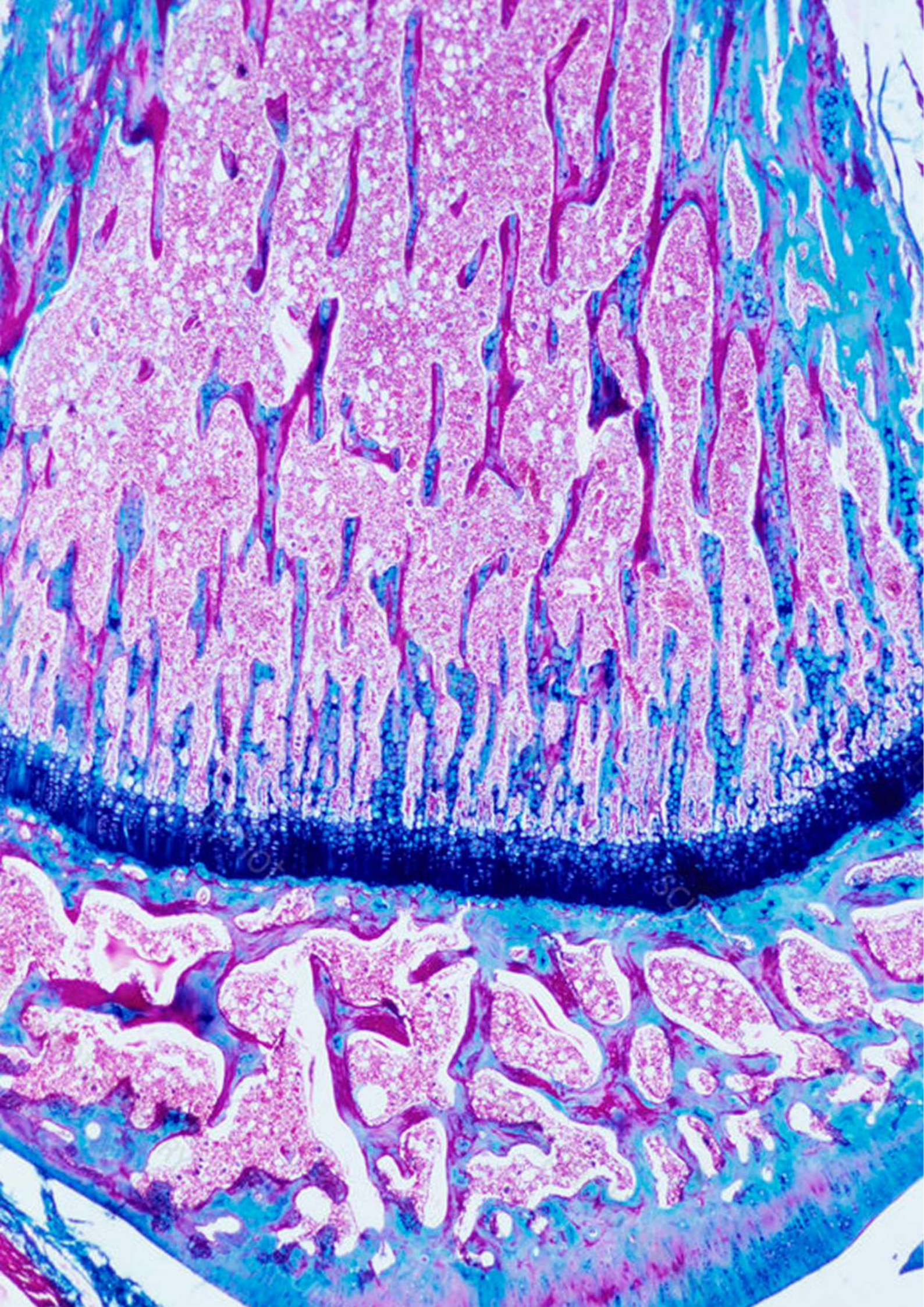


Figure 7: adopted from Marquis ME et al., Frontiers in Bioscience 14(3):1023-106719

3.3 OSSGROW®, A PERSONALIZED NOVEL CELL THERAPY FOR BONE REGENERATION

- OSSGROW® is a targeted and personalized bone cell therapy option for curative treatment of non-union fractures.
- Bone cell therapy using OSSGROW® involves implantation of autologous adult live-cultured osteoblasts derived from the bone marrow of the patient. Being autologous, there will be no risk of immune rejection and it is a minimally invasive surgical therapy.
- Osteoblasts of OSSGROW® forms 3-dimensional new bone. Therefore, slowly, the joint regains structure, strength and function, and in the best-case scenario, accelerated healing of the fracture.
- According to previous studies [23,24], the novel autologous cultured osteoblasts (OSSGROW®) has been proven effective and safe and are recommended as a treatment option for curing osteonecrosis of the femoral head.
- OSSGROW® has received marketing authorization and license for commercial sale from the Indian FDA (DCGI), Ministry of Family, Health and Welfare.

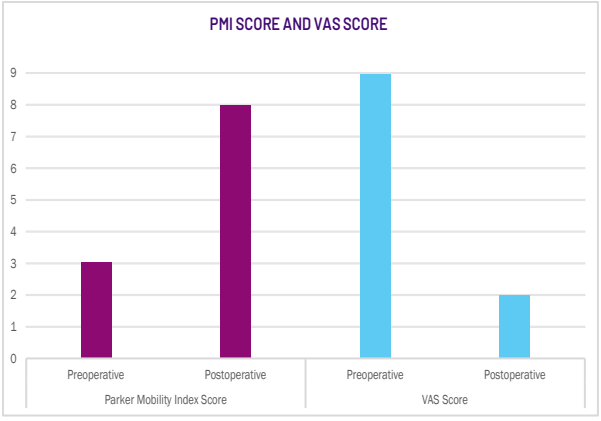


4. USE OF OSSGROW® IN TREATING NON-UNION FRACTURE: RESULTS OF A CASE SERIES OF 7 PATIENTS

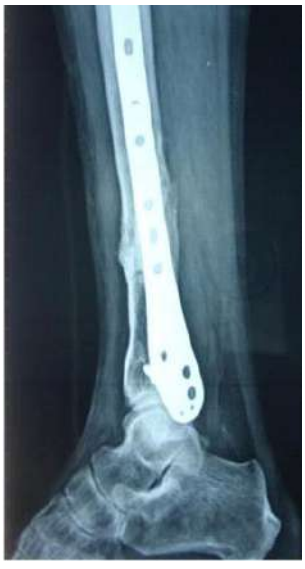
PATIENT 1

AGE	58
GENDER	FEMALE
FRACTURE TYPE	NON-UNION
FRACTURE LOCATION	RIGHT TIBIA FIBULA LOWER 1/3RD
REASON OF FRACTURE	FALLING DOWN

Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 3 to 8
Visual Analogue Scale (VAS) score reduced from 9 to 2



Pre-op Xray



Post-op Xray
1 YEAR

Pre- Operative X-ray

- Non- Union oblique fracture distal 1/3 rd.Shaft of RT tibia is seen.
- The Gap between fracture fragments is 1 cm.
- Fracture of prosthesis is noted.

Post- Operative X-ray

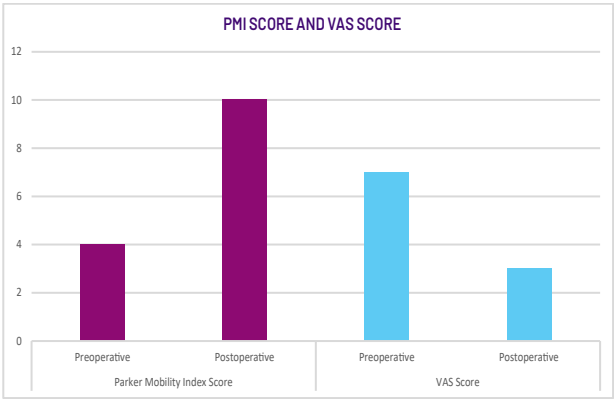
- Remodeling of callus - Healed fracture distal 1/3 rd shaft of Tibia is seen.
- No gap is seen.
- Nail-plate in-situ is noted.
- mRU score 12.

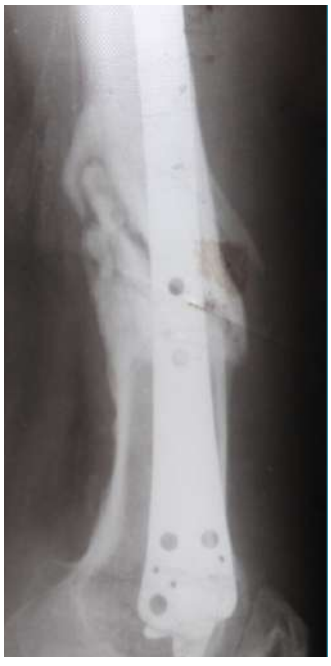
We thank Dr. D.D.Tanna and team for sharing this case report.

PATIENT 2

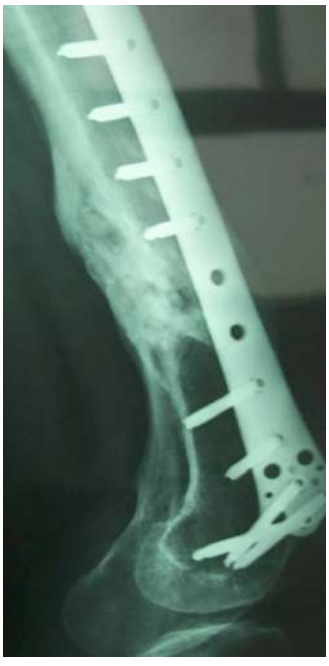
AGE	32
GENDER	MALE
FRACTURE TYPE	NON-UNION
REASON OF FRACTURE	ACCIDENT

Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 4 to 10
Visual Analogue Scale (VAS) score reduced from 7 to 3

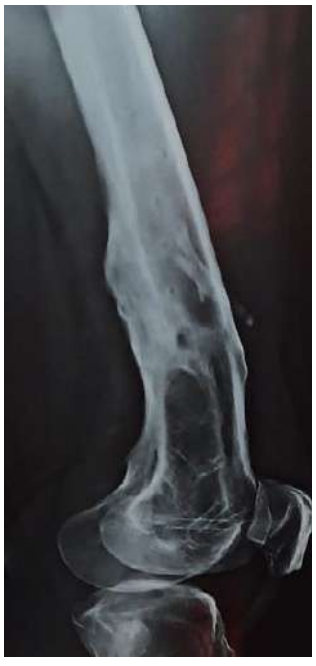




Pre-op Xray



Post -op X-ray
13 months



Post -op X-ray
127 months

Pre- Operative X-ray

- Oblique Non-union fracture of distal 1/3 rd shaft of femur is noted.
- There is no callus.
- Fracture of Nail is also seen.

Post- Operative X-ray

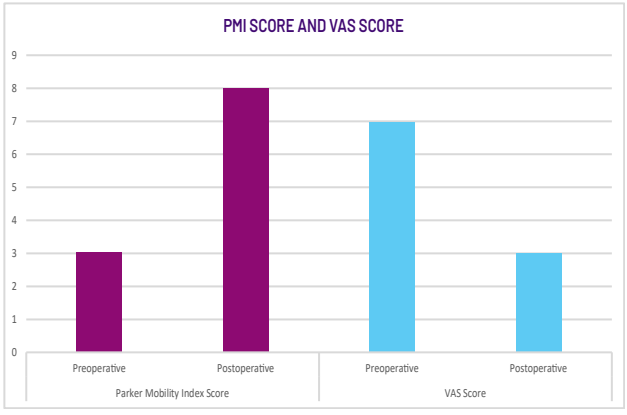
- Ossified and remodelled callus at distal 1/3 rd shaft fracture with nail-plate in-situ is seen.
- mRU score – 12.

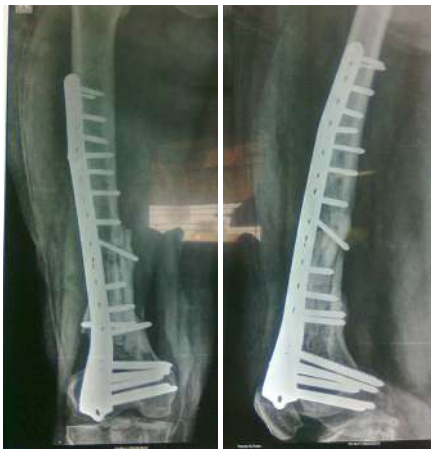
We thank Dr. M.E. Luther and team for sharing this case report.

PATIENT 3

AGE	51
GENDER	MALE
FRACTURE TYPE	NON-UNION
FRACTURE LOCATION	RIGHT FEMUR
REASON OF FRACTURE	ACCIDENT

Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 3 to 8
Visual Analogue Scale (VAS) score reduced from 7 to 3





Post -op X-ray

Post-Op X- ray 7 years

Pre- Operative X-ray

- Nail plate at distal shaft and condyle of Femur is seen.
- Non Union of communiated fracture of Distal 1/3 shaft of femur is seen.
- The Gap is 0.5 mm.

Post- Operative X-ray

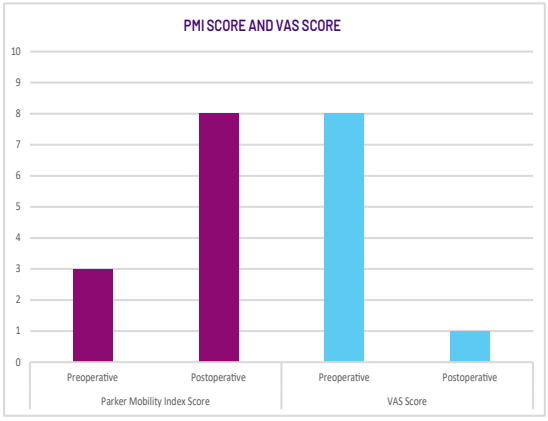
- Remodeled callus at fracture of femur distal shaft with Intra-medullary Nail in situ is seen.
- mRU score is 12.

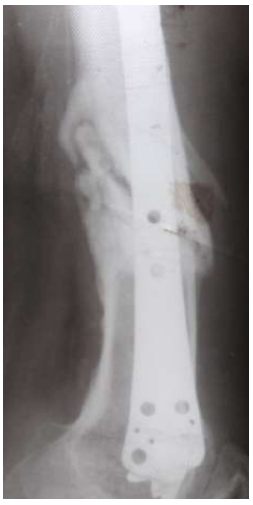
We thank Dr.Nilesh Shah and team for sharing this case report.

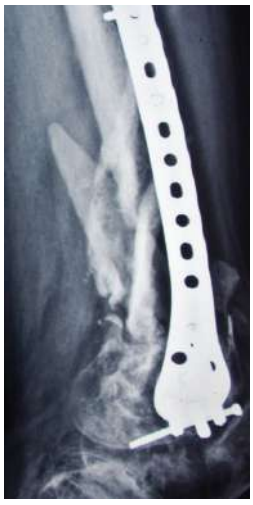
PATIENT 4

AGE	33
GENDER	MALE
FRACTURE TYPE	NON-UNION
FRACTURE LOCATION	LEFT FEMUR
REASON OF FRACTURE	ACCIDENTLY FALLING DOWN

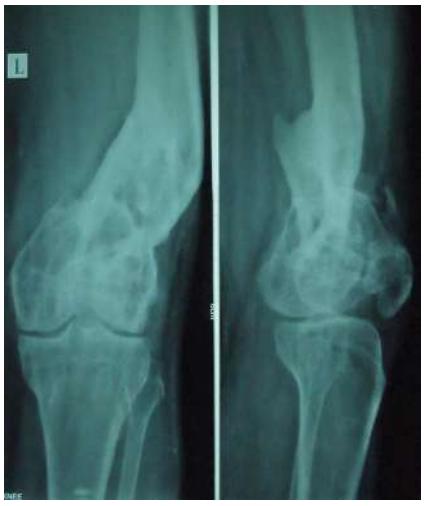
Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 3 to 8
Visual Analogue Scale (VAS) score reduced from 8 to 1







Pre -op X-ray



Post-op X-ray 7 years

Pre- Operative X-ray

- Comminuated Fracture of Distal 1/3 rd Femur shaft with fractured Nail is seen.
- Significant Gap at fracture site is seen.

Post- Operative X-ray

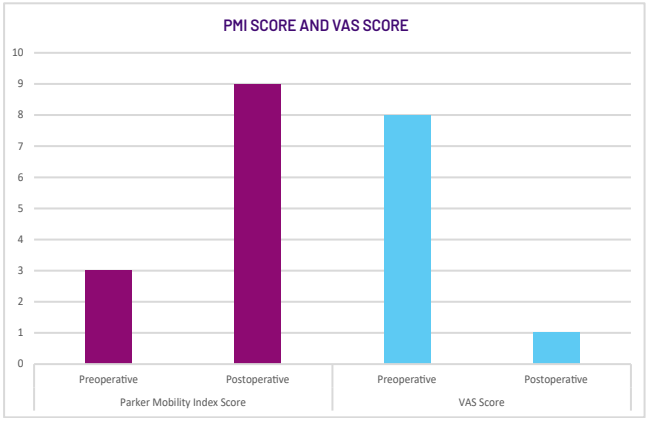
- Remodeled Callus at Distal 1/3 rd shaft Femur is seen.
- mRU score is 12.

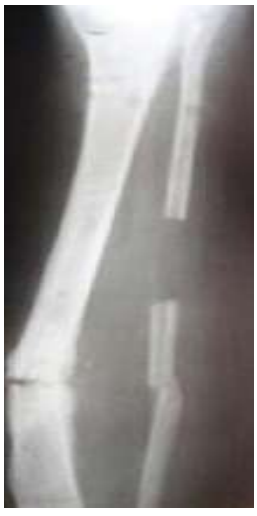
We thank Dr.Durious Soonawal and team for sharing this case report.

PATIENT 5

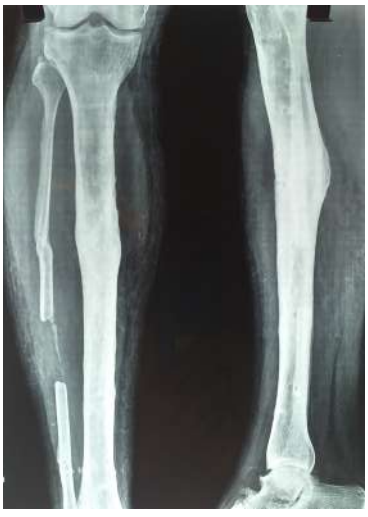
AGE	35
GENDER	MALE
FRACTURE TYPE	NON UNION
FRACTURE LOCATION	RIGHT DISTAL TIBIA
REASON OF FRACTURE	BIKE ACCIDENT

Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 3 to 9
Visual Analogue Scale (VAS) score reduced from 8 to 1





Pre -op X-ray



Post-op X-ray 7 Years

Pre- Operative X-ray

- Transverse Fracture of mid-leg femur is seen.

Post- Operative X-ray

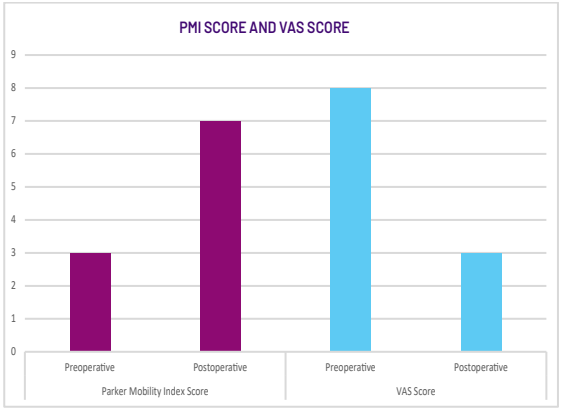
- Remodeled callus at mid shaft femur is seen.
- mRU score is 12.

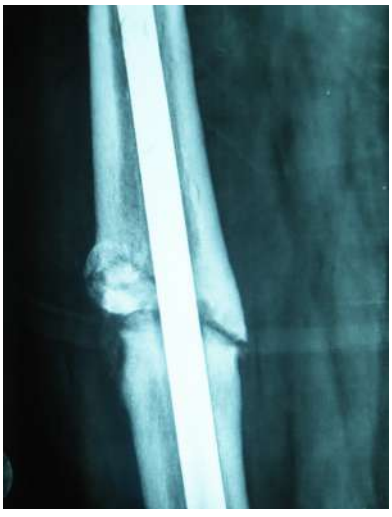
We thank Dr.R.G. Khedekarand team for sharing this case report.

PATIENT 6

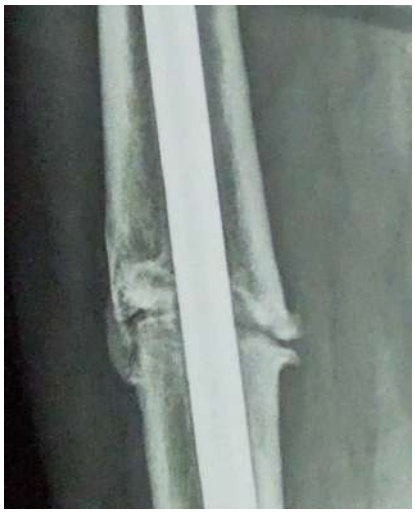
AGE	53
GENDER	MALE
FRACTURE TYPE	NON UNION INFERTION
FRACTURE LOCATION	FIBULA FRACTURE, RIGHT LEG

Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 3 to 7
Visual Analogue Scale (VAS) score reduced from 8 to 3





Pre -op X-ray



Post-Op X-ray 6 Years

Pre- Operative X-ray

- Transverse non-union fracture of mid shaft femur is seen.
- Gap is 1 cm.
- Intramedullary Nail in-situ is seen.

Post- Operative X-ray

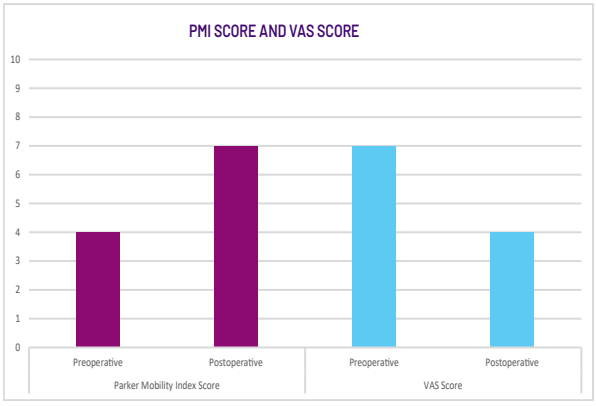
- Bridging callus at lateral side of mid shaft femur is seen.
- callus at lateral cortex is seen.
- mRU score 8.

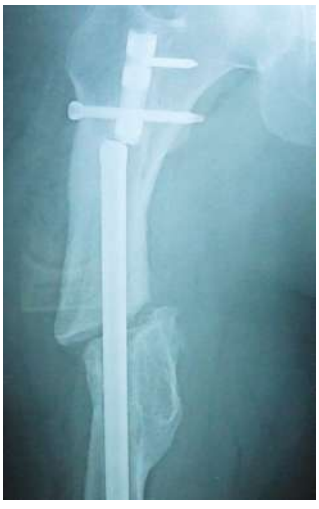
We thank Dr. R.G. Khedekar and team for sharing this case report.

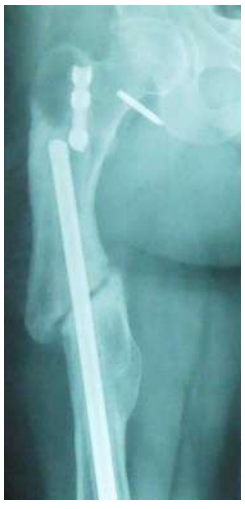
PATIENT 7

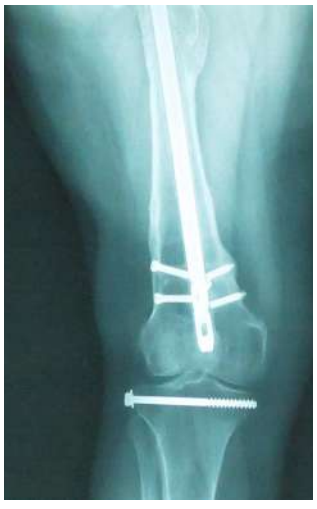
AGE	31
GENDER	MALE
FRACTURE TYPE	NON UNION
FRACTURE LOCATION	RIGHT FEMUR

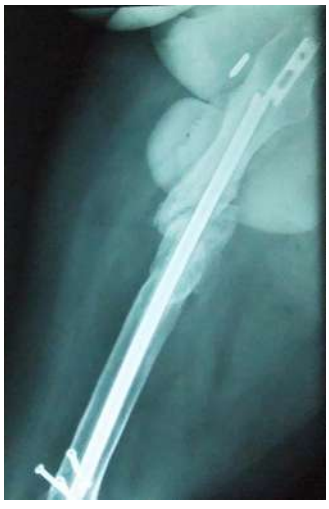
Post Ossgrow® treatment:
Parker Mobility Index (PMI) score improved from 4 to 7
Visual Analogue Scale (VAS) score reduced from 7 to 4











Pre-op X-ray

Post-Op X-ray 4 years

Pre- Operative X-ray

- Non Union of Oblique fracture of proximal shaft femur is seen.
- Intra-medullary Nail in situ is seen.
- Gap is 1.5 cm.

Post- Operative X-ray

- Ossifying Remodeled callus at proximal shaft Femur is seen.
- Intra-medullary Nail in situ is seen.
- mRU score-12.

We thank Dr. Sridhar mustyala and team for sharing this case report.

5. SUMMARY

- Limitations in current treatments for non-union fractures creates a need for an effective solution for long-term bone healing.
- Implantation of autologous adult live cultured osteoblasts achieves 3-dimensional bone union proves to be a successful alternative.
- Patients reported significant decrease in pain and were able to return to their daily routine activities.
- Thus, OSSGROW® has clinically demonstrated to be a safe treatment and effective in new bone formation.

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