General

State of the Nonunion: A review of the latest literature

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The distinction between prolonged bone healing and nonunion in long bone fracture remains a historical challenge in the field of orthopedics. Despite numerous proposed definitions and scoring systems, a consensus remains elusive, thereby complicating both diagnosis and treatment. An accurate diagnosis is necessary, facilitated by a range of imaging modalities. Bone nonunion management encompasses surgical and non-surgical options, including external or internal fixation, and bone grafting, tailored to the nonunion type. This review discusses the pathophysiology of nonunion, risk factors, diagnosis and treatment. It particularly addresses early detection and the impacts of nonunion on the patient. The aim of this review is to obtain a global and updated point of view regarding nonunion of the bone as well as to reflect on the potential use of untraditional methods in their treatment such as orthobiologics, along with emerging and non-invasive technologies including shockwave therapy, gene therapy, tissue engineering, regenerative medicine and 3D printing

DEFINITION

There is a historical challenge in distinguishing between prolonged healing and nonunion in long-bone fractures, dating back to 1847, which remains a persistent issue in orthopedics. Despite substantial progress in understanding the pathophysiology, diagnosis, and treatment of these conditions, there is a notable absence of a universally accepted definition for nonunion.[1]

One widely accepted standard definition, proposed by the FDA in 1998, mainly focuses on the time interval between the occurrence of a fracture and nonunion (a minimum of nine months without signs of healing for three months). Unfortunately, this definition lacks sufficient detail on the characteristics of bone healing, both radiologically and clinically, which poses a significant limitation.[2]

In a more recent development, the Danish Orthopedic Trauma Society put forth a concise and pragmatic interpretation of nonunion as "a fracture that will not heal without further intervention."[3] However, the challenge lies in describing the fracture characteristics that would prompt a clinician to conclude that healing will not occur without additional intervention.

While nonunion definitions remain elusive, established classifications guide the treatment and grading of nonunion. The Weber and Cêch classification, founded in 1976, assesses nonunion fragments' vitality and biological reactivity through radiographic evaluation, and this system splits nonunions into three categories.[4]

- Hypertrophic: Showing an abundant callous formation without union, signifying instability but a favorable biological response.
- Atrophic: Displaying minimal or no callous formation, indicating an unfavorable biological healing response.
- Oligotrophic: Demonstrating incomplete callous formation, bridging the gap between hypertrophic and atrophic cases.

PATHOPHYSIOLOGY OF NONUNION

Upon sustaining trauma, the body generates a hematoma at the fracture site, inciting the recruitment of cells. Consequently, the inflammatory response is initiated, causing coagulation of the hematoma at the ends of the fracture as a template for the formation of callus.[5] Inflammation is initiated by cells of the monocyte-macrophage system, fighting off the initial stimulus.[6] However, this process is further modulated for bone repair and remodeling. Additionally, specific derivatives from the multipotent mesenchymal stem cells (MSCs) are needed, including osteoblasts and chondrocytes.[6] After migration of MSCs to the injury site, they differentiate into osteoblasts, capable of secreting the bony matrix and inducing bone mineralization, thereby depositing new bone tissue.[7] Osteoblasts also play a role in bone remodeling, by either undergoing apoptosis or incorporating into the matrix through alkaline phosphatase calcification to become osteocytes.[6] Osteocytes are the main

cells regulating mineral metabolism in bone. This process of remodeling necessitates a balance between osteoclast-driven hard callus resorption and osteoblast-driven lamellar bone deposition.[5] Osteoclasts are responsible for resorption of bony matrix through acidic decalcification and proteolytic dissolution.[6]

Growth factors and cytokines promote cellular proliferation, differentiation, and ECM synthesis, accelerating the process of healing. These include platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), insulin-like growth factor, and bone morphogenetic protein (BMP).[6-8] In addition, cytokines, including interleukin-6 (IL-6), IL-1, and tumor necrosis factor alpha (TNF-α), are responsible for stimulating MSC migration to initiate the healing process.[6]

Dysregulation of the processes described above leads to the phenomenon of nonunion of bone. Finally, the process of neo-angiogenesis is essential to avoid bone nonunion.[6] It is mediated through vascular endothelial growth factor interactions with BMPs.[9] Consequently, the deficient supply of nutrients, oxygen, and other essential factors leads to abnormal bone healing and a high risk of nonunion.

RISK FACTORS

Gender: Nonunion occurs more frequently in the older female population, which is believed to be caused by the reduced levels of estrogen post-menopause, altering bone formation, since estrogen promotes anabolic processes stimulation and catabolic processes inhibition.[10]

Age: Children's periosteum is well vascularized and rich in osteoblasts, promoting faster bone regeneration and higher fracture union rates.[10]

Nutrition: Nutritional shortages appear to have the greatest impact on the later stages of bone callus development. However, fracture union is not significantly delayed by a lack of nutritional support.[10]

Diabetes: Patients with diabetes have been found to have a definite decrease in the production of collagen in the bone callus and a notable decrease in the number of cells necessary for the repair process. Patients who are receiving insulin therapy and have well-controlled diabetes are at lower risk.[10]

Osteoporosis: Osteoblast production is decreased, which also affects the formation of calluses. Osteoporosis treatment must start as soon as possible.[10]

Smoking: One of the most frequently addressed modifiable risk factors that hinders normal bone regeneration. It reduces the bone's vascular supply and is linked to higher parathyroid hormone (PTH) levels and vitamin D insufficiency. Additionally, nicotine is thought to reduce osteoblast activity in a dose-dependent way.[10]

NSAIDs: These contribute to the decline in osteoblastic activity and prevent the production of prostaglandins, which delays the development of bone callus. However, the likelihood of nonunion development may not be significantly affected by the brief use of NSAIDs for pain relief. Long-term use does significantly increase the likelihood of nonunion.[11]

Mechanism of trauma: Nonunion is infrequent in low-energy trauma due to the relatively small amount of hematoma at the fracture site, the more stable fracture pattern, and the minimal injury to the periosteum and soft tissues.[12]

Malalignment: Nonunion and malunion have been linked to unsatisfactory fracture reduction. Surgical revisions are needed for managing malalignment in the treatment of nonunion.[12]

Infection: Even in the absence of a direct clinical presentation, infection must be suspected for individuals with fracture nonunion, particularly in patients who suffered open fractures and those who underwent open surgery.[12]

Interfragmentary movement (IFM): High IFM, large fragmentary gap, high tissue strain, and transverse shearing movements impair routine bone healing.[12]

IMAGING MODALITIES IN NONUNION FRACTURES

Traditional methods for evaluating fracture healing often rely on sequential X-rays to track callus formation and the disappearance of the fracture line. However, this approach has drawbacks, including inconsistent definitions of healed fractures among orthopedic surgeons and the limitations of two-dimensional X-ray images, especially in the presence of metal implants. Detecting callus formation may take 6 to 8 weeks, and the reliable indicator of union, the cortical callus bridge, often becomes visible only after three months.[13]

Computed Tomography (CT) scanning is increasingly used to evaluate bridging callus in the late stages of healing and confirm union. It provides high-resolution multi-planar imaging, especially when visualization is difficult due to trauma implants.[13]

Magnetic Resonance Imaging (MRI) is useful for detecting deep collections, atypical inflammation, and sinus tracts in bone and soft tissue. It may also be able to evaluate the vascularity of nonunion sites, with potential applications in predicting successful union.[13]

Ultrasound has shown promise in monitoring fracture healing by detecting early callus formation, particularly in non-operatively managed fractures. It is cost-effective, does not involve ionizing radiation, and may become increasingly popular as evidence for its effectiveness emerges.[13]

An article authored by Gandhi and Rabadiya explored the utility of bone scans in evaluating biological activity in nonhypertrophic fracture nonunions. The authors introduce scintigraphic uptake patterns to aid in treatment decisions, particularly the use of autologous bone grafting for cases displaying photon-deficient areas.[14] Moreover, Liodakis and colleagues conducted an initial retrospective inquiry into the utility of single photon emission computed tomography (SPECT) for diagnosing and strategizing treatment for atrophic nonunions affecting the upper and lower extremities. This yielded a sensitivity of 50% and a specificity of 100%.[15]

TREATMENT STRATEGIES

The initial management of any bone nonunion consists of immobilizing the fracture for a prolonged time or applying external bone stimulation, such as pulsed low-intensity ultrasound, regardless of the nonunion site. On the other hand, operative treatment is tailored to the type of nonunion.[16] In general, the goal of surgical intervention is to achieve a healed bone that is pain-free and has the highest functionality.[17]

Two requirements should be met for the successful treatment of nonunion. First, mechanical stability, which is achieved with internal or external fixation. Second, enhancing the biological milieu with bone grafting to stimulate fibrocartilaginous callus formation to complete the healing process.[18] For atrophic nonunion, treatment aims at restoring the local biology and mechanical stability with local debridement of the nonunion area, bone grafting, and replacing or modifying the implants' length and thickness. Hypertrophic nonunion is treated with surgical excision of the hypertrophied zone and replacing or modifying the implant. In cases of infection, treatment occurs in a stepwise fashion. First, all implants should be removed, followed by local excision and debridement, with specimens sent for culture and pathology. Then, an external fixator may be used for initial stability, and antibiotic therapy is indicated. Once eradication of the infection is confirmed, permanent fixation is performed using the appropriate implant.[19] Neumann et al. discuss the "diamond concept" scheme of treatment, which is reported to have a 100% success rate. It includes four components: 1) debridement; 2) stimulation of callus formation with grafting; 3) improvement of the mechanical environment; and 4) improvement of the biological and cellular environment with osteoinductive components.[19]

BONE GRAFTING

Due to the complex factors that contribute to nonunion, multiple types of grafts may be used to target the primary cause and promote bone healing. The types of grafts include autogenous fresh cancellous bone, cortical bone, and free vascular grafts.[18] These include allografts (cortical, corticocancellous, or cancellous bone), autogenous grafts (iliac crest bone graft, iliac crest aspirate, or intramedullary bone graft), and various biologic substitutes, recombinant bone morphogenetic protein, and demineralized bone matrix.[20] Bone grafts are used for the treatment of various conditions, and their success relies on an adequately vascularized host bed. Vascularized bone grafts, with an intrinsic blood supply, accelerate the healing process and have a higher success rate. Thus, they are the grafts of choice in cases of decreased blood supply. Vascularized grafts are classified according to different factors: their structure, size, donor site, need for anastomosis, and combination with other tissues. Vascularized allografts promote an early cell-mediated and humoral immune response, which provides advantages in treating large bone defects and decreases complication risks.[18]

Iliac crest bone grafts remain the benchmark for the treatment of nonunion regardless of age.[20] While autologous bone graft is the preferred type of grafting, its major disadvantage is the morbidity that results from harvesting. Alternatively, medullary bone graft can be acquired with the reamer/irrigator/aspirator (RIA) technique from reaming long bones, with similar results to standard autologous grafting.[21]

INTERNAL FIXATION

Internal fixation of non-unions is achieved with plate and screw osteosynthesis, or Internal fixation of nonunions is achieved with plate and screw osteosynthesis or intramedullary implants. It is suitable for the treatment of most cases. Several studies have been conducted to assess the success rate of internal fixation for different fractures and nonunions. Plate fixation is the treatment of choice for clavicle nonunion after conservative management, and recent studies found that bone grafting is not necessary in the majority of cases. Since most humeral shaft nonunions are atrophic, the preferred treatment is plating with bone grafting. The majority of tibial or femoral diaphyseal fractures are treated with intramedullary nailing. If aseptic nonunion occurs, exchange nailing is the preferred management and is believed to be superior to dynamization if comminution or persistent fracture gap is present from the primary procedure. In cases of septic femoral nonunions, novel intramedullary nails with antibiotic coating are now available as an alternative to the staged approach.[21]

EXTERNAL FIXATION

External fixation is utilized for definitive stabilization of nonunion in about 50% of cases and rises to 90% in infected cases. It may also be used intraoperatively as an aid for reestablishing anatomical alignment and length.[22] The use of external fixators is associated with minimal soft tissue disruption and provides fracture control while preserving periosteal and medullary blood supply to the nonunion site. They provide multiaxial stability while minimizing strain at the fracture site, which is critical for bone healing. They are particularly advantageous in treating infected nonunions because they limit the surface area and hinder biofilm formation, preventing intramedullary bacterial dissemination, aiding in soft tissue healing following debridement, and providing fixation when the treatment plan is set to occur in multiple stages.[22] While the benefits of external fixation are numerous, disadvantages still exist, including long periods of treatment, risk of pin-track infections (with an incidence rate of 55% to 100%), and noncompliance.[22]

ORTHOBIOLOGICS IN TREATMENT OF NONUNION

A proper understanding of the healing process of fractures has allowed scientists and researchers to propose the use of orthobiologics as potential agents for the treatment of nonunion. These include platelet-rich plasma (PRP), bone

morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose-derived stem cells (ASCs), and induced pluripotent stem cells (iPSCs), among others.[23]

Growth factors such as platelet-derived growth factor (PDGF), TGF-beta 1, and IGF-1 have shown increasing promise in treating nonunion.[22] Street et al found decreased PDGF levels in the fracture hematoma of patients older than 75 years compared with patients younger than 40.[24]

The use of orthobiologics to increase local growth factor concentrations has also been studied extensively, with Ghandi and colleagues finding a 4-fold increase in PDGF, a 3-fold increase in TGF-β1, a 3-fold increase in VEGF, and a 1.5-fold increase in IGF-I expression after local PRP injections in diabetic rats at fracture sites.[25] The use of recombinant human BMP-2 (rhBMP-2) in a diabetic rat segmental defect model was found to yield significant increases in bone formation on histology at the 3-week and 6-week time points and increased radiographic healing at 6 weeks, as well as increased angiogenesis compared to control groups.[26] With BMP already approved for use in tibial nonunions, it has major potential as a treatment modality for nonunion of other long bones.[23]

PRP has been studied extensively for its potential use to enhance bone healing since alpha granules of platelets contain growth factors, cytokines, VEGF, PDGF, and even metalloproteases, while γ-granules release ATP, ADP, and calcium, which all increase cellularity and promote bone healing.[27] Mesenchymal stem cells are another potential therapeutic modality for nonunion due to their ability to differentiate into various cell types. While clinical evidence for their use in the treatment of nonunions is limited, their potential is undeniable. Another factor accentuating their potential is their ability to suppress fibrosis and apoptosis.[27]

NEW TECHNOLOGY IN THE TREATMENT OF NONUNION

Various emerging technologies have been developed to improve fracture nonunion treatment outcomes. Low-Intensity Pulsed Ultrasound (LIPUS) therapy is a noninvasive and cost-effective treatment option that involves the application of low-intensity, high-frequency sound waves to the affected area, stimulating bone growth and accelerating the healing process. It has been shown to accelerate healing by increasing the production of cytokines and growth factors, like bone morphogenetic proteins (BMPs) and vascular endothelial growth factor (VEGF), that promote bone regeneration and healing.[28-30] Moreover, LIPUS has also been found to have antibacterial[21] and anti-inflammatory effects,[22] reducing the risk of infection and inflammation at the site of a bone nonunion.[23-34] It can be used alone or in combination with other treatments such as surgery or bone grafting, depending on the severity and location of the nonunion.

Extracorporeal Shockwave Therapy (ESWT) is a non-invasive treatment that utilizes high-energy sound waves to stimulate bone healing. Studies have shown its effectiveness in promoting fracture healing by enhancing angiogenesis, increasing growth factor expression, and stimulating osteogenesis.[35]

Gene therapy and tissue engineering can be alternative treatment modalities. By introducing specific genes, such as those encoding bone morphogenetic proteins (BMPs) or vascular endothelial growth factors (VEGF), gene therapy aims to enhance the body's natural healing processes. Jones et al. in 2016 showed that the development of scaffolds that mimic the extracellular matrix can be seeded with osteogenic cells and growth factors to promote bone formation.[36]

Stem cell therapy holds great promise in the treatment of fracture nonunion. Mesenchymal stem cells (MSCs), derived from various sources, such as bone marrow or adipose tissue, have shown the ability to differentiate into bone-forming cells and promote fracture healing.[37]

Another promising technology used in the treatment of bone nonunion is 3D printing. In this context, it allows for the creation of patient-specific implants and scaffolds tailored to the individual's anatomy that can provide mechanical stability and promote bone regeneration.[38]

COMPLICATIONS OF TREATMENT

Surgical site infection (SSI) may result in permanent functional loss or even amputation of the affected limb in patients who may otherwise be expected to achieve complete, uneventful healing.[39] Infection rates may range from as low as approximately 1% after operative fixation of closed low-energy fractures to more than 30% in complex open tibia fractures.[40]

Infected non-unions present two interrelated orthopedic problems: deep bone infection and a failure of fracture healing.[41] Various strategies exist to address these issues[42]:

- Treat the fracture and then the infection definitively (antibiotic suppression with removal of metalwork following fracture union).
- Treat the infection definitively and then the fracture (excision of the non-union and secondary bone transport or the Masquelet technique).
- Address both simultaneously (acute shortening).
- Neither specifically: (amputation).

PREVENTION AND EARLY DETECTION

Prevention of non-union resides not only in early detection but also in obtaining a good fracture reduction while maintaining a favorable environment for bone healing and vascularity. However, the assessment of fracture healing remains, to this day, a subjective tool for even the best clinicians. Fracture union can be assessed clinically and radiographically. For clinical examination, the fracture site is evaluated for

IMPACTS OF NON-UNION

A retrospective cohort study conducted in Australia from January 2007 until December 2013 included 3,886 fracture patients. Within 2 years of the initial admission, 315 patients (8.1%) needed to be readmitted for fracture healing complications. The primary cause for readmission was nonunion (6.8%, 264 patients).[43] Kanakaris and Giannoudis calculated a "best-case scenario" cost identification, meaning the cost using a gold standard method of treatment, minimal antibiotic prophylaxis of 3 doses, a standard period of thromboprophylaxis, a standard number of outpatient visits and investigations, and a minimum number of physiotherapy sessions. The overall cost per patient suffering from a fracture non-union was estimated at around £15,566 for a humeral pseudarthrosis, with the cost increasing to £16,330 for a tibial non-union and reaching £17,000 for a femoral pseudarthrosis.[44] In the US, the median cost of treating fracture non-unions has been estimated at $25,556 USD per open tibial fracture, doubling that of patients without a nonunion, as well as a more frequent healthcare resource use and increased consumption of opioids and NSAIDs.[45]

It can be safely said that not only is non-union difficult to treat, but it also imposes an important financial burden in terms of direct and indirect costs. Indirect costs, such as loss of productivity and impairment of function, are the key drivers of the overall financial burden of non-unions. Zeckey et al. found that, when compared to patients with uneventful fracture healing, patients with tibial and femoral non-union had worse physical and mental health, as well as an increased need for medical aids such as crutches and wheelchairs. Moreover, patients with femoral non-union had significantly higher rates of early retirement and unemployment.[46] Similarly, in 2014, Wichlas et al. evaluated the long-term effects of tibial non-unions on patients' quality of life with a mean follow-up of 5 years after treatment. Patients with tibial non-union were found to have a substantial decrease in their quality of life, mainly due to increased pain and limitations in function, as well as physical health-related and emotional problems.[47] Lower limb non-unions were also linked to increases in morbidity and damage to physical, emotional, and mental health.[48,49] Some studies highlighted the effects of non-union and impaired mobility on low mood and suicidal thoughts.[49,50]

It is unquestionable that collaborative work between clinicians, radiologists, orthopedic surgeons, and physiotherapists is crucial in treating a non-union of the bone. However, all these arguments favor a multidisciplinary approach in the management of non-union, including the implementation of psychological support along with early detection of psychiatric distress in this category of patients. The strategies of treatment should aim to reduce healing time and favor a rapid resumption of activities to not only improve the medical outcome for the patient but also to reduce the financial burden in fracture non-union patients.

CONCLUSION

Various definitions and scoring systems have been suggested for non-union, but no consensus has been achieved, complicating its diagnosis and treatment. The management of nonunion heavily relies on understanding the intricate cellular and molecular processes of bone healing, highlighting the need for targeted therapy. An accurate diagnosis is necessary, with various imaging modalities. Bone nonunion management includes surgical and non-surgical options. As we delve deeper into the intricacies of cellular and molecular interactions, the precision of tissue engineering approaches is poised to improve, bringing us closer to the goal of restoring bone integrity with unprecedented efficiency. Ongoing investment in research and development is crucial to refine these approaches, ensuring their safety, efficacy, and accessibility to patients worldwide.

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