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Factors Influencing Nonunion of Fractures and Research Progress in Their Treatment

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Abstract

This article focuses on the factors influencing fracture nonunion, classification and treatment. The article emphasizes the importance of understanding the influencing factors and mechanisms of fracture healing for developing effective treatment strategies and improving patients' quality of life. It also points out the challenges of current treatment, such as patient compliance and limitations of treatment methods, and looks at future treatment directions.

Keywords

Nonunion of Fractures, Research Progress, Influencing Factor

1. Introduction

Fracture healing is a critical process that restores the integrity and function of broken bones. Proper healing ensures that individuals can return to their normal activities without long-term disability or pain. The healing process involves several stages, including inflammation, soft callus formation, hard callus formation, and remodeling [1]. Each stage is essential for the successful restoration of bone structure and function.

Nonunion, on the other hand, is a serious complication where the bone fails to heal properly, leading to persistent pain, disability, and the need for additional medical interventions. Nonunion can occur due to various factors, such as inadequate blood supply, infection, poor nutrition, and mechanical instability [2]. It often requires surgical intervention to achieve healing, which can be costly and time-consuming.

Understanding the factors that influence fracture healing and the mechanisms behind nonunion is crucial for developing effective treatment strategies and improving patient outcomes. By addressing these factors, healthcare providers can better manage fractures and reduce the incidence of nonunion, ultimately enhancing the quality of life for patients.

The purpose of this article is to introduce the influencing factors and treatment methods of bone nonunion, so that clinicians can better use new methods to solve the clinical problems of bone nonunion.

2. Definition and Classification

2.1. Definition

Nonunion refers to a failure of a fractured bone to heal properly after a significant period, usually several months [3]. This condition occurs when the normal biological processes of bone healing are disrupted or impaired, leading to the absence of bone union at the fracture site.

2.2. Classification of Nonunion

Nonunion can be classified into several categories based on the biological activity and the radiographic appearance of the fracture site:

1) Hypertrophic Nonunion [4] is characterized by abundant callus formation around the fracture site. It is typically caused by inadequate stabilization or excessive movement at the fracture site. Radiographic appearance usually Shows significant callus formation but no bridging bone across the fracture.

2) Atrophic Nonunion [4] is marked by a lack of callus formation and poor biological activity at the fracture site. It is often due to poor blood supply, infection, or severe soft tissue damage. Radiographic appearance usually Shows minimal or no callus formation, with the fracture ends appearing atrophic or tapered.

3) Oligotrophic Nonunion [4] shows limited callus formation and poor biological activity, falling between hypertrophic and atrophic nonunion. It can result from inadequate reduction and fixation or a combination of factors. Radiographic appearance usually Displays minimal callus and incomplete healing.

4) Septic Nonunion [5] is nonunion associated with an infection at the fracture site. It is due to contamination during injury or surgical intervention. Radiographic appearance: usually may show signs of infection, such as osteomyelitis, along with nonunion characteristics.

3. Factors Influencing Nonunion of Fractures

Nonunion of fractures occurs when a broken bone fails to heal properly within the expected time frame. Several factors can influence the likelihood of nonunion:

3.1. Biological Factors

Patient Health and Comorbidities: Conditions such as diabetes, osteoporosis, rheumatoid arthritis, and vascular diseases can impair the body's natural healing processes [6].

Genetic Factors: Genetic predisposition can affect bone healing capabilities, influencing the likelihood of nonunion.

Nutrition: Adequate intake of vitamins and minerals, particularly calcium, vitamin D, and protein, is essential for bone health. Nutritional deficiencies can delay or prevent proper healing.

3.2. Mechanical Factors

Fracture Type: High-energy fractures (e.g., from car accidents) and open fractures (where the bone breaks through the skin) are more prone to nonunion due to the severe damage and increased risk of infection [7].

Fracture Location: Certain bones, such as the tibia and femur, are more susceptible to nonunion due to their load-bearing nature and blood supply [8].

Stability and Fixation: Proper alignment and stabilization of the fracture is crucial. Inadequate fixation or excessive movement at the fracture site can impede healing.

Infection: The presence of infection at the fracture site can significantly hinder the healing process, leading to nonunion.

3.3. Lifestyle Factors

Smoking: Nicotine and other chemicals in cigarettes can restrict blood flow, reduce oxygen supply to the bone, and impair the healing process.

Alcohol Use: Excessive alcohol consumption can interfere with bone metabolism and delay healing.

Physical Activity: Both excessive immobilization and inappropriate physical activity can affect fracture healing. Controlled and appropriate physical activity is beneficial for bone regeneration.

These factors can interact in complex ways, making the management of fractures and prevention of nonunion a multifaceted challenge. Addressing these factors through proper medical management, patient education, and lifestyle modifications is essential for promoting successful bone healing and reducing the risk of nonunion.

4. Current Treatment Strategies for Nonunion

4.1. Non-Surgical Treatments for Nonunion

4.1.1. Bone Stimulation

Electrical Stimulation: Uses low-level electrical currents to stimulate bone growth. The currents can enhance the activity of bone-forming cells, promote blood flow, and accelerate healing.

Ultrasonic Stimulation: Utilizes low-intensity pulsed ultrasound waves to stimulate bone regeneration. This method is non-invasive and can be applied externally to the fracture site to encourage healing.

4.1.2. Pharmacological Interventions

Bone Growth Stimulators: Medications such as bone morphogenetic proteins (BMPs) and other osteoinductive agents can be used to promote bone formation and healing.

Anti-Inflammatory Drugs: These medications can reduce inflammation around the fracture site, creating a more favorable environment for bone healing.

4.1.3. External Fixation Devices

Bracing and Splinting: Non-invasive methods that provide stability to the fracture site, allowing the bone to heal properly. These devices can be adjusted as needed to maintain proper alignment and support.

4.1.4. Physical Therapy

Controlled Exercise: Guided physical therapy exercises can help stimulate bone healing by promoting blood flow and maintaining muscle strength around the fracture site. This approach must be carefully monitored to avoid excessive stress on the healing bone.

4.2. Surgical Treatment of Bone Nonunion

4.2.1. Internal Fixation

Plates and Screws: Metal plates and screws are used to stabilize the fracture by holding the bone fragments together. This provides the necessary stability for the bone to heal properly.

Intramedullary Nails: A metal rod is inserted into the marrow canal of the bone to provide internal support. This method is commonly used for long bone fractures, such as the femur or tibia.

4.2.2. Bone Grafting (Figure 1)

Autografts: Bone is harvested from the patient's own body, usually from the iliac

2152997	Source	Advantages	Disadvantages	Common Uses
Autografts	Patient's own bone	No immune rejection, rich in growth factors	Donor site pain and complications	Primarily used for spinal fusion, bone defect repair
Allografts	Donor or cadaver bone	No need for autograft surgery, abundant resource	Possible immune rejection, risk of infection	Used for large bone defect repair, reconstructive surgeries
Xenografts	Animal bone (usually bovine or porcine)	Abundant supply, no donor site surgery	High risk of immune rejection, complex processing	Used in dental implants, bone repair
Synthetic Grafts	Artificial materials	Customizable shapes,no immune rejection	Limited bioactivity, lacks all properties of natural bone	Used for bone defectfilling, support structures
Composite Grafts	Combination of materials	Combines advantages of multiple materials, improves bone regeneration	Complex preparation,high cost	Suitable for bone repairs needing extra strength and bioactivity

Figure 1. Sources of several different bone grafts and their advantages and disadvantages.

crest (hip bone), and transplanted to the fracture site. This type of graft has the advantage of being highly compatible and reducing the risk of rejection.

Allografts: Bone is obtained from a deceased donor or cadaver and transplanted to the fracture site. It undergoes processing to reduce the risk of immune rejection and infection.

Synthetic Grafts: Man-made materials, such as ceramics, polymers, and bioactive glass, are used to fill gaps in the bone and promote healing.

4.2.3. Use of Growth Factors

Bone Morphogenetic Proteins (BMPs): BMPs are applied to the fracture site to stimulate bone formation and accelerate healing. They are proteins that naturally occur in the body and have osteoinductive properties.

Platelet-Derived Growth Factor (PDGF): PDGF is used to attract and stimulate cells necessary for bone healing.

5. Research Progress and Innovations in Nonunion Treatment

5.1. Advancements in Biological Approaches for Fracture Healing

5.1.1. Stem Cell Therapy

Stem cell therapy has shown great promise in enhancing fracture healing. **Mesenchymal stem cells (MSCs)** are particularly effective due to their ability to differentiate into bone-forming cells (osteoblasts) and their capacity to modulate the local inflammatory environment. Recent research has focused on improving the homing abilities of MSCs to the injury site and enhancing their osteogenic potential.

1) Mesenchymal Stem Cells (MSCs) Types

MSCs can be derived from various tissues, including:

- **Bone Marrow:** The most common source, known for its high differentiation potential.
- **Adipose Tissue**: Easily accessible and abundant, with similar differentiation capabilities.
- **Umbilical Cord Blood:** Contains a high number of MSCs and is less invasive to collect.
- **Dental Pulp**: A newer source with promising regenerative potential.

2) Delivery Methods

The delivery of MSCs can be done through several methods:

- Intravenous (IV) Infusion: MSCs are administered directly into the bloodstream, allowing them to travel throughout the body and target areas of inflammation or injury through a process called homing.
- Intraarticular Injection: MSCs are injected directly into a joint, such as the knee or shoulder, to help regenerate cartilage and reduce inflammation in conditions like osteoarthritis.
- Intramuscular Injection: MSCs are injected into muscle tissue, which can be useful for treating muscle injuries or degenerative conditions.
- Subcutaneous Injection: MSCs are injected under the skin, which can be used for various therapeutic purposes, including wound healing and tissue repair.

3) Clinical Trial Results

Recent clinical trials have shown promising results for MSC therapy in bone nonunion:

- **Phase III Clinical Trial**: A study involving autologous CD34+ cell transplantation showed a significant reduction in healing time for tibia and femur nonunion patients. The time to radiological fracture healing was 2.8 times shorter compared to historical controls, with no safety concerns observed.
- **Systematic Review**: A review of multiple studies found that MSC therapy can enhance bone healing, although results were heterogeneous due to varying study designs and patient populations [9].
- **Pilot Clinical Trial**: A phase I/IIa trial using granulocyte colony-stimulating factor-mobilized $CD34^+$ cells with an atelocollagen scaffold showed radiological healing in 71.4% of patients within 12 weeks, with no life-threatening adverse events [3].

5.1.2. Tissue Engineering

Tissue engineering combines scaffolds, cells, and bioactive molecules to create an environment conducive to bone regeneration. Bioactive scaffolds provide a three-dimensional structure that mimics the extracellular matrix of bone, promoting cell adhesion and differentiation. Growth factors like bone morphogenetic proteins (BMPs) and vascular endothelial growth factors (VEGFs) are often incorporated to stimulate bone cell recruitment and angiogenesis.

5.1.3. Gene Therapy

Gene therapy involves the delivery of specific genes to the fracture site to promote bone healing. Bone morphogenetic proteins (BMPs) are commonly used genes due to their osteoinductive properties. Recent advancements include the use of viral and non-viral vectors to ensure sustained gene expression and targeted delivery. Combining gene therapy with tissue engineering has shown potential in treating large segmental bone defects and nonunion fractures.

5.2. Technological Advances

5.2.1. 3D Custom Printing for Bone Nonunion

3D printing technology has revolutionized the field of bone tissue engineering by enabling the creation of customized scaffolds that support bone regeneration. The choice of materials for these scaffolds is crucial, as it affects their biocompatibility, mechanical properties, and degradation rates. Here are some commonly used materials and their impact on bone healing:

- **Bio ceramics**

Bio ceramics, such as hydroxyapatite (HA) and tricalcium phosphate (TCP), are widely used due to their excellent biocompatibility and similarity to natural bone minerals. They promote osteoconduction, providing a scaffold for bone growth. However, their brittleness can be a limitation.

- **Metals**

Metals like titanium and its alloys are known for their high strength and durability. They are often used in orthopedic implants to provide mechanical support. Recently, biodegradable metals such as magnesium, calcium, zinc, and iron have gained attention. These metals can gradually degrade in the body, reducing the need for a second surgery to remove the implant.

- **Natural Polymers**

Natural polymers, such as collagen and gelatin, are biocompatible and promote cell attachment and proliferation. However, they often lack the necessary mechanical strength for load-bearing applications.

- **Synthetic Polymers**

Synthetic polymers, like polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA), offer tunable mechanical properties and degradation rates. They can be combined with other materials to create composite scaffolds that balance strength and biocompatibility.

Impact on Bone Healing

The choice of 3D printing material significantly impacts bone healing. Bio ceramics and biodegradable metals provide excellent support and promote bone growth, while natural and synthetic polymers offer flexibility in scaffold design. Composite materials that combine these properties can offer the best of both worlds, enhancing bone regeneration and mechanical stability

5.2.2. Minimally Invasive Surgical Techniques

Minimally invasive surgical techniques aim to reduce surgical trauma and improve recovery times. These methods involve smaller incisions and specialized instruments to access and treat the fracture site with minimal disruption to surrounding tissues. Examples include:

Percutaneous Screw Fixation: Involves inserting screws through small incisions to stabilize the fracture.

Sacroplasty: A minimally invasive procedure used to treat sacral nonunion by injecting bone cement into the sacrum to provide stability and pain relief.

Combining 3D custom printing with minimally invasive techniques can significantly enhance the treatment of bone nonunion, leading to better outcomes and improved patient recovery.

6. Challenges and Future Directions

6.1. Challenges

One of the current challenges is patient adherence, the ability of patients to use medications or other treatments as prescribed when using biologics or other treatments.

Specific Strategies to Improve Adherence

- Patient Education Educating patients about the importance of adhering to treatment plans, including medication schedules, physical therapy, and follow-up appointments can significantly improve adherence.

- Simplifying Treatment Regimens Simplifying medication schedules, reducing the frequency of appointments, and providing clear, easy-to-follow instructions can help patients stay on track with their treatment.
- Effective Pain Management Ensuring that patients have access to appropriate pain relief can improve their quality of life and encourage them to adhere to their treatment plan.
- Regular Follow-Up and Support Regular follow-up appointments and continuous support from healthcare providers can help monitor progress and address any concerns or barriers to adherence. This can include phone calls, text reminders, or telehealth consultations.

The second challenge is that although the current treatment methods are numerous and complex, the means that can be actually used in clinical practice are quite limited, so we need to accelerate the process of translating from basic research to clinical application.

Strategies to Accelerate the Translation of Bone Nonunion Treatments from Basic Research to Clinical Applications

- **Enhance Collaboration Between Researchers and Clinicians**

Strengthening collaboration between basic researchers and clinicians ensures that experimental findings can be quickly translated into clinical applications. Joint research projects, data sharing, and result dissemination can shorten the time from laboratory to clinic.

- **Optimize Clinical Trial Design**

Designing more efficient clinical trials, including using adaptive trial designs and multi-center trials, can accelerate clinical research progress. Ensuring scientific rigor and effectiveness while reducing unnecessary time and resource wastage is key.

- **Policy Support and Funding**

Government and institutional policy support, along with sufficient funding, are crucial for accelerating the translation of research findings. Policies that encourage the translation of research results and provide dedicated funding can significantly promote the development and application of new therapies.

- **Strengthen Technological Platforms**

Building and improving technological platforms, such as biomaterial development platforms and stem cell preparation platforms, can enhance research efficiency and translation rates. Sharing advanced technologies and equipment helps accelerate research progress.

- **Promote Standardization and Regulation**

Establishing and enforcing standardized and regulated research and clinical application processes can reduce variability and uncertainty, ensuring the reproducibility and reliability of research findings. This is vital for the rapid promotion and application of new therapies.

By implementing these strategies, the translation process from basic research to clinical application for bone nonunion treatments can be accelerated, improving treatment outcomes and the quality of life for patients.

The third challenge is that the current treatment methods, especially biologics and 3D printing custom materials, are too expensive, and the economic conditions of patients are also something we should consider.

6.2. Future Directions

The future direction must be in the direction of minimally invasive and individual medicine, which reduces the pain and shortens the length of hospital stay for patients, which is the general trend of the development of the medical industry. Individualized medicine also solves the problem of different patients with different conditions and economic conditions, so minimally invasive and individual medicine will become a vital part in the future.

7. Conclusions

This article mainly introduces the influencing factors, classification, treatment methods and new scientific and technological materials of bone nonunion, which has a guiding role for clinicians in the treatment of patients with bone nonunion.

7.1. Summary of Key Takeaways

7.1.1. Enhance Collaboration between Investigators and Clinicians

Highlight the necessity of close collaboration between researchers and clinicians to ensure rapid translation of research findings into clinical applications.

Emphasize cooperation in medical management, patient education, and lifestyle modification to develop effective treatment strategies and promote patient recovery.

7.1.2. Optimize Clinical Trial Design

Advocate for the use of more efficient clinical trial designs, such as adaptive trial designs, to hasten the translation of experimental discoveries into clinical applications.

Stress the importance of joint research efforts to expedite the progress of clinical trials.

7.1.3. Improve Patient Compliance

Present specific strategies to improve patient adherence, including simplifying treatment regimens, effective pain management, and regular follow-up and support.

Highlight the significance of patient education in promoting adherence to treatment.

7.1.4. Standardization and Normalization in Research and Clinical Application

Point out the importance of establishing standardized research and clinical application processes to enhance patient quality of life.

Emphasize that scientific rigor and transparency are essential for the swift rollout and application of new therapies.

7.1.5. Application of Biological Methods in Fracture Healing

Present the potential of biological factors (e.g., MSC therapy) in fracture healing and the results of clinical trials.

Mention systematic reviews that indicate MSC therapy can enhance bone healing, though results vary depending on study design and patient population differences.

7.1.6. Challenges and Future Directions

Identify current challenges, including patient compliance and the diversity of treatment approaches.

Stress the need for future research to address these issues and explore more effective treatment strategies.

7.2. Specific Recommendations for Future Research or Clinical Practice

7.2.1. Strengthening Interdisciplinary Collaboration

Encourage interdisciplinary collaboration among researchers, clinicians, patients, and stakeholders to accelerate the translation and application of research findings.

7.2.2. Optimize Clinical Trial Design and Execution

Adopt flexible and adaptive clinical trial designs to rapidly assess the efficacy and safety of new therapies.

Enhance the supervision and quality control of clinical trials to ensure accurate and reliable results.

7.2.3. Improve Patient Engagement and Adherence

Boost patient engagement and adherence through education, personalized treatment plans, and regular follow-up.

Utilize modern technology (e.g., telehealth consultations, mobile health apps) to support patients in managing their health conditions.

7.2.4. Promote Standardization and Regularization

Establish unified standards for research and clinical application to improve study comparability and result reliability.

Strengthen regulatory collaboration to facilitate rapid approval and widespread adoption of new therapies.

7.2.5. Deep Dive into Biological Approaches

Continue researching the potential of biological factors (e.g., stem cell therapy, gene therapy) in fracture healing and other diseases.

Conduct large-scale, multi-center clinical trials to validate the efficacy and safety of new therapies.

7.2.6. Focus on Patient Needs and Experiences

Continuously address patient needs and experiences in research and clinical practice to ensure treatments are both effective and humane.

Gather patient feedback and suggestions to constantly improve and optimize treatment options.

Finally, the authors deem that the number of nonunion fractures will be reduced with the combined efforts of orthopedic clinicians.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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