An exploration into the principles and theoretical progress of fracture treatment based on the mechanism of fracture healing

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ABSTRACT

Fractures are a common category of diseases in the field of orthopaedics with a high incidence in archaeologically obtained bones. These diseases may occur in various human activities. In the context of technological advancement, the annual incidence of fractures is increasing due to traffic accidents, sports injuries, and ageing. Besides, the classification of fracture diseases is also changing, making them one of the main orthopaedic diseases that affect the quality of life of patients and national medical expenditure. There are some basic principles in the treatment of fractures, and the understanding of the causes, types, and pathogenesis of fractures is constantly improved with technological development. Hence, there are sustained efforts to explore fracture treatment methods and examine even widely popular concepts, such as Arbeitsgemeinschaft für Osteosynthesis (AO) and biological osteosynthesis (BO) principles. However, nonhealing fractures, fracture infections, and other treatment problems can still not be eliminated based on these concepts. In addition, some new perspectives on the treatment principles of fractures have been proposed by surgeons based on their clinical experience. In this paper, the latest research results on fracture healing are summarised, and our views and opinions on the application of AO or other new concepts in fracture treatment are also elucidated. During the investigation of the advantages and disadvantages of fracture treatment concepts, the shortcomings of current fracture treatment strategies or theories are also reviewed. These findings may provide clinicians with theoretical support for fracture treatment and inspire scholars to delve into fracture treatment principles.

Keywords:
AO principles; Fracture; Healing mechanism; Therapeutic theory; Treatment principles

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1. Introduction

Fractures are highly prevalent in archaeologically obtained bones, and these diseases may be induced by various human activities. In the context of technological advancement and population ageing, transportation, sports injuries, and ageing result in an increasing number of patients with fractures worldwide. If these patients cannot receive proper treatment in time, they may experience delayed healing, nonhealing, or malunion of fractures. In patients with severe conditions, fractures can lead to disability and impose a heavy burden on patients and their families (**Figure 1**). From 1990 to 2019, the incidence, prevalence, and disability rate of fractures in China increased from 12.54 million, 28.35 million, and 1.71 million in 1990 to 21.27 million, 67.85 million, and 3.79 million in 2019, which increased by 70%, 139%, and 122%, respectively.[1] Therefore, exploring fracture treatment approaches is essential for maintaining the stability of the national healthcare system. Fractures refer to the cracking or breaking of bone integrity and continuity, which may be caused by direct violence, indirect violence, and fatigue factors. The treatment principles of fractures include reduction, fixation, functional exercise, and rehabilitation. Systemic factors such as age,[2] health status,[3] and local factors (like fracture types[4] and infections[5]) can all affect

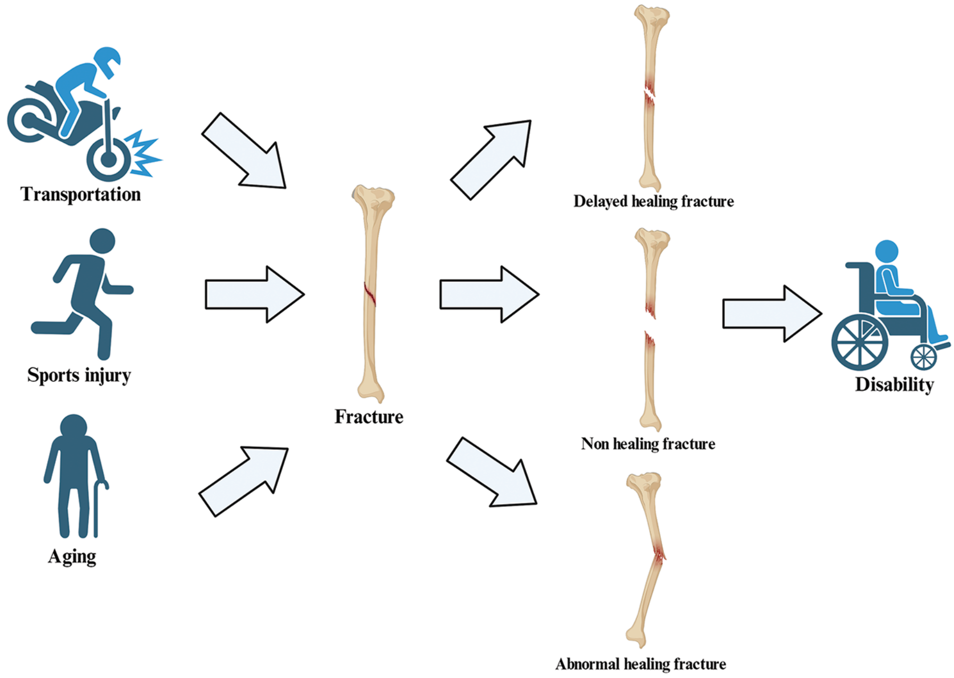

Figure 1. Pathogenic factors and consequences of fractures. Created with BioRender.com.

fracture healing (**Figure 2**). Patients without displacement or with poor overall condition can be treated by conservative methods, such as plaster and splint fixation.[6] In contrast, those with severe fractures require internal fixation treatment.[7] The commonly used internal fixation methods for fractures include plate and screw internal fixation[8] or intramedullary nail internal fixation,[9] and the former is more widely used in clinical practice. There are sustained explorations into the causes, types, and pathogenesis of fractures, as well as improvements in fracture treatment plans and concepts. For example, the Arbeitsgemeinschaft für Osteosynthesis (AO) concept centered on protecting the organisation and allowing early functional rehabilitation training, and the biological osteosynthesis (BO) concept pursuing a balance between fracture stability and soft tissue integrity, etc. However, these concepts can still not eliminate the problems in fracture treatment, such as infections, delayed healing, nonunion, or malunion. In this review, the principles and latest theories of modern fracture treatment are summarised based on the latest research results in fracture treatment and the experience from clinical fracture treatment. Besides, the shortcomings of current fracture treatment strategies or theories are also reviewed while exploring the advantages and disadvantages of fracture treatment concepts. These findings are expected to provide clinicians with theoretical support on fracture treatment and inspire scholars to further delve into fracture treatment principles.

2. Retrieval strategy and selection criterial

Data for this review were identified by searching of PubMed and CNKI, and references of relevant articles using the search terms: "fracture healing", "bone healing", "bone fracture", "bone", "fracture", "fracture treatment concept", "Arbeitsgemeinschaft für Osteosynthesis", "biological osteosynthesis", "Chinese osteosynthesis", "memory osteosynthesis", "relative stability of fracture", "absolute stability of fracture", and "osteogenic differentiation". We also seclected the references which relative to our review.

3. Mechanisms of fracture healing

3.1. Research progress on fracture healing mechanisms

The fracture healing process is composed of several stages, including haematoma inflammation organisation, primitive callus formation, and callus remodelling and shaping. Within 6 hours after the occurrence of a fracture, the activation of the endogenous coagulation system causes haematomas around the fracture and the formation of granulation tissues, which may last until about 2 weeks after the fracture when fibre connections are formed under the action of growth factors. About 3–6 months after the fracture, the callus is gradually strengthened, and clinical healing of the fracture is achieved. Within 1–2 years after the fracture, both the bone marrow cavity and the fractured bone surface return to normal. Through the efforts of relevant scholars, many new studies have emerged

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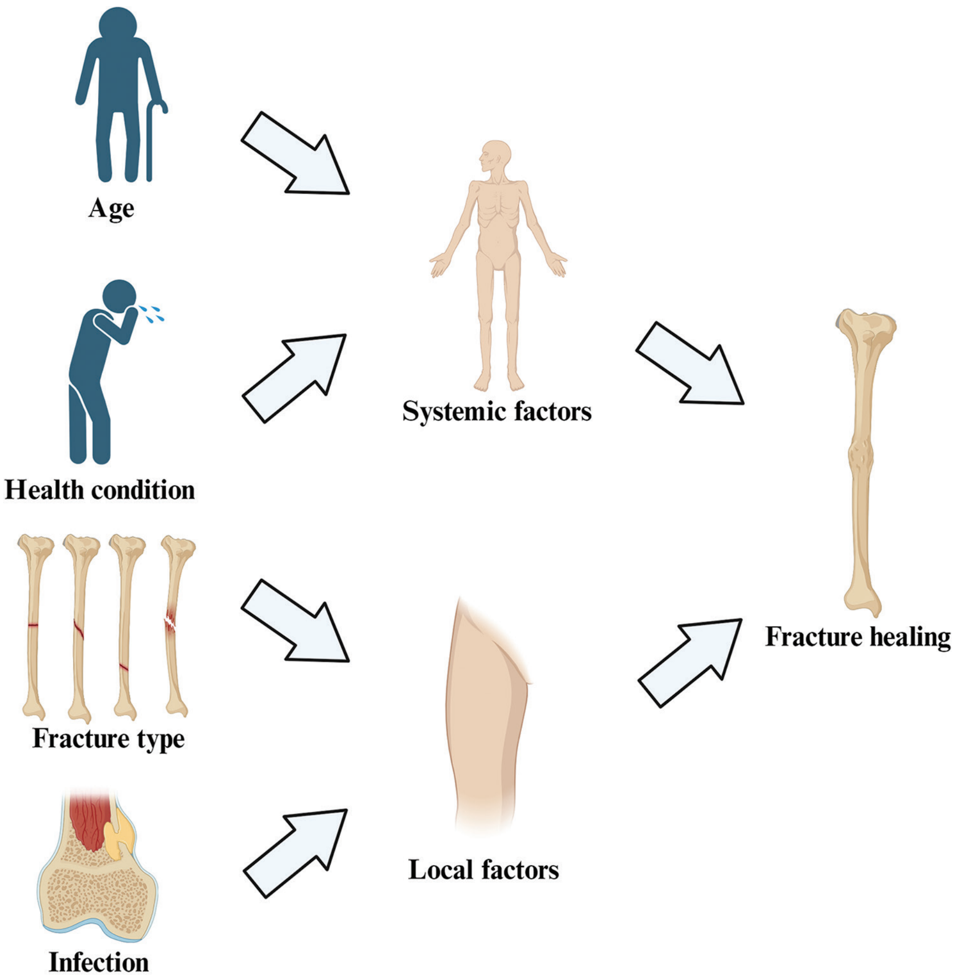

Figure 2. Factors in fracture healing. Created with BioRender.com.

in the field of fracture healing, enriching the exploration of the fracture healing process and providing convenience for clinicians to understand the essence of fracture healing.[10,11] In research related to fracture healing, scholars not only explore the essence of this pathophysiological process from the perspective of fracture healing but also investigate the effects of different treatment methods on special types of fractures under different conditions. These findings can provide novel ideas and strategies for clinicians to treat fractures.[12,13]

Inoue *et al.*[14] conducted a study on osteoporotic fractures and found that high-intensity ultrasound can promote chondrogenesis and the hypertrophic differentiation of chondrocytes in the fracture callus. When the ultrasound intensity was further increased, the number of osteoblasts and newly formed bones in the callus increased, which accelerated endochondral ossification. This effect can be weakened by spider toxin peptide (GsMTx4) to inhibit the mechanosensitive ion channel protein Piezo-type mechanosensitive ion channel component 1 (Piezo1). Chinipardaz *et al.*[15] discussed the fractures in diabetes. They found that the expression of forkhead box protein O1 (Foxo1) was up-regulated, while that of intraflagellar transport 80 homolog (IFT80) was down-regulated. Besides, the number of primary cilia decreased in the femoral fracture callus of animals with streptozotocin-induced type 1 diabetes. The advanced glycosylation end products also damaged the formation of cilia in osteoblasts and reduced extracellular mineralisation products. This process can be reversed by the knockout of Foxo1 in osteoblasts, confirming the role of inhibiting Foxo1 and/or restoring the formation of osteoblast cilia in fracture healing. The emergence of contradictions between traumatic brain injuries and bone loss promotes fracture healing. Jahn *et al.*[16] found that in cortical impact mice, the β2-adrenergic receptor (ADRB2) was involved in the reduction of the bone volume in non-fractured bones and bone healing in injured bones. Norepinephrine can stimulate the expression of vascular endothelial growth factor A and calcitonin gene-related peptide-α in periosteal cells through ADRB2, thus promoting the formation of osteogenic H-shaped blood vessels in the fractured callus, which may contribute to fracture healing. The mechanical force is an indispensable factor in fracture healing, and its destruction can lead to delayed or nonhealing of bones. Liu *et al.*[17] found that tissue proteases and periosteal stem/progenitor cells in the bone callus after fractures can target mechanical forces through the mechanosensitive protein polycystic protein-1 transcription coactivator (TAZ) axis, which affected the generation of the bone cartilage and cortical bone, ultimately regulating the fracture healing process. The long non-coding RNA (lncRNA) is also considered an indispensable factor in the process of fracture bone healing and the osteogenic differentiation of stem cells. Dong *et al.*[18] confirmed that the expression of the serum lncRNA MAGI2-AS3 was down-regulated in patients with delayed fracture healing. Further, the up-regulated expression of this lncRNA can promote the proliferation and inhibit the death of the mouse embryonic osteoblast precursor cell line MC3T3-E1. However, the above process can be reversed by up-regulating the expression of osteogenic markers in cells and knocking down MAGI2-AS3 in cells, and this regulatory process was related to targeting miR-223-3p. In recent years, the non-thermal atmospheric pressure plasma therapy has attracted the attention of medical scholars. Saito *et al.*[19] conducted some experiments based on a LEW/SsNSlc rat model and found that non-thermal atmospheric pressure plasma can promote the healing ability of nonhealing fracture animal models and enhance the osteogenic differentiation ability of MC3T3-E1 cells in vitro. Nano-drug delivery systems can also target fractures to achieve bone healing. Xiao *et al.*[20] developed a nanoparticle drug delivery system composed of poly (styrene maleic anhydride)-b-poly (styrene). This system can target the accumulation of tartrate-resistant acid phosphatase at the fracture site, deliver the glycogen synthase kinase-3β inhibitor AR28, and act on macrophages to change their phenotypes, which can further up-regulate anti-inflammatory factors and down-regulate pro-inflammatory factors, thus promoting fracture healing. The use of traditional Chinese medicine substances to promote fracture healing has a long history. Xiang *et al.*[21] found that icariin can activate the antioxidant nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signalling pathway both in vivo and in vitro to inhibit the ferroptosis of osteoblasts and promote osteoporotic fracture healing. The healing of fractures also depends on the enhancement of mineralisation at the fracture site. Dejea *et al.*[22] confirmed that zinc participated in the accumulation and reabsorption of minerals in the fracture healing process. In the early stages of mineralisation, zinc exhibited a similar spatiotemporal trend with the matrix remodelling compound matrix metallopeptidase 13, and iron and zinc can synergistically promote the mineralisation process of fracture healing (**Table 1**).

There are many new mechanisms involved in the fracture healing process, covering the entire perioperative period from diagnosis,[23] treatment,[24] to prognosis.[25] The focus of previous studies is placed on the treatment factors that may promote fracture healing, such as ultrasound,[26] drug-loaded nanoparticles,[27] and medicine and food homology substances.[28] The basic research contents related to fracture healing have been enriched by some specific mechanisms that regulate the fracture healing process, such as signalling pathways,[29] signalling axes,[30] lncRNAs,[31] and microRNAs,[32] as well as various actions that regulate fracture healing, such as mechanical stimulation,[33] mineral calcification,[34] and cell differentiation[35] (**Figure 3**). However, these studies are currently in the preclinical stage, and most of them are theoretically reported to promote fracture healing. A new plan for fracture healing is illustrated in **Figure 1**. In this paper, our viewpoints on fracture healing are elucidated based on innovative research and years of clinical experience in fracture treatment. In future research, it is necessary to further identify whether micro motions and forces are necessary conditions for fracture healing and whether fractures can heal in an environment without mechanical stimuli. Furthermore, the method to explore the mechanism of fracture healing in a weightless environment without muscle tension may become a new research direction.

3.2. Considerations on fracture healing mechanisms

Fracture healing is a long-term process triggered by mechanical signals[36] involving multiple tissues in the body.[37] This process

Table 1. Mechanism of fracture healing

Fracture type	Intervention measure	Action site or cell	Mechanism	Reference
Osteoporotic fracture	Ultrasonic	Osteoblasts from bone callus, newly formed bone, cartilage	Regulate GsMT×4 to inhibit the mechanosensitive ion channel protein Piezo1	14
	Epimedium	Osteoblasts	Activate the antioxidant Nrf2/HO-1 signaling pathway both to inhibit ferroptosis of osteoblasts	21
Type 1 diabetes combined with fracture	Streptozotocin	Osteoblasts from bone callus	Regulate Foxo1 and/or restore the formation of osteoblast cilia	15
Traumatic brain injury combined with fracture	Norepinephrine	Osteoblasts from bone callus, periosteum cells	Regulate ADRB2 and subsequently affect the formation of osteogenic H-shaped blood vessels	16
Fracture	Mechanical force	Tissue proteases and periosteal stem/progenitor cells in the bone callus	Target mechanical forces through the mechanosensitive protein polycystic protein-1 transcription coactivator TAZ axis	17
	lncRNA MAGI2-AS3	Mouse embryonic osteoblast precursor cell line MC3T3-E1	Target miR-223-3p	18
	Non-thermal atmospheric pressure plasma	Mouse embryonic osteoblast precursor cell line MC3T3-E1	Enhance the osteogenic differentiation ability of cell line	19
	Nanoparticles (PSMA-b-PS)	Fracture site and macrophages	Target the accumulation of tartrate-resistant acid phosphatase, change macrophage phenotypes, and affect inflammation	20
	Metallic element zinc	Bone mineral	Participate in the accumulation and reabsorption of minerals, and affect mineralisation	22

Abbreviations: ADRB2: β2-adrenergic receptor; Foxo1: Forkhead box protein O1; GsMTx4: Spider toxin peptide; HO-1: Heme oxygenase-1; lncRNA: Long non-coding RNA; Nrf2: Nuclear factor erythroid 2-related factor 2; PSMA-b-PS: Poly (styrene maleic anhydride)-b-poly (styrene); TAZ: Transcriptional coactivator.

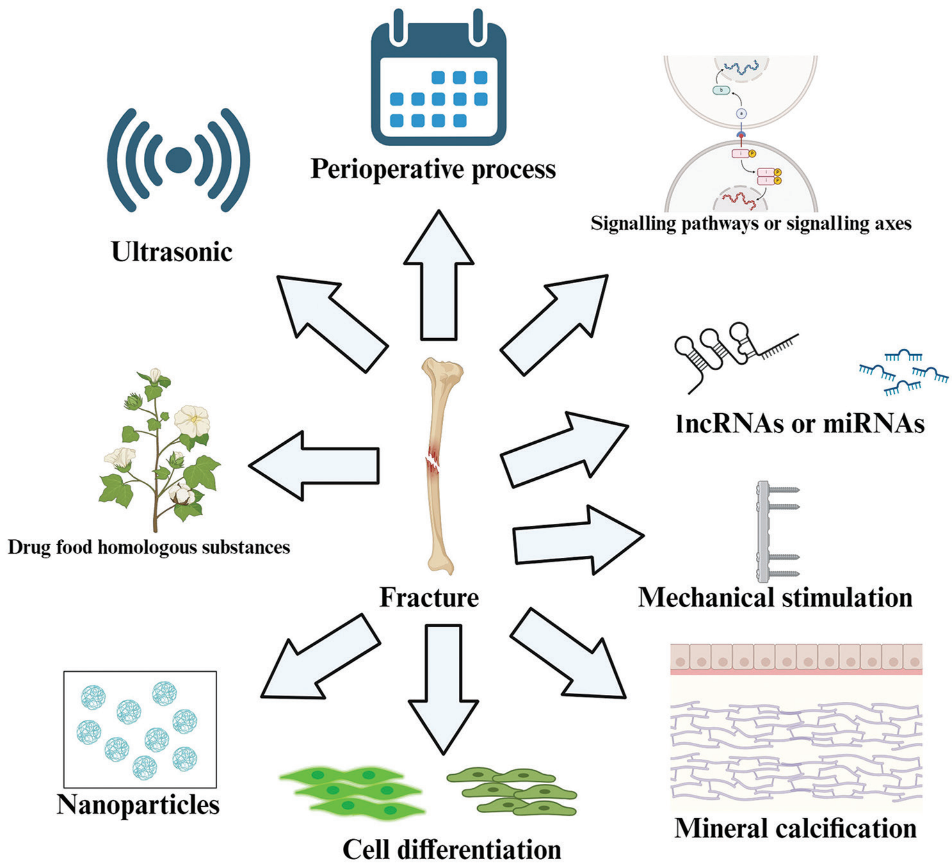

Figure 3. Basic research on fractures. Created with BioRender.com.
Abbreviations: lncRNA: Long non-coding RNA; miRNA: MicroRNA.

may be regulated by various factors,[38] and fractures may be gradually repaired by cell differentiation,[39] ultimately achieving new bone formation, broken end connection, and skeletal scaffold function recovery. This process takes 12 weeks or even longer in normal adults. Adverse changes in the biomechanical or biological environment in the healing process can lead to delayed healing or nonhealing of fractures. If there is no human intervention for treatment, unstable fractures in patients are likely to result in nonunion or malunion of fractures. The research on fracture treatment in humans has never stopped. The splints discovered in Egyptian archaeology and the wooden small splints in traditional Chinese medicine are both manifestations of the ancient people's fixation concept for fracture treatment. With the advancement of technology, the research and understanding of fractures have been improved, which contributes to the extensive application of open reduction and internal fixation. On that basis, the early AO principles are proposed, including strong internal fixation,[40] early functional exercise, prevention of joint stiffness caused by long-term braking fixation, and maximum function recovery. With the development of internal fixation surgery techniques and the theoretical practice of AO, some new problems have gradually emerged, such as internal fixation failure,[41] infections,[42] and nonunion of fractures caused by neglecting local tissue blood supply or premature aggressive functional exercise.[43] Hence, researchers are also aware of the deficits in early fracture treatment concepts, necessitating further improvement and modification. In the biomechanical research of fracture healing, especially in the study of fracture biomechanics under internal fixation intervention, orthopaedic clinicians have accumulated rich surgical experience and developed fracture treatment strategies. The new concept emphasises the protection of soft tissues rather than strong internal fixation,[44] and absolute and relative stability theories are also proposed for the internal fixation of fractures, such as the spectrum range of stability for the hypothetical internal fixation of fractures. The absolute stable internal fixation can achieve primary healing of fractures, while the relatively stable internal fixation may lead to secondary healing of fractures, constituting the current treatment strategy for fractures. However, is this strategy the most perfect? Are there any defects? Are there any other conflicting options in fracture treatment in clinical practice? Can our fracture treatment strategy be further improved and upgraded? All of these need to be further improved by orthopaedic clinicians in combination with basic research and clinical practice.

4. Internal fixation concepts for fractures

4.1. Changes and progress in the internal fixation concepts for fractures

From ancient times to the present, the concept of fracture treatment has gone through simple external fixation, traction reduction, open reduction, and internal fixation (**Figure 4**). After 1958, with the establishment of the Internal Fixation Research Society, scholars in the AO school began to advocate internal fixation technology. The core concept of internal fixation is to protect tissues and allow early functional rehabilitation training while providing safe open reduction and firm internal fixation for fractures. The AO principles are still the mainstream concepts in the field of fracture treatment.[40] However, it also has certain shortcomings, which have prompted the emergence of other concepts. New concepts such as BO emphasise indirect reduction and biological fixation, pursuing a balance between fracture stability and soft tissue integrity.[44] For example, the concept of Chinese osteosynthesis emphasises the combination of traditional Chinese medicine and Western medicine in the treatment of fractures, highlighting the importance of "balancing muscles and bones, combining movement and stillness, treating both internal and external factors, and promoting doctor-patient cooperation".[45] Finally, the memory osteosynthesis principle emerges as a new type of fracture healing treatment with the aid of special instruments for the treatment of fractures, known as shape memory bone grafting.[46] The new concept can be recognised as a supplement to the existing concept. It is believed that with the development of medical technology, many schools may flourish in the field of fracture treatment (**Figure 5**, and **Table 2**).

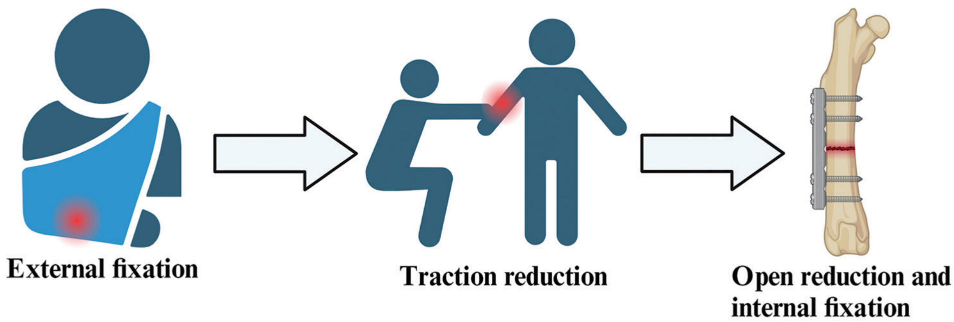

Figure 4. Changes in fracture treatment concepts. Created with BioRender.com.

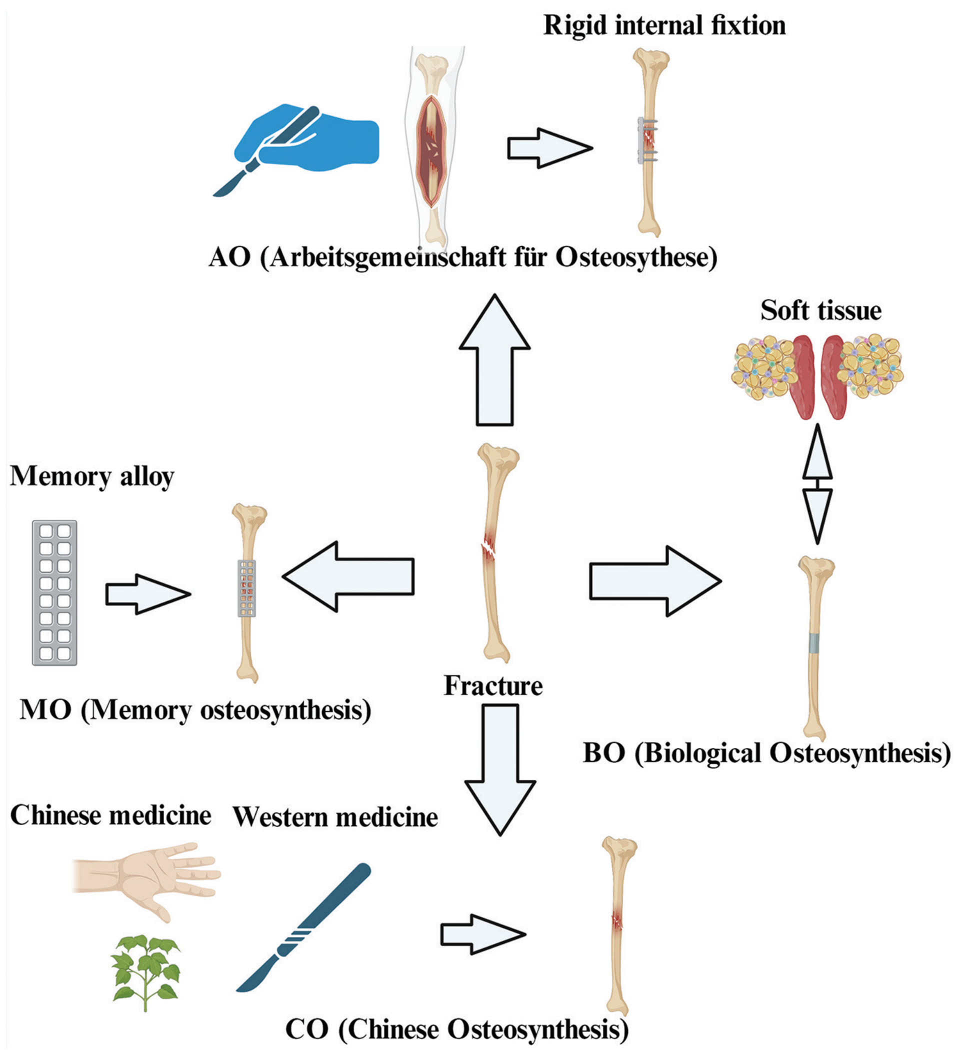

Figure 5. Internal fixation concepts for fractures. Created with BioRender.com.

Table 2. Advantages and disadvantages of the concept of internal fixation for fractures

Concept	Advantage	Disadvantage
AO	The patient's fracture can achieve primary healing, and early limb activity and rehabilitation exercises can be carried out	Disrupting the blood supply around the fracture and affecting the healing effect of the fracture
BO	Protected the tissue around the fracture	Fractures belong to secondary healing and require a longer shaping period
CO	Balancing muscles and bones, combining movement and stillness, treating both internal and external factors, and promoting doctor-patient cooperation	Fractures belong to secondary healing
MO	Synchronization of fracture reconstruction and functional recovery	Some patients require a second surgery to remove the internal fixation

Abbreviations: AO: Arbeitsgemeinschaft für Osteosynthesis; BO: biological osteosynthesis; CO: Chinese osteosynthesis; MO: memory osteosynthesis.

In addition to the above main fracture treatment principles, there are also differences in treatment concepts for different fracture types. Many scholars have summarised the treatment principles for some special fracture types. Malisorn maintained that minimally invasive surgery, open reduction, and arthroscopic surgery were all effective treatment methods for first metacarpal fractures. Besides, needle fixation, direct screw fixation, indirect screw fixation, and mini plate fixation can all be used for the treatment of first metacarpal fractures.[47] Morisaki *et al.*[48] reported a patient with traumatic comminuted fractures of the cricoid cartilage and found that the airway was maintained by the anterior part of the cricoid cartilage, and sound production depended on the posterior part of the cricoid cartilage. During surgical treatment, a sufficient inner diameter should be maintained in the anterior part of the cricoid cartilage, and the correct position should be maintained in posterior reconstruction. For clavicle fractures, previous conservative therapies have exhibited a high nonunion rate. Frima *et al.*[49] discussed conservative and surgical treatment options and indications for medial, diaphyseal, and lateral clavicle fractures. They concluded that non-displaced fractures can be treated conservatively, while surgical treatment was required for displaced fractures. Fischer *et al.*[50] summarised the treatment of proximal femoral fractures in elderly patients. They revealed that pain management, maintenance of fluid balance, and management of underlying diseases constituted the basis for the treatment of such patients. Intramedullary nail surgery is preferred for intertrochanteric and subtrochanteric fractures, while bedridden patients or patients with biologically younger non-displaced femoral neck fractures can undergo bone-setting surgery. However, elderly patients and patients with significantly displaced femoral neck fractures may select total hip replacement or hemiarthroplasty. Sander *et al.*[51] analysed the perioperative data of 268 patients (aged ≥ 18 years) with distal radius fractures who were admitted to their hospital from 2013 to 2015. They found that the number of patients with types A and C based on the AO classification for distal radius fractures was roughly the same, with fewer patients with type B. Whether these patients underwent surgical treatment depended on the severity of fractures, regardless of the age of these patients. Kremer *et al.*[52] analysed 261 patients with phalanx fractures who received treatment in their hospital from 2017 to 2018. They found that 74% of patients were treated conservatively and 26% of patients required surgery. Surgical treatment is usually performed through Kirschner wire surgery, and surgical decisions are made based on the specific angle and/or rotational deformity of the phalanx fracture, intra-articular step, and dislocation degree, regardless of age and gender. Liau *et al.*[53] proposed a method based on age and evidence-based algorithms to guide orthopaedic surgeons in the treatment of paediatric femoral shaft fractures. They corroborated that non-surgical treatment was preferred for paediatric patients under 6 years old, such as Pavlik harness treatment for those under 6 months old and early spica casting treatment for those aged 6 months to 6 years. Elastic stable intramedullary nail and intramuscular plate surgery can be used for paediatric patients aged 6–12 years, while rigid anterograde intramedullary fixation is recommended for those over 12 years old. Ma *et al.*[54] retrospectively analysed the data from 67 patients with Lauge Hansen type II supine adduction ankle fractures. They found that patients treated based on the medial pilon fracture surgical concept had better postoperative outcomes than those based on the ankle fracture surgical concept. Nonunion is a symptom that may occur after fracture surgery. Tanner *et al.*[55] analysed 76 patients over 60 years old with nonunion and found that the bone consolidation rate of these patients after one-step treatment was higher than that of those treated with Masquelet. However, according to the "diamond concept", with the age of patients as a risk factor for treatment outcomes, it was found that one-step treatment did not affect these patients, while Masquelet treatment had a negative impact on these patients. Ultimately, it was demonstrated that patients with infectious nonunion may benefit from two-stage surgical treatment, while those with non-infectious nonunion may benefit from one-step surgical treatment. Tao *et al.*[56] analysed 66 patients with proximal humeral fractures and found that the concept of "shoulder protection" was of great significance for the treatment of three- and four-part fractures of the proximal humerus. Proximal humeral internal locking osteosynthesis system fixation with rotator cuff closure is an effective treatment method. Liu *et al.*[57] analysed different anaesthesia methods for percutaneous kyphoplasty treatment of osteoporotic vertebral fractures in patients over 90 years old based on the enhanced recovery after surgery concept. From the rapid recovery perspective, they recommended percutaneous kyphoplasty treatment for the treatment of such patients under local anaesthesia.

In summary, in the fracture treatment process, in addition to the widely accepted AO principles among orthopaedic surgeons, there are also different concepts for different types of fracture treatment. Only when the surgeon's concept is promoted and accepted by the public can more influential concepts be formed. Therefore, both macro and micro concepts, as well as broad and narrow concepts, coexist in fracture treatment. Different concepts may constitute a driving force for the surgeon's reflection on internal fixation surgical treatment methods for fractures, gradually supplementing and improving fracture treatment concepts. However, the nonunion of fractures and fracture infections can still not be eliminated based on these concepts. Therefore, it is necessary to critically examine these concepts and identify the shortcomings of current fracture treatment strategies or theories, thus contributing to more effective fracture treatment strategies.

4.2. Changes in the fracture internal fixation concepts guided by AO principles

AO principles are still the mainstream concepts in the field of fracture treatment, and the development of other concepts cannot be independent of AO principles. Under the guidance of AO principles, many scholars are also striving to improve or perfect AO principles, finding the balance point of AO principles from clinical practice. Furthermore, research by scholars and clinicians may involve multiple aspects of AO principles, including changes in surgical concepts guided by AO principles, as well as interdisciplinary research such as artificial intelligence,[58] classification methods,[59] and imaging techniques[60] guided by AO principles, which may contribute to better outcomes in patients with fractures (**Figure 6**).

Under the guidance of the Children's Fracture Classification System of the AO Foundation/Orthopaedic Trauma Association, Binh *et al.*[58] developed a multi-class convolutional neural network model related to distal forearm fractures in children. They performed training for this model with wrist X-ray images to achieve the first mock examination type automatic diagnosis of distal forearm fractures in children, which was comparable to radiologists and orthopaedics in terms of accuracy. Huitema *et al.*[60] investigated the inter-observer consistency of six commonly used tibial plateau fracture classification systems using X-ray imaging and two-dimensional or three-dimensional imaging techniques. They

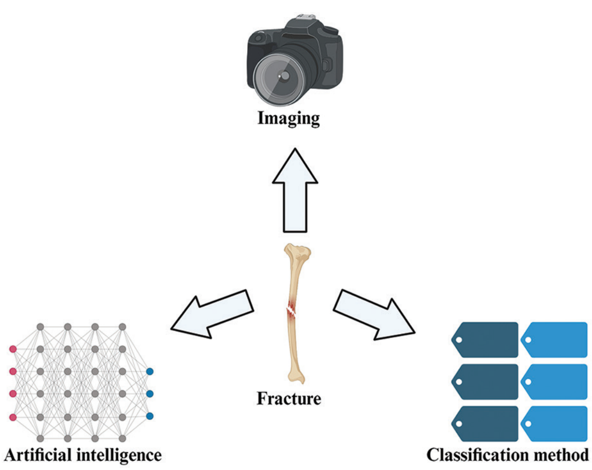

Figure 6. Related research of fracture healing guided by AO principles. Created with BioRender.com.
Abbreviation: AO: Arbeitsgemeinschaft für Osteosynthesis.

unraveled that two-dimensional computed tomography had favourable effects on the Schatzker classification, AO Foundation/Orthopaedic Trauma Association classification, and Hohl classification of tibial plateau fractures. Their results indicated that the progress of imaging technology was not consistent with the consensus among observers on fracture classification. Yao *et al.*[61] evaluated the intra-observer and inter-observer reliability of three widely used classification systems, including Schatzker (AO Foundation/Orthopaedic Trauma Association) and the updated three-column concept of ten-segment classification in two- and three-dimensional computed tomography scans. They confirmed that the use of three-dimensional computed tomography was crucial for the reliable diagnosis and identification of tibial plateau fractures, and the ten-segment classification system showed a high degree of intra-observer and inter-observer consistency. This also indicates that it is necessary to further improve different classification standards. Kweh *et al.*[59] described the origin of the AO spinal sacral and pelvic classification system by combining it with the historical sacral and pelvic grading system. They proposed that the AO classification system was a universally applicable system that could be employed to realise the biomechanical stability of the posterior pelvic complex and the classification of spinal pelvic stability while considering the state of nerves. Based on this classification system, historical fracture morphology can be redefined and sorted into a reasonable hierarchical structure. Heifner *et al.*[62] simulated type AO A2 non-articular distal radius fractures and contralateral type AO C3 articular fractures on one side of cadaver specimens. They proved that using a fixed angle subchondral support palmar locking plate to support the scaphoid bone and lunar fossa alone can provide considerable fixation strength and resist displacement between joint and non-joint fracture modes. Wang *et al.*[63] designed a micro-motion-based balanced drilling system and established a fixed-locking plate (Arbeitsgenmeinschaft Für Osteosynthesefragen-The Association for the Study of Internal Fixation (AO/ASIF) 33-A3) model with a gap of 2 cm for distal femoral fractures. They performed internal fixation surgery using standard and eccentric sleeves and found that the drill bit and matching sleeve enabled the transformation of conventional locking compression plates into an internal fixation system, thereby improving the balance movement of the proximal and distal cortices. Adjusting the diameter of the drill bit and the eccentricity of the sleeve can control the strain at the fracture site. Yao *et al.*[64] retrospectively analysed computed tomography images of tibial plateau fractures based on AO Foundation/Orthopaedic Trauma Association classification and four-column nine-segment classification. They discussed the correlation between the proximal tearing of five ligaments and injury mechanisms. Their results suggested that in patients with tibial plateau fractures, the incidence of proximal tearing of five ligaments was 7.3%, and the four-column nine-segment classification was validated to be a detailed method for recording these ligament injuries. Marintschev and Hofmann[65] used a novel locking nail implant to treat pelvic dorsal ring fractures classified as AO or pelvic fragility fractures. They demonstrated that surgical instruments for pelvic dorsal ring fractures should be maintained as stable as this new locking nail, which can be used for percutaneous reduction and fixation, thus immediately bearing weight and reducing the incidence of complications. Wegmann *et al.*[66] introduced a realistic simulation device for distal radius fractures. Based on AO/ASIF recommendations and the four-corner concept, high-energy pulses were used to establish a realistic model of distal radius fractures on cadaver specimens. Among them, 11 fractures were classified as type 23C3.2, and 1 fracture was classified as type 23C3.3. According to the four-corner concept, they were evenly divided into subtype C, providing a more realistic teaching model. Li *et al.*[67] corroborated that the classification method was not ideal for distal radius fractures. They compared AO Foundation/Orthopaedic Trauma Association classification with Melone classification. Besides, they retrospectively analysed 59 patients with AO Foundation/Orthopaedic Trauma Association 23C3 fractures, among whom 35 patients met the criteria of Melone classification. Therefore, they validated that the Melone classification system was not suitable for characterizing all C3 fractures, and the fragmentation of small fracture fragments on the dorsal medial side should be highlighted when reducing fractures.

Overall, no concept is perfect in the treatment of fractures, which should be improved constantly. Clinicians and scholars from different fields have made efforts to improve and develop AO principles. Based on the above results, AO principles may be further improved, and new methods and technologies may be used to explore fixation systems that are more consistent with human biomechanics. Additionally, more precise imaging can be achieved based on new technologies to realise a more accurate diagnosis or artificial intelligence diagnosis. Moreover, the AO classification system developed under AO principles also needs to be modified. Although it is currently the most widely used fracture classification system, it cannot fully include all types of fractures. With the improvement of the AO classification system, AO principles may become more effective in fracture treatment. The causes, types, and pathogenesis of fractures may also be clarified with technological and medical improvements.

4.3. Thoughts on the internal fixation concepts for fractures

In clinical practice, the author has also reflected on the rationality and modifiable content of AO principles, including their deficits and corresponding resolutions. In the fracture treatment process, the degree of stability achieved by internal fixation of the fracture can be compared to a spectrum of stability. One end of the spectrum is absolutely stable, while the other end is unstable. On that basis, the internal fixation stability of fractures would fall on a certain point on the stability spectrum, resulting in relative stability, and secondary healing is the final healing process of fractures.[68] If the stability strength of internal fixation falls on the absolute stable end of the spectrum, the fracture would be repaired through primary healing without obvious callus formation, the opposite extreme instability results in nonhealing fractures.[69] Currently, it is common to estimate target stability based on the condition of the fracture,[70] aiming to achieve absolute stability and fracture healing through a one-stage healing process. Besides, it is still necessary to achieve relative stability in fracture fixation and repair fractures through secondary healing. This can be regarded as a treatment strategy for orthopaedic surgeons, and the variable on the spectrum is only the degree of stability achieved after internal fixation of the fracture (**Figure** 7). Hence, internal fixation treatment is more like a race between fracture healing and internal fixation

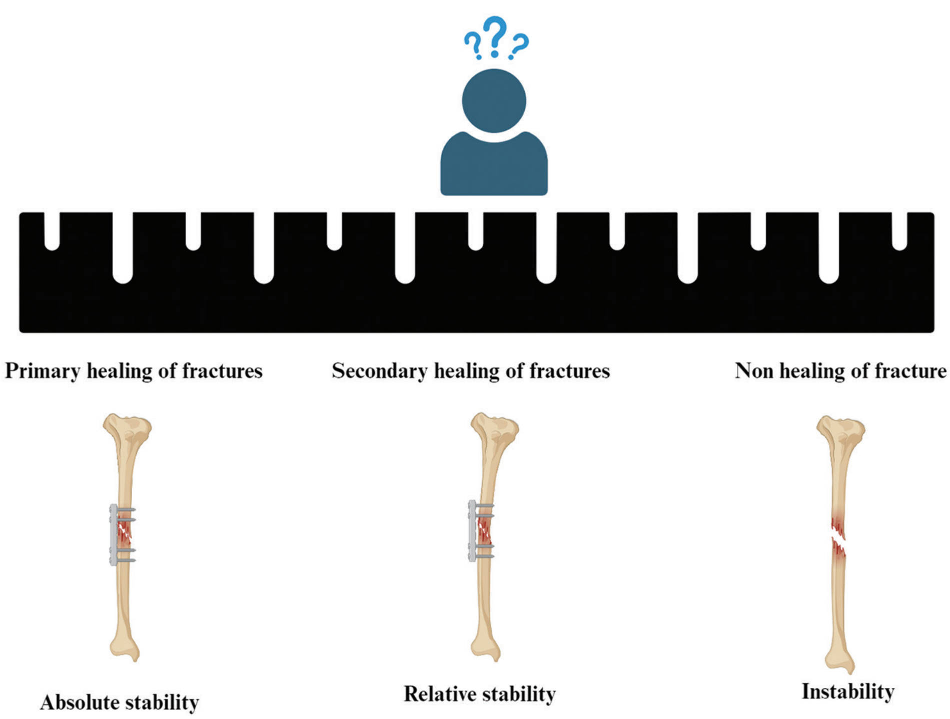

Figure 7. Relationship between stability and fractures. Created with BioRender.com.

fatigue. This indicates that effective fracture healing involves a long-term process, and the repair of most human tissues is less time-consuming compared with fracture repair. In addition, the stability inside the fracture will change over time. Fixing the stability level within a single time point is not a dynamic process. Is it reasonable and does it have one sidedness? The stability of internal fixation of the fracture may also vary at the position of the stability spectrum in the fracture healing process. Therefore, if the variable of time is added, the stability of internal fixation in each patient will gradually change in the fracture healing process. This may result in two outcomes: increasing stability and moving towards absolute stability, or decreasing stability and moving towards instability, ultimately leading to nonhealing of the fracture.

The absolute stability of internal fixation of fractures is defined as the absence of movements between the fracture ends under physiological loads; while the instability of internal fixation of fractures is defined as the excessive movement between fracture ends under physiological loads. Hence, relative stability can be considered the range between absolute stability and instability. Whether to achieve absolute stability and expect first-stage healing of the fracture or relatively stable, and whether to achieve second-stage healing, the decision has already been made in the planning before surgery.[71] When we decide to implement internal fixation with absolute stability as the goal of fracture treatment, how many cases can truly achieve absolute stability and primary healing? Is there a possibility of secondary healing or even nonhealing of fractures in this process? In clinical experience, it can be observed that nonunion of fractures may occur in the treatment of patients with absolutely stable fractures.[72] Under this circumstance, most surgeons will attribute the nonunion of the fracture to unfriendly technology and excessive biological factors that damage the blood supply of soft tissues. Is the nonhealing of the fracture due to biological factors, or is it caused by excessive loads that may induce instability at the fracture end? How to define the physiological load? Is the physiological load a quantitative or variable factor? Is the physiological load generated by patients with a high body mass index the same as that generated by patients with a low body mass index? Is the first-stage healing that we see in clinical practice strictly defined as first-stage healing, or is the small amount of bone callus that cannot be displayed on X-rays causing patients not to achieve first-stage healing? Or even for patients who have truly undergone primary healing, have they all experienced the impact of physiological loads? Are there still some patients who limit their weight-bearing capacity and reduce it, resulting in a lack of micromovements at the fracture site and leading to primary healing? If the above conjectures are true, it is impossible to achieve strictly absolute stable treatment goals. In other words, the strength that we can achieve in the treatment of fracture reduction and internal fixation is relatively stable. When an orthopaedic surgeon performs anatomical reduction and strong internal fixation, there may be no micromovement at the fracture end under limited loads, which may result in a process similar to normal bone repair, namely the first-stage healing of the fracture. When the fracture is not anatomically reduced and there is a moderate micromovement at the fracture end under limited loads in an internally fixed environment, haematomas, cell differentiation, and callus formation may be induced in the body, ultimately leading to secondary healing of the fracture.

The absolute stability of a fracture is achieved through compression fixation at the fracture site,[73] which generates frictional force at the fracture site to prevent micromovement under physiological loads. The intra-articular fracture can be considered an indication of absolute stability,[74] and some specific metaphyseal and diaphyseal fractures are also indications of absolute stability, such as metaphyseal fractures involving the joint surface, which require compression fixation of the articular bone fragment while fixing the metaphyseal fracture. Absolute stability can also be achieved in simple fractures of the backbone through compression fixation. In theory, absolute stability is required for joint fractures; however, in practice, absolute stability can also be achieved in many intra-articular fractures through this compression fixation method. However, there are few reports on the treatment strategy of compression fixation to achieve absolute stability for specific joint fractures. For example, the treatment of tibial plateau fractures, joint stability, the recovery of force lines, the anatomical reduction of the joint surface, and the use of raft technology to support the joint surface are the main considerations in surgical treatment. This may be explained by that it is difficult and often impossible to achieve compression fixation in the face of crushed and collapsed joint surface bone fragments. It is also difficult to achieve absolute stability in the treatment of Pilon fractures under the same circumstances. Only simple intra-articular fractures can be treated with screw compression, and absolute stability may be achieved by neutralizing plate protection. However, the rehabilitation guidance for all fracture surgical therapies has varying degrees of requirements for limiting weight-bearing or active strength exercises in the early stages of rehabilitation. In fact, it is recommended to decrease the load, reduce the occurrence of fracture instability, and ensure smooth fracture healing, which contradicts the definition of absolute stability of fractures. However, if it is relatively stable, these treatment strategies would become reasonable. Simple fractures of the backbone can be regarded as an indication of absolute stability, manifested in forearm fractures. However, in simple lower limb fractures, regardless of simple or comminuted fractures, the intramedullary nail, as a relatively stable treatment method, is recommended as the gold standard,[75] which contradicts the theory of absolute stability. In summary, absolute stability is not entirely applicable to all intra-articular fractures. Some specific metaphyseal fractures and simple diaphyseal fractures can meet the actual treatment criteria for absolute stability fixation. Although fracture fixation may be performed according to the goal of absolute stability, its fixation strength may not necessarily achieve the expected effect of absolute stability. Alternatively, absolute stability of the fracture can only be achieved by fracture healing, namely no micromovement under physiological loads. Under this circumstance, fracture fixation may be relatively stable. The maximum relative stability can only be achieved by applying compression at the fracture end under simple anatomical reduction, approaching the absolute stable end of

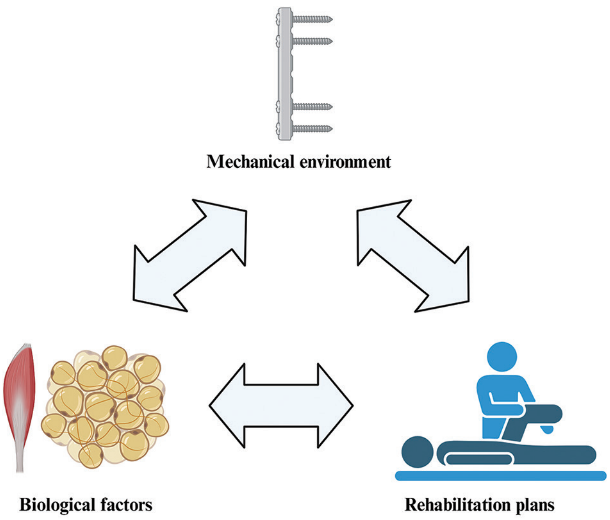

Figure 8. Balanced triangle in the fracture treatment. Created with BioRender.com.

the stability spectrum infinitely, resulting in the expected first-stage healing. However, the relative stability of anatomical reduction and compression fixation fails to produce the result of second-stage healing.

Another common view is that absolute stable internal fixation in fracture treatment can be achieved by extensive soft tissue dissection, thus sacrificing the blood supply of the fracture fragment and achieving absolute stability in unfriendly conditions to soft tissues. Under this circumstance, achieving relative stability in fracture treatment will be more conducive to soft tissues. In fact, with the maturity of surgical techniques and the advancement of reduction and fixation instruments, the extensive dissection of soft tissues is not required for some fractures during absolutely stable fixation.[76] This implies that simple anatomical reduction of fractures, combined with compression of the fracture end and protection of the bone plate, can be achieved with soft tissue-friendly technology. This is different from the traditional views, requiring relevant modifications in the treatment process.

The definition of relative stability is controlled motion between fracture fragments under physiological load, which has been used as a guiding strategy for modern fracture treatment to this day. The relatively stable goal of internal fixation for fractures has been set before surgery, and it is mainly used for fractures in the metaphysis and diaphysis, especially for complex types of fractures. It does not require anatomical reduction of all fracture fragments, only restoring the normal relationship between adjacent joints of the fracture. Relative stability is achieved through secondary healing generated by callus formation. Currently, almost all fixation materials such as locking plates, intramedullary nails, and external fixation frames can achieve relative stability in fracture fixation. After surgery, gradual rehabilitation can be used to reduce the physiological burden of early fracture healing and minimize the occurrence of unstable fractures. One end of the spectrum of stability is absolutely stable, while the other end is unstable, with relative stability located between the two ends. In practice, the relative stability of fractures is easier to achieve, has a wider range of applications, and is more similar to the natural process of fracture healing.

Our review also has certain limitations. Firstly, since the exploration of fracture healing mechanisms is not the focus of our discussion, the literature in the field we have summarised is not very sufficient. Secondly, the exploration of fracture treatment principles and theories is also based on our daily work experience, and the selected literature only represents the hot topics in the field we want to discuss. There are also some other treatment principles and concepts that have not been discussed by us. But this does not affect the content of our review.

5. Conclusions

Absolute stability is a definition that cannot be quantified. Whether the defined absolute stability can be truly achieved during internal fixation of fractures requires further in-depth research, or it is simply the ultimate goal of fracture treatment and healing. The concept of relative stability is more in line with practical situations and can better explain most clinical outcomes. Alternatively, our strategy is to maximise relative stability in a soft tissue-friendly environment by implementing appropriate rehabilitation plans, such as early avoidance of weight-bearing and active exercise. This may reduce the load on the fracture site and minimize or avoid micromovements, thereby achieving primary healing resulting from anatomical reduction and secondary healing resulting from non-anatomical reduction. In fact, satisfactory fracture treatment outcomes may be obtained by a balanced relationship between the mechanical environment of fracture fixation strength, soft tissue blood supply, the presence or absence of an infectious environment with biological activities, and reasonable rehabilitation plans. If the balance is broken, fracture healing will not be achieved, which significantly increases nonunion and infection risks (**Figure 8**).

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Ethics approval and consent to participate
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