Common Causes of Aseptic Fracture Fixation Failure

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Mark Johnson, Grayson Norris, Jake Checketts, and Brent L. Norris

Introduction

Millions of fractures occur annually across the globe. Treating these injuries to union with maintenance of limb alignment and function is the ultimate goal. Surgical and nonsurgical management are used to treat these injuries and are often based on a multitude of factors including, but not limited to, fracture type, fracture displacement and associated injuries. When surgery is chosen, physicians must know the most likely outcome and certainly the possible complications that may occur, including nonunion of the fracture. It is estimated that up to 8–10% of all fractures will go onto nonunion [1]. When a fracture is treated surgically with internal fixation and a nonunion occurs, it is very likely the internal fixation will fail. Failed fixation in a delayed fashion is practically pathognomonic for a nonunion. When this occurs, the root cause of the nonunion must be identified. The following chapter is meant to help guide surgeons in the management of aseptic fracture fixation failure and the associated nonunion. It will reflect on the normal bone healing process, review how the biomechanics of the different surgical devices affect healing and finally, review the types of nonunions and the biomechanical and metabolic causes for nonunion.

M. Johnson
Department of Orthopaedic Surgery, Creighton University, Omaha, NE, USA

G. Norris
University of Oklahoma College of Medicine, Oklahoma City, OK, USA

J. Checketts · B. L. Norris (✉)
Department of Orthopaedic Surgery, Oklahoma State University College of Medicine, Tulsa, OK, USA
e-mail: brent.norris@otsok.com

Bone Healing Process

The physiologic processes governing bone healing are multifaceted and complex.

However, the general principles behind the various types of fracture healing are well described. It is commonly held that there are two major pathways by which bones can heal, either through the primary (direct) or secondary (indirect) pathway. The direct pathway generally follows an intramembranous physiologic course whereas the indirect pathway involves aspects of both intramembranous and endochondral ossification. The understanding of both physiologic pathways is critical in the management of various fractures so that complications such as delayed union, nonunion and malunion can be avoided [2].

Indirect fracture healing is the most common form of fracture healing, and it is most notably associated with nonoperative treatment but is also associated with relatively stable (nonrigid) surgical fixation of a fracture (external fixators and intramedullary nails) [3, 4]. Indirect healing

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occurs over the span of weeks to months and is a complex process involving many physiologic components. Indirect healing begins with the acute inflammatory phase, which involves the formation of a hematoma surrounding the fractured ends. This hematoma contains blood from both the periphery and medullary canals as well as bone marrow cells. Upon the formation of the hematoma, an inflammatory response mediated by macrophage release of tumour necrosis factor (TNF) promotes hematoma coagulation, angiogenesis and osteogenic differentiation of mesenchymal stem cells (MSCs). Other inflammatory mediators that aid in this process include interleukin-1 (IL-1), IL-6, IL-11 and IL-18 [5]. Following this inflammatory response, granulation tissue forms at the fracture site, which allows structure for endochondral activity to take place [6]. This initial endochondral activity forms what is commonly referred to as the soft callus, a collagenous medium that provides a semi-stable structure. Simultaneous to the formation of the soft callus, intramembranous ossification occurs at each end of the fracture creating what is referred to as the periosteal hard callus [3]. It has been previously described that the TGF superfamily plays an essential role in the signalling process of endochondral ossification, whereas bone morphogenetic protein-5 (BMP-5) and −6 have been shown to be predominant signalling molecules for intramembranous ossification [7].

Following the formation of the cartilaginous callus, angiogenesis and revascularization occur through the actions of vascular endothelial growth factor (VEGF), in combination with chondrocyte apoptosis, so that blood vessels may penetrate the callus. Once the soft callus has been constructed and revascularized, new bone formation begins. This process involves the simultaneous central movement of the periosteal hard callus, combined with the mineralization and resorption of chondrocytes within the soft callus. Soft callus hypertrophic chondrocytes undergo calcification of the extracellular matrix via calcium and phosphate precipitation. These precipitates will later undergo homogeneous nucleation in the process of apatite crystal formation [8]. The combination of both endochondral and intramembranous ossification creates a hard callus structure that ultimately undergoes TNF-/IL-1-mediated osteoclastic/osteoblastic transformation into woven bone via the formation of Howship's lacunae [3].

Direct fracture healing occurs over the span of a few months to years and requires an anatomic reduction of the fracture and rigid internal fixation (often associated with open reduction and internal fixation with plates and screws). The direct healing process can occur through two different physiologic pathways depending on the size of the fracture gap, contact healing and gap healing. When the fragments are less than 0.01 mm apart and there is an interfragmentary strain of less than 2%, the direct process known as contact healing can take place [6, 9]. When the fragments are around 1 mm apart, the bone can still heal via direct bone healing through a process known as gap healing.

Contact healing begins with the formation of cutting cones on both fragments closest to the fracture site. The front ends of the cutting cones contain osteoclasts, which can cross the fracture line and generate longitudinal canals between the two fragments. Following the formation of these canals, osteoblasts located on the rear ends of the cutting cones lay down new bone and establish a union between fragments [10]. Additionally, the formation of this union restores the Haversian system allowing for angiogenesis and migration of osteoblastic precursors. These precursor cells subsequently remodel the bridged osteons into lamellar bone, eliminating the need for periosteal callus formation [11].

Gap healing differs from contact healing due to additional steps at the beginning of the healing process. Due to the larger fracture gap, the remodelling of the Haversian system and formation of bridging osteons do not occur synchronously [10]. Instead, lamellar bone is initially laid down perpendicular to the long axis of the bone to lessen the size of the gap. This initial structure of lamellar bone is subsequently replaced by correctly orientated vascularized osteons that deliver osteoblastic progenitor cells, which produce a structure that then allows for a secondary remodelling process comparable to contact healing to take place. The additional bone forming steps prior to secondary remodelling

observed in gap healing are believed to take anywhere from 3 to 8 weeks [9].

Influence of Mechanics on Fracture Healing

Though there are many challenges to managing fracture healing, advances in treatment methods have progressed rapidly over the last century. Management options include casting, pins, plates/screws, intramedullary devices, uni–/biplanar external fixators, ringed external fixators and arthroplasty [12]. Overall, the aims of these treatment methods are to provide mechanical stability to the fracture and support/direct the biological factors associated with fracture healing. Despite these advances, fracture nonunions continue to occur. Furthermore, hardware failure due to nonunion or poor construct mechanics and new fractures around previously placed orthopaedic hardware are becoming increasingly common as the population ages [13, 14]. Both of these conditions present additional challenges to the treating surgeon from both a practical and a biological standpoint.

Stability and Strain Theory

Fracture healing has been thoughtfully described by Norris et al. as a spectrum of stability. At one end of the spectrum is absolute stability which will induce primary bone healing. At the other end of the spectrum is instability which will likely result in nonunion of the fracture site. In the middle of the spectrum is relative stability which will result in secondary bone healing. If blood supply and soft tissue coverage are adequate, fracture healing will be greatly influenced by the type of mechanical environment induced by the chosen fixation method. Thus, when managing fractures operatively, great care and thought must be placed regarding the environment one is aiming to produce at the fracture site through internal or external fixation. Understanding the fracture healing environment cannot be done without first understanding the strain theory postulated by Perren et al. [15]. This theory summarizes the concept of fracture strain as the degree of deformity or motion that is present at the fracture gap as a consequence of the fixation construct's inherent stability. Strain is measured by comparing the original fracture gap to the size of the gap when it is stressed. If the strain is calculated to be $\leq 2\%$, it can be determined an environment for absolute stability, and thus primary bone healing has been created. However, if the strain is measured between 2% and 10%, a relative stability construct has been obtained and fracture healing will occur in a secondary fashion through a cartilage medium. Understandably, if the strain is measured over 10%, the healing will be through a fibrous tissue intermediate and likely result in nonunion of the fracture site.

Intraoperatively an environment of absolute stability can be obtained through proper technique and fixation of the fracture being managed. This is primarily performed with simple fracture patterns (transverse, oblique and spiral). It is additionally employed in fractures involving the articular surfaces. Absolute stability is primarily accomplished by creating compression at the fracture site utilizing lag screws or compression plates, buttress plates and tension band constructs [12] The goal in treatment using these methods is to approximate the fracture to a point where there is no gapping present to allow cutting cones and appositional bone growth to occur.

Conversely, an environment of relative stability can be obtained where some interfragmentary motion between the fracture fragments occurs. This can be advantageous for several fracture types, including metaphyseal or diaphyseal fractures with comminution in which the conditions of absolute stability would likely not be met. Examples of constructs aimed at relative stability include casting, external fixation, bridge plating or intramedullary nail devices.

Proper preoperative planning and construct selection is essential to increase the odds of fracture healing; however, proper execution of the plan is also of the utmost importance. For example, if the goal is to treat a fracture using an absolute stability construct but fracture gapping is present, a delayed union or nonunion may occur. On the other hand, if one's goal is to treat a fracture with a relative stability construct, but their

construct allows too little motion (<2% strain), the construct will be too stiff and a nonunion may occur. An example of this would be attempting to treat a comminuted fracture with bridge plating but placing screws too close to the fracture site, thus creating a short working length and a stiff construct. Conversely, if too much motion is allowed at the fracture site due to inadequate fixation of the fracture fragments (>10% strain), callus formation may occur, but consolidation or bridging may not occur resulting in a nonunion. A classic example of this is seen when treating a proximal tibia and distal femur fractures with intramedullary nailing where too much motion is allowed at the fracture site, and thus delayed or nonunion may occur. Knowledge of fracture healing types, strain theory and construct stability and selection is essential to managing fractures effectively. As stated by Norris et al. [12]' All the preoperative planning based on biomechanics will not overcome severe shortcomings in the biological environment of the fracture. Maintaining and maximizing the healing capacity of a fracture must always be considered when formulating a preoperative plan.'

Plate Fixation Mechanics

Depending on the goals of the treatment, plate constructs have a myriad of possibilities and functions resulting in either primary or secondary fracture healing. These included compression, bridging, neutralization, buttress and tension band constructs. It should be noted that these functions are carried out through the surgical technique applied, not the specific plate selected [16]. When treating fractures with plating, the surgeon is directing and determining the extent of the forces the fracture fragments endure during the healing process. These forces are bending, torsional and axial forces, and for the fixation to endure and fracture healing to occur the construct must provide the stability necessary for either primary or secondary healing. In addition to the forces endured by the fracture, the construct selected affects the biomechanical principles present at the fracture. Other biomechanical properties that must be factored into fracture management are affected by the bone density, geometry of the fracture, plate thickness (which is directly proportional to the construct stiffness) and bone–plate interface friction. When a construct has load applied to it, the interface between the cortex and hardware utilized is where the forces are directed and the stability of the construct during this load is dependent on friction (non-locking screws) and interlocking mechanical forces (locking screws).

Nonlocking plates (such as compression and buttress plates) classically rely on interlocking mechanical forces (screw torque) and bone–plate friction for their construct stability. Higher screw torque and frictional forces are seen when bone density increases, indicating increased stability of the construct when placed in quality bone. Due to this principle, a different type of plate construct was created for better fixation in poor quality or osteoporotic bone. Locking plates work through different principles, as they primarily serve as internal fixators. They do this by creating a fixed angle construct and a more stable bone–plate unit by using threaded screw heads that interdigitate with the threaded holes of the plate. Thus, stability is determined by the interlocking mechanical forces of the screw to the plate allowing a stiffer construct in less dense bone. However, the biomechanics of the bone–plate construct rely on several factors outside of whether it is locking or nonlocking. The distribution and variety of screws as well as the length of the plate also play a large role in the mechanics of the construct [17]. The resistance to pull out forces is directly proportional to the length of the plate on each side of the fracture as well as the spread of the screws in the plate. The distance between the screws closest to the fracture on each side is defined as the working length, and the closer this distance, the stiffer the construct will be. Conversely, the screws subject to the highest degree of pullout forces are those that are closest to the fracture on each side as they bear the greatest proportion of load. Furthermore, increasing the distance between the proximal and distal screws on each side of the fracture increases the stability of that segment and adding additional screws on each segment increases the torsional rigidity. Finally, the material of the plate used can

be a factor in regard to fracture healing. Traditionally, stainless steel plates have been used with great success. However, in recent years the use of titanium plates has been met with enthusiasm as titanium's modulus of elasticity is much closer to bone than stainless steel (less stiff) thus potentially promoting greater osseointegration and healing.

Intramedullary Device Mechanics

Diaphyseal and metadiaphyseal fractures of long bones are common, and to restore length, alignment and rotation, operative intervention is usually necessary. Over the last century, intramedullary fixation has evolved and advanced to become the most prevalent means of stabilizing diaphyseal and metadiaphyseal fractures of the long bones. From a biological perspective, intramedullary nails have advantages that are not seen with plates and screw constructs. When placing an intramedullary device, the incision and access to the long bone is generally at the proximal or distal end of the bone, likely some degree of distance away from the fracture site. Because of this, the biology of fracture healing is maintained and undisturbed as it often is with the direct access necessitated for plate and screw constructs. Furthermore, because the nail is intramedullary in nature, there is less periosteal injury that is associated with a bone–plate construct. The biomechanics of the nail and its relationship with bone can have a direct effect on fracture stability and healing. One of the ways intramedullary nails affect fracture healing is through their flexibility, which is a result of nail material, size and geometry. As such, modern intramedullary nails are largely composed of titanium alloy metals as they have a better modulus of elasticity compared to stainless steel and more closely resemble that of bone. These characteristics promote a relatively stable construct and promote callus formation/fracture healing. Because long bones are exposed to bending and torsional forces to a high degree, intramedullary implants must be able to resist these stresses during fracture healing while still allowing the natural elasticity of bone. At baseline, intramedullary fixation will provide a high degree of bending stability in the sagittal and coronal planes; however, to overcome torsional forces, proximal and distal interlocking screws are introduced on each side of the fracture creating a construct that provides the necessary stability to both bending and torsional forces [18]. When a fracture is treated with intramedullary nailing, there is inherent flexibility as it acts as an internal fixator, and as a result micromovements of the fracture are expected. Because of this, fractures treated with intramedullary devices will heal with secondary healing and callus formation. Furthermore, because locked intramedullary nails provide stability in all planes, early weight-bearing is often encouraged for the patient and this likely also positively influences secondary bone healing.

External Fixators Mechanics

There are two types of external fixation, and they have both evolved significantly over the past few decades. Uniplanar external fixation is predominantly used to provisionally stabilize open fractures or fractures that are too swollen to be treated in an open fashion acutely. Ring fixation has now become associated with a form of definitive fixation for not just complex problems like bone transport, infected nonunions with poor soft tissues and also complex periarticular fractures. For the most part, external fixators are a form of relative stability and behave much like bridge plating or intramedullary nailing. They can however be modified to become very rigid and act like plates placed for absolute stability. In some ways, external fixation, especially ringed fixators, is the ideal surgical treatment as you can dial in the necessary level of stability needed for any given situation. Having said this, the use of the ringed fixator has a steep learning curve and is probably the least well-tolerated device by most patients.

Definition of Nonunion

Every fracture treated with surgical fixation becomes a race of achieving osseous union versus a nonunion with ensuing fixation failure. If osseous union has not been achieved within

9 months or a fracture has failed to show progressive healing over 3 consecutive months on radiographs, a nonunion can be declared [19, 20]. When this occurs the internal fixation present continues to endure cyclical stress and motion. Eventually, the hardware will reach its breaking/endpoint leading to a hardware failure. Failure can be simply loosening of the fixation or catastrophic failure (breakage of the implant).

Types of Nonunion (Septic)

A primary consideration in nonunion revision surgery is understanding the type of nonunion present. The primary factor that must be ruled out first and foremost is whether the fracture failed to unite because of an infectious process (septic nonunion). Septic nonunions are probably the most common type of nonunion. One of the most critical steps in a nonunion workup is to rule out infection. An infection at the nonunion site changes the goals of any revision surgery from achieving union to first eradicating infection. Nonunions with an unknown infection present at the time of definitive treatment have demonstrated an increased need of further surgeries and decreased chance of achieving union when compared to true aseptic nonunions [21–23].

Ruling out an infection begins with taking a thorough history, including mechanism and type of the initial injury, medical comorbidities, social habits, surgical procedures performed and any complications. Details such as history of an open fracture, the environment in which the open fracture occurred, the degree of initial contamination, the Gustilo-Anderson type of open fracture, length of time to soft tissue coverage/closure, extended period in external fixators before conversion to intramedullary nail, history of smoking, persistent wound drainage and prior number of surgeries for nonunions have all been associated with infection and should be clues to the surgeon for further investigation.

Clinical signs of infected nonunions can be obvious or subtle, local or systemic, associated with or without abnormal laboratory findings and associated with or without radiographic abnormalities. Obvious signs of a fracture-related infection are a sinus tract or wound breakdown with purulent drainage. Subtle signs of infection include systemic signs like night sweats, fever or malaise. Local signs like swelling, pain, can also suggest local infection.

In addition to these findings, elevated laboratory values are often seen with septic nonunions [24]. Common inflammatory markers used to examine for infection are white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [24]. Recently, IL-6, D-Dimer and other inflammatory markers have been examined to see whether they can further aid in the diagnosis of a fracture-related infection, but much more data will need to be obtained before they can be recommended to be part of the screening process [25, 26].

Signs of infection are not always present and when they are not, it can make the process of diagnosing a septic nonunion extremely difficult. If the systemic, local and radiographic signs do not indicate an infection, surgeons rely on inflammatory markers to help rule out infection. However, inflammatory markers remain within normal limits with low virulent organisms [27–29].

Finally, radiographs (plain film, computed tomography [CT] and even magnetic resonance imaging [MRI]) are not diagnostic of infection. They can certainly suggest it with signs like sclerosis, erosive changes to the bone/fracture or even hardware loosening [24]. MRI can also show signs suggestive of infection. Typical findings of osteomyelitis seen on MRI are decreased T1 signal and increased T2 signal due to marrow oedema. However, these can also be seen in the setting of stress reaction, reactive marrow and neuropathic arthropathy.

This places the gold standard for diagnosing fracture/nonunion-related infections intraoperatively. This occurs by having at least two positive cultures from separate deep tissue/implant specimens and/or the presence of microorganisms in deep tissue specimens confirmed by histopathological examination [24]. Ultimately, this makes preoperatively diagnosing an indolent septic nonunion very difficult and places an importance of obtaining intraoperative cultures. Therefore, any revision surgery must include gram stain and cultures to rule out infection (Fig. 2.1). This has led

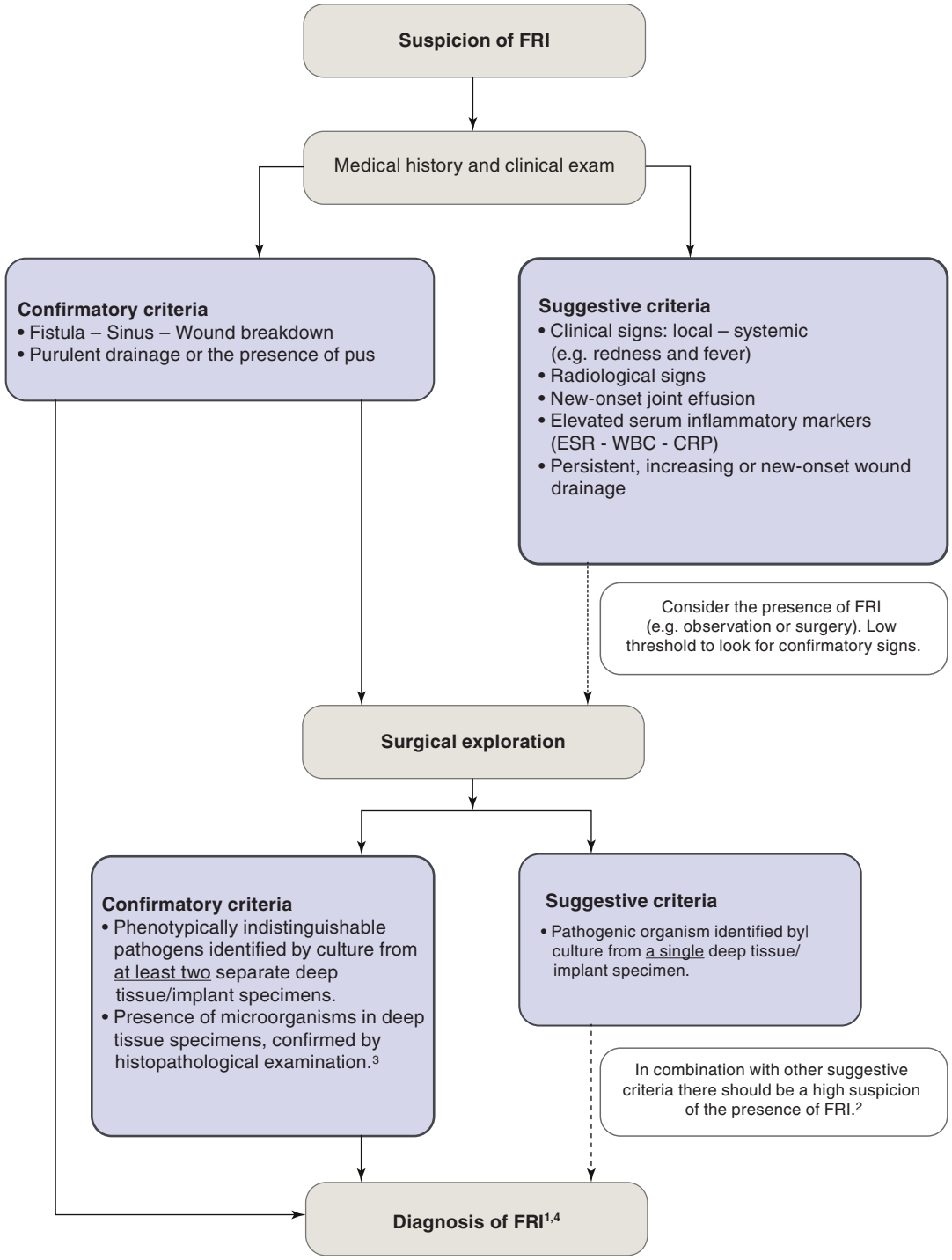

Fig. 2.1 Algorithm for fracture/nonunion-related infection. From WJ Metsemakersa, SM Morgenstern, MA McNally, TF Moriarty, I McFadyen, M Scarborough, NA Athanasou, PE Ochsner, R Kuehl, M Raschke, O Borens, Z Xie, S Velkes, S Hungerer, SL Kates, C Zalavras, PV Giannoudis, RG Richards, MHJ Verhofstad. "Fracture-related infection: A consensus on definition from an international expert group." *Injury*, vol. 49, 2108, pp. 505–510

a lot of surgeons performing staged treatment of the nonunion with first ruling in or out infection followed by definitive treatment if negative cultures are obtained. This is especially important if you are planning on placing an autogenous bone graft.

Types of Nonunion (Aseptic)

Assuming we have ruled out sepsis as the cause of the nonunion, we must then work up and identify any shortcomings of the mechanical and biological requirements that were not met during the prior intervention. Identifying and then correcting these will help optimize the outcome in revision surgery and provide the best chance for union.

Aseptic nonunions are divided into four categories: hypertrophic, oligotrophic, atrophic and pseudoarthrosis. Hypertrophic nonunions are viable and possess adequate blood supply for union but lack fracture stability required to complete union. This results in an abundance of callus present at the fracture with an interfragmentary gap consisting of fibrocartilage persisting (Fig. 2.2). If stability is provided, mineralization of fibrocartilage can occur, which will eventually lead to the formation of mature bone [30]. Hypertrophic nonunions are most frequently seen in internal fixation with inadequate strength such as undersized intramedullary nails and external fixators used for definitive treatment and in nonoperative treatment.

Atrophic nonunions are nonviable and lack any purposeful biological activity. This leads to a lack of callus formation (Fig. 2.3). The nonviability is demonstrated at the fracture edges where sclerotic avascular bone is seen. This can be due to traumatic or systemic causes. Large displacement of the fracture at the time of injury can lead to significant periosteal and soft tissue stripping, potentially devitalizing the fracture. Aggressive surgical dissection and endosteal reaming can also devitalize the bone, limiting the biological response at the fracture site. Systemic causes such as smoking and diabetes can decrease microvascular blood flow to the fracture, limiting the ability to create a biological response.

Oligotrophic nonunions are likely also viable and possess an adequate blood supply, but they result in minimal to no callus formation (Fig. 2.4). The viability can be demonstrated at the fracture

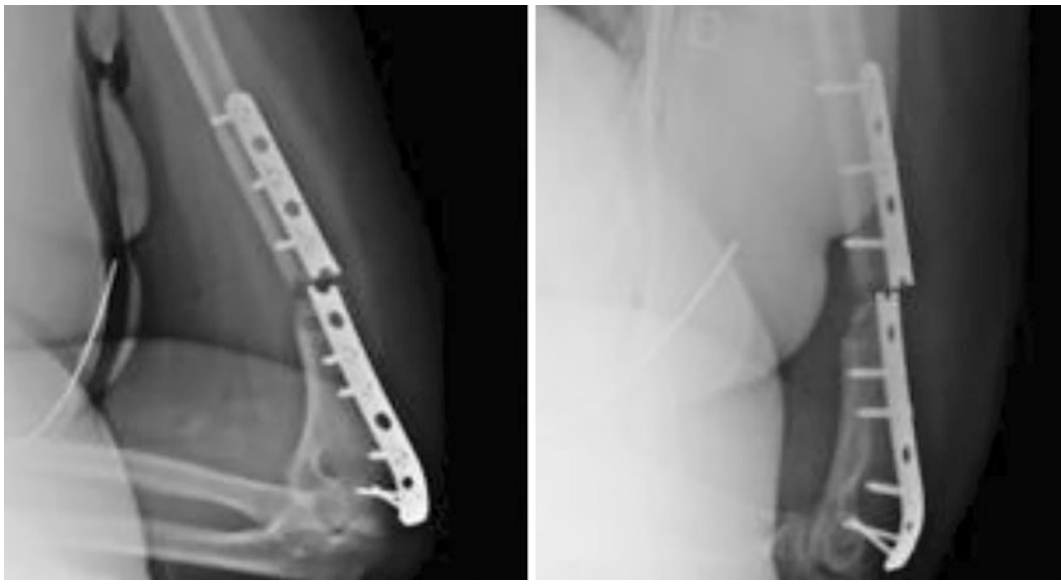

Fig. 2.2 AP and lateral radiographs of left humeral atrophic nonunion

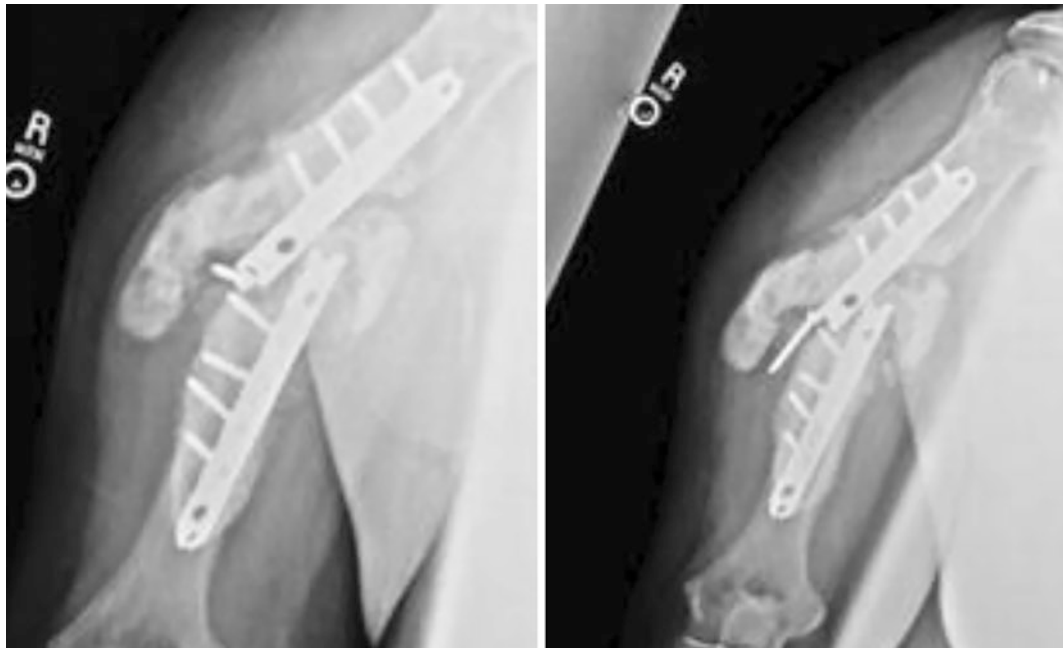

Fig. 2.3 AP and lateral radiographs of left humeral hypertrophic nonunion

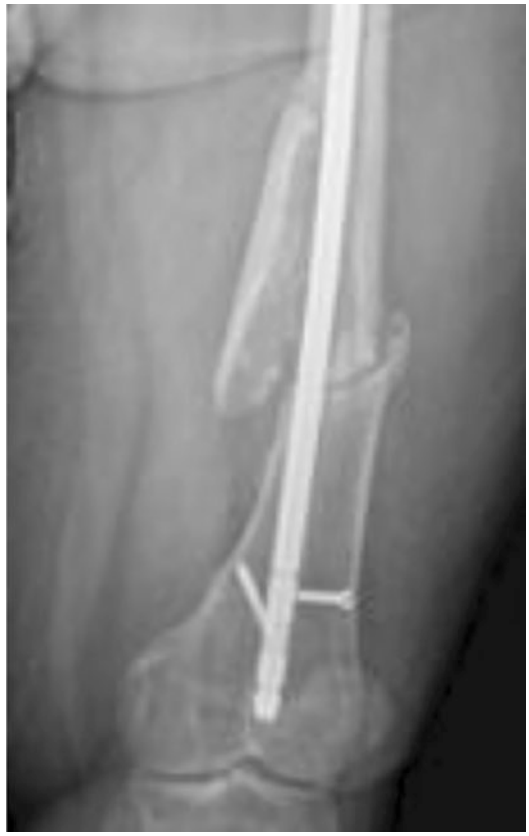

Fig. 2.4 AP radiograph of the left femur showing oligotrophic nonunion

edges with a lack of sclerosis and bleeding present. They are most often caused by inadequate reduction that results in little to no contact at the displaced osseous surfaces.

Pseudoarthrosis is an unusual type of nonunion that can occur for many reasons but commonly occurs when there is excessive motion at a fracture site. There is some thought that this condition might have a genetic predisposition. It can occur from surgical and nonsurgical treatment of the fracture. When it occurs from operative treatment, the surgical stabilization will have failed leading to excessive motion at the fracture. Secondary to the excessive motion, the tissue between the fragments is fibrocartilaginous and/or granulation tissue in nature. This tissue seals off the medullary canal and forms a cavity that will often be lined in synovial-type cells. This cavity bathes the nonunion in fluid giving this type of nonunion its namesake. This type of nonunion is common in the femur, tibia and humerus.

Radiographic and Mechanical Workup for Nonunion

Radiographs from all stages of the injury and treatment should be obtained. Injury films can help determine the initial displacement of the injury and the type of fracture pattern. Fractures with a large displacement can have extensive periosteal stripping, limiting the biological capacity of the fracture after the index surgery. Postoperative imaging allows for assessment of the reduction, fixation technique and the overall hardware construct. Follow-up films will provide a sequential glance of the fracture to see if any healing of comminuted, butterfly or segmental pieces occurred. Follow-up films also help determine if deformity occurred and if it did whether it was a gradual process or if it was a sudden event with hardware failure. Radiographs obtained should include:

- Full length anteroposterior (AP) and lateral of the bone involved.
- AP, lateral and oblique views of the nonunion site.
- Bilateral AP and lateral 51-inch alignment radiographs for lower extremity nonunions to assess length discrepancies and malalignment.
- Flexion and extension lateral radiographs to determine the arc of motion of the adjacent joint to the nonunion site [30].

Even with this extensive amount of radiographs, it may be difficult to determine whether a fracture has healed. A CT scan can be used to help determine this even in the presence of metallic artifact. Healing or healed fractures display greater than 25% of the cross-sectional area while nonunions demonstrate bridging callus over less than 5% of the cross-sectional area [33]. CTs can also be used to determine whether any rotational deformities are present that need to be corrected in the following surgery.

Collecting all this radiographic information allows the surgeon to determine the type of nonunion, if deformity is present, type and status of the hardware implanted and how/when hardware failure occurred. If the wrong fixation technique was paired with a specific fracture, the bone could have been forced down a healing pathway that did not lead to union. This is important when creating a revision operative plan to maximize the hardware construct but also to prevent from using the wrong technique.

This can be seen when surgeons attempt primary bone healing and do not achieve an anatomic reduction and when attempting secondary bone healing and incorrectly place too rigid of a surgical construct around comminuted fractures. In both of these situations the fracture gap is too large to allow primary bone healing, but the fracture is placed in too rigid of an environment to allow secondary bone healing.

If an anatomic reduction cannot be achieved, there are multiple ways to increase motion at the fracture site. Increasing motion can help drive fracture strain to 2–10% where relative stability and secondary bone healing occur [15]. Relative stability is best used to treat comminuted fractures, osteoporotic fractures, paediatric fractures and fractures of the long bones in the lower extremity. Common relative stability treatment methods include casting, intramedullary nails, bridge plating and external fixators.

Creating and maintaining an environment of relative stability during fracture healing is dependent on the surgeon. Surgeons can decrease the construct's rigidity to increase motion at the fracture site with factors including plate design, plate length, plate size, plate material, screw length, screw type, screw density and working length. The working length of a plate construct is defined as the distance between the first screw on either side of the fracture [31]. In the setting of a simple fracture pattern anatomically reduced, a short working length can be advantageous by decreasing the strain at the fracture pushing the bone towards primary bone healing. However, in the setting of comminuted fractures, a shorter working length will create a low strain environment and drive the bone to attempt primary bone healing. If the fracture gap is too large, healing will not occur and an oligotrophic nonunion will likely occur.

Shorter working lengths can also have undesirable effects on the hardware as well. Shorter plates have shown to be a risk factor for hardware failure on distal femur fractures [32]. A short plate limits the amount of working length that can be obtained. Shorter working lengths create a high-stress environment at the fracture that is transferred to the hardware leading to hardware failure if bony union cannot occur prior to the breaking point of the hardware. A longer working length decreases the stress seen by the hardware decreasing the risk or hardware failure. Increasing the working length in fractures treated with relative stability has shown to increase flexibility, increase strain and in theory promote secondary bone healing, callus formation and fracture healing [33].

Fixation constructs are one of the few things surgeons can control when treating fractures. It is extremely important to critically analyse any hardware failure on how the construct could have prevented failure and promoted union. An ignorance of failed constructs can lead to repeating the same surgical misadventures that previously failed all while expecting a different result to occur. Placing the fracture or nonunion in the optimal mechanical environment will provide the best chance possible for union.

Metabolic Workup for Nonunion

Creating the ideal fracture construct and environment still may not overcome severe shortcomings in the healing capacity of a patient. A variety of contributing factors have been described that deter the biological environment of fracture healing and these must be corrected to place the fracture in the optimal healing environment.

This can start with an assessment of medications the patient uses. Bisphosphonates, systemic corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and quinolones have all shown to have negative effects on bone healing [34]. The offending medications should be changed or discontinued if possible prior to revision surgery.

Social habits such as smoking and alcohol consumption should be examined. Smoking has not only been shown to slow and inhibit fracture healing but also be a risk factor for osteomyelitis, infection and complications in healing fractures [35–39]. Chronic alcoholism can result in an osteopenic skeleton by suppressing osteoblastic differentiation of bone marrow and promoting adipogenesis [40]. Excessive alcohol in the postinjury period interferes with the fracture healing process by creating bone with decreased strength, density and mineral content [41, 42].

Excessive alcohol use not only changes the biology and healing response of the bone, but also causes falls and noncompliance with postoperative precautions leading to potential hardware failure. Alcohol use of greater than 15 drinks a week has been shown to be a cause for multiple reoperations in clavicle fractures treated operatively [43]. Patients with these habits should be offered assistance in quitting the addiction. Cessation of the habit would be most ideal; however, it may be unrealistic to expect this to occur.

A thorough workup for potential metabolic or endocrine aetiologies of nonunion should be performed prior to any operation. Brinker et al. demonstrated that 84% of patients who failed to heal a simple fracture demonstrated correctable endocrine or metabolic abnormalities [44]. This should be performed by obtaining serum levels of calcium, vitamin D, parathyroid hormone, thyroid panel and an haemoglobin A1c. Brinker et al. even recommend patients with nonunions to be evaluated by an endocrinologist if they fall into one of these criteria: (1) persistent nonunion despite adequate treatment without any obvious technical errors; (2) a history of multiple low-energy fractures with at least one progressing to a nonunion or (3) a nonunion of a nondisplaced pubic rami of sacral ala fracture (Fig. 2.5). This protocol allows endocrine processes such as central hypogonadism to be diagnosed and treated.

Vitamin D, calcium and parathyroid hormone (PTH) have the most direct effect on bone metabolism during fracture healing. Irregularities in their values can be present in up to 50% of people

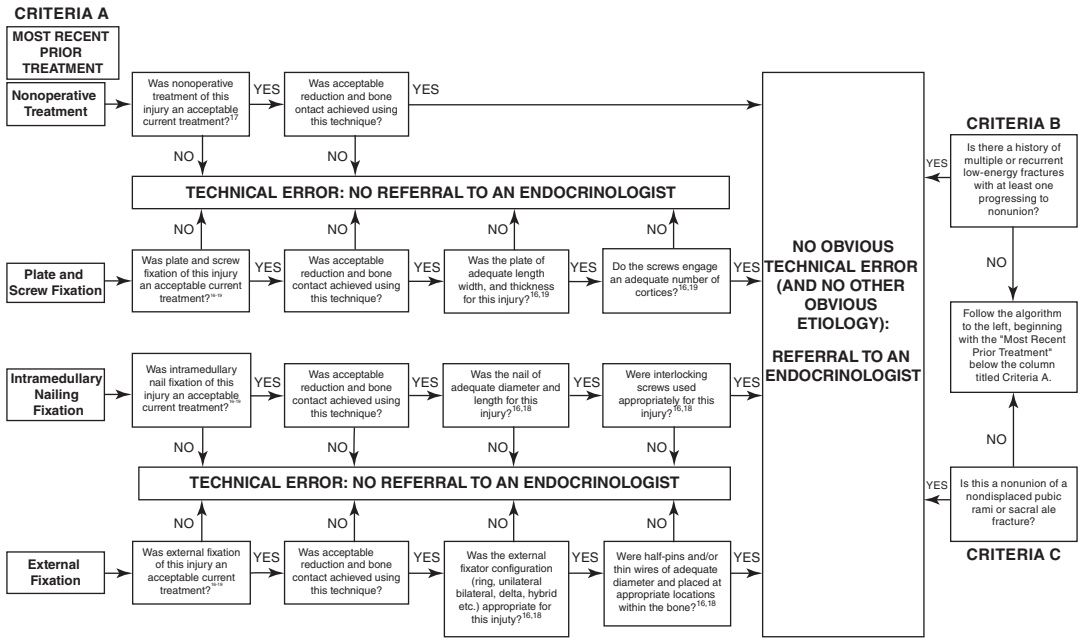

Fig. 2.5 Flowchart for endocrinology referral for patients with nonunion of a fracture. From Brinker, Mark R., et al. "Metabolic and endocrine abnormalities in patients with nonunions." *Journal of Orthopaedic Trauma*, vol. 21, no. 8, 2007, pp. 557–570

[45, 46]. However 68% of patients with nonunions have demonstrated having irregularities in these labs. Some patients (almost 25%) with these abnormal labs may achieve union with just correcting the abnormal labs [44].

Protein deprivation has shown to have an adverse effect on fracture healing [47]. Serum level albumin, total lymphocyte and transferrin should be obtained and if the levels are below normal limits a nutritional consultation is recommended [48]. It is imperative that this is identified and reversed with optimization occurring prior to revision surgery if possible. Reversal of the malnourished state is shown to increase bone mineralization promoting a larger and stronger fracture callus during the healing state [49].

Diabetes has been shown to have detrimental effects in bone healing that lead to decreased callus size, decreased bone formation and decreased mechanical strength [50]. However these effects can be reversed with adequate glycaemic control [51]. Long-term glycaemic control can be monitored with haemoglobin A1c and is best to delay surgery until it approaches 7% [48].

Much like diabetes, hypothyroidism has been shown to cause decreased callus size and bone formation. This is due to the inhibition of endochondral ossification during fracture healing. These effects can be reversed with thyroid supplementation to normalize hormone levels [52].

Hyperthyroidism as well has shown to affect osseous health and healing. Thyrotoxicosis can promote secondary osteoporosis leading to bone that is more prone for hardware failure [53]. Iatrogenic hyperthyroidism, due to oversupplementation, has shown to be present in persistent nonunions [45]. Patients with existing thyroid issues should have a thyroid panel drawn to ensure their medication is being prescribed appropriately. Once again, normalization of these hormones should be achieved prior to revision surgery.

Metabolic abnormalities should be evaluated and addressed as part of the workup for fractures with failed fixation and/or nonunion. If the surgeon neglects this exercise prior to undertaking any revision surgery for the failed fixation/nonunion, they are setting themselves up for continued failure.

Conclusion

For a variety of reasons, fractures fail to heal and become nonunions. If surgical stabilization was used in the initial treatment, failed fixation is not uncommon and almost uniformly needs to be removed and/or revised to obtain bone union. The treating surgeon must remember the cause of nonunion may be multifactorial. First and foremost, septic nonunion must always be ruled out. A thorough preoperative history, physical exam, radiographic studies and laboratory analysis should be undertaken. Additionally, the type of nonunion gives us a clue as to the root cause of nonunion, which can be biological, mechanical, patient related, injury related or even treatment related.

Successful management requires adequate and correct assessment of any/all discernible cause(s) of the nonunion. These include eradicating infection, correcting metabolic abnormalities, adequately stabilizing the bone, introducing biology with bone grafting, cell-based therapies, biological adjuvants and finally restoring a sound vascular environment. Nonunion surgery remains a difficult clinical entity that will challenge your professional acumen and require adherence to sound biological/mechanical principles to adequately restore limb alignment/function and achieve a successful outcome.

References

1. Zura R, Xiong Z, Einhorn T, et al. Epidemiology of fracture nonunion in 18 human bones. JAMA Surg. 2016;151(11):e162775. https://doi.org/10.1001/jamasurg2016.2775. Pub 2016 Nov 16
2. Marsell R, Einhorn TA. The biology of fracture healing. Injury. 2011;42(6):551–5. https://doi.org/10.1016/j.injury.2011.03.031.
3. Gerstenfeld LC, Alkhiary YM, Krall EA, et al. Three-dimensional reconstruction of fracture callus morphogenesis. J Histochem Cytochem. 2006;54(11):1215–28.
4. Pape HC, Giannoudis PV, Grimme K, et al. Effects of intramedullary femoral fracture fixation: what is the impact of experimental studies in regards to the clinical knowledge? Shock. 2002;18(4):291–300.
5. Cho HH, Kyoung KM, Seo MJ, et al. Overexpression of CXCR4 increases migration and proliferation of human adipose tissue stromal cells. Stem Cells Dev. 2006;15(6):853–64.
6. Rahn BA. Bone healing: histologic and physiologic concepts. In: Fackelman GE, editor. Bone in clinical orthopedics. Stuttgart/New York: Thieme; 2002. p. 287–326.
7. Marsell R, Einhorn TA. The role of endogenous bone morphogenetic proteins in normal skeletal repair. Injury. 2009;40(Suppl 3):S4–7. [PubMed: 20082790]
8. Ketenjian AY, Arsenis C. Morphological and biochemical studies during differentiation and calcification of fracture callus cartilage. Clin Orthop Relat Res. 1975;107:266–73. [PubMed: 48443]
9. Shapiro F. Cortical bone repair. The relationship of the lacunar-canalicular system and intercellular gap junctions to the repair process. J Bone Joint Surg Am. 1988;70(7):1067–81.
10. Kaderly RE. Primary bone healing. Semin Vet Med Surg (Small Animal). 1991;6(1):21–5.
11. Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res. 1998;355(Suppl):S7–21.
12. Norris BL, Lang G, Russell TAT, Rothberg DL, Ricci WM, Borrelli J Jr. Absolute versus relative fracture fixation: impact on fracture healing. J Orthop Trauma. 2018;32(Suppl 1):S12–6.
13. Checketts JX, Dai Q, Zhu L, Miao Z, Shepherd S, Norris BL. Readmission rates after hip fracture: are there prefracture warning signs for patients most at risk of readmission? J Am Acad Orthop Surg. 2020;28(24):1017–26.
14. Pivec R, Issa K, Kapadia BH, et al. Incidence and future projections of periprosthetic femoral fracture following primary total hip arthroplasty: an analysis of international registry data. J Long Term Eff Med Implants. 2015;25(4):269–75.
15. Perren SM. Physical and biological aspects of fracture healing with special reference to internal fixation. Clin Orthop Relat Res. 1979;138:175–96.
16. Kfuri M, Fogagnolo F, Pires RE. Biomechanics of plate and screw constructs for fracture fixation. In: Crist BD, Borrelli Jr J, Harvey EJ, editors. Essential biomechanics for orthopedic trauma: a case-based guide. Springer International Publishing; 2020. p. 171–8.
17. Törnkvist H, Hearn TC, Schatzker J. The strength of plate fixation in relation to the number and spacing of bone screws. J Orthop Trauma. 1996;10(3):204–8.
18. Kempf I, Grosse A, Beck G. Closed locked intramedullary nailing. Its application to comminuted fractures of the femur. J Bone Joint Surg Am. 1985;67(5):709–20.
19. Bhandari M, et al. Variability in the definition and perceived causes of delayed unions and nonunions: a cross-sectional, multinational survey of orthopaedic surgeons. J Bone Joint Surg Am. 2012;94(15):1091–6.

20. Bell A, et al. Nonunion of the Femur and Tibia: an update. Orthop Clin North AM. 2016;47(2):365–75.
21. Olszewski D, et al. Fate of patients with a "surprise" positive culture after nonunion surgery. J Orthop Trauma. 2016;30(1):19–23.
22. Amorosa LF, et al. A single-stage treatment protocol for presumptive aspetic diaphyseal nonunions: a review of outcomes. J Orthop Trauma. 2013;27(10):582–6.
23. Arsoy D, et al. Outcomes of presumed aspetic long-bone nonunions with postive intraoperative cultures through a single-stage surgical protocol. J Orthop Trauma. 2018;32(Suppl 1):S35–9.
24. Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I, Scarborough M, Athanasou NA, Ochsner PE, Kuehl R, Raschke M, Borens O, Xie Z, Velkes S, Hungerer S, Kates SL, Zalavras C, Giannoudis PV, Richards RG, Verhofstad MHJ. Fracture-related infection: a consensus on definition from an international expert group. Injury. 2018;49:505–10.
25. Wang Z, et al. Usefullness of serum D-dimer for preoperative diagnosis of infected nonunion after open reduction and internal fixation. Infect Drug Resist. 2019;12:1827–31.
26. Zhao X-Q, et al. Interleukin-6 versus common inflammatory biomarkers for diagnosing fracture-related infection: utility and potential influencing factors. J Immunol Res. 2021;14:616–38.
27. Brinker MR, et al. Utility of common biomarkers for diagnosing infection in nonunion. J Orthop Trauma. 2021;35(3):121–7.
28. van den Kieboom J, et al. Diagnostic accuracy of serum inflammatory markers in late fracture-related infection. Bone Joint J. 2018;100-B(12):1542–50.
29. Sigmund IK, et al. Limited diagnostic value of serum inflammatory biomarkers in the diagnosis of fracture-related infections. Bone Joint J. 2020;102-B(7):904–11.
30. Browner BD, Jupiter JB, Krettek C, Anderson PA, et al., editors. Chapter 25: skeletal trauma: basic science, management, and reconstruction. 5th ed. Saunders/Elsevier; 2009. p. 643–61.
31. Hoffmeier KL, et al. Choosing a proper working length can improve the lifespan of locked plates. A biomechanical study. Clin Biomech. 2011;26(4):405–9.
32. Ricci WM, et al. Risk factors for failure of locked plate fixation of distal femur fractures: an analysis of 335 cases. J Orthop Trauma. 2014;28(2):83–9.
33. Chen G, et al. Computational investigations of mechanical failures of internal plate fixation. Proc Inst Mech Eng H. 2010;224(1):119–26.
34. Wheatley BM, et al. Effects of NSAIDs on bone healing: a meta-analysis. J Am Acad Orthop Surg. 2019;27(7):330–6.
35. Zawawy HB, et al. Smoking delays chondrogenosis in a mouse model of closed tibia fracture healing. J Orthop Res. 2006;24:2150–8.
36. Little CP, et al. Failure of surgery for the scaphoid non-union is associated with smoking. J Hand Surg (Br). 2006;31:252–5.
37. Hak DJ, et al. Success of exchange reamed intramedullary nailing for femoral shaft nonunion or delayed union. J Orthop Trauma. 2005;14:178–82.
38. Castillo RC, et al. Impact of smoking on fracture healing and risk of complications in limb-threating open tibia fracture. J Orthop Trauma. 2005;19(3):151–7.
39. Scolaro JA, et al. Cigarette smoking increases complications following fracture: a systemic review. J Bone Joint Surg Am. 2014;96(8):674–81.
40. Chakkalakal DA. Alcohol-induced bone loss and deficient bone repair. Alcohol Clin Ex Res. 2005;29(12):2077–90.
41. Chakkalakal DA, et al. Inhibition of bone repair in a rat model for chronic and excessive alcohol consumption. Alcohol. 2005;36(3):201–2014.
42. Elmali N, et al. Fracture healing and bone mass in rats fed on liquid diet containing ethanol. Alcohol Clin Exp Res. 2002;26(4):509–13.
43. Schemitsch LA, et al. Prognostic factors for reoperation after plate fixation of the midshaft clavicle. J Orthop Trauma. 2015;29(12):533–7.
44. Brinker MR, et al. Metabolic and endocrine abnormalities in patients with nonunions. J Orthop Trauma. 2007;21(8):557–70.
45. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81(3):353–73.
46. Bogunovic L, et al. Hypovitaminosis D in patients schedule to undergo orthopedic surgery: a single-center analysis. J Bone Joint Surg. 2010;92(13):2300–4.
47. Day SM, DeHeer DH. Reversal of the detrimental effects of chronic protein malnutrition on long bone fracture healing. J Orthop Trauma. 2001;15(1):1947–53.
48. Cross MB, et al. Evaluation of malnutrition in orthopaedic surgery. J Am Acad Orthop Surg. 2014;22(3):193–9.
49. Hughes MS, et al. Enhanced fracture and soft tissue healing by means of anabolic dietary supplementation. J Bone Joint Surg Am. 2006;88(11):2386–94.
50. Kayal RA, et al. Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoblastic activity. J Bone Miner Res. 2007;22(4):560–8.
51. Kayal RA, et al. Diabetes causes the accelerated loss of cartilage during fracture repair which is reversed by insulin treatment. Bone. 2009;44(2):357–63.
52. Urabe K, et al. Inhibition of endochondral ossification during fracture repair in experimental hypothyroid rats. J Orthop Res. 1999;17(6):920–5.
53. Bassett JHD, Williams GR. Role of thyroid hormones in skeletal development and bone maintenance. Endocr Rev. 2016;27(2):135–87.