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Fracture healing: A review of clinical, imaging and laboratory diagnostic options

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ABSTRACT

A fundamental issue in clinical orthopaedics is the determination of when a fracture is united. However, there are no established "gold standards," nor standardized methods for assessing union, which has resulted in significant disagreement among orthopaedic surgeons in both clinical practice and research. A great deal of investigative work has been directed to addressing this problem, with a number of exciting new techniques described. This review provides a brief summary of the burden of nonunion fractures and addresses some of the challenges related to the assessment of fracture healing. The tools currently available to determine union are discussed, including various imaging modalities, biomechanical testing methods, and laboratory and clinical assessments. The evaluation of fracture healing in the setting of both patient care and clinical research is integral to the orthopaedic practice. Weighted integration of several available metrics must be considered to create a composite outcome measure of patient prognosis.

Introduction

There are an estimated six million fractures occurring annually in the United States, with 5–10% of these fractures proceeding to nonunion [1]. While no standardized definition of nonunion exists among orthopaedic surgeons, the Food and Drug Administration (FDA) defines nonunion as a fracture that persists for a minimum of nine months without signs of healing for at least three months [2]. The risk of developing nonunion varies significantly across cases and is attributable to a variety of factors. A history of smoking, for example, is one variable that has been demonstrated to increase risk of nonunion in long bone fractures by 12% [3]. Injury type, particularly open fractures, and anatomical location, such as the scaphoid bone, can also predispose a patient to nonunion [4–8]. Infection can present as a delay or failure of fracture repair, and the clinician should always consider this in their differential diagnosis.

Treating patients with nonunions requires a dramatic utilization of resources, which are significantly greater than those fractures that have uncomplicated healing [9–12]. A recent study demonstrates the enormous cost discrepancy between treating tibial shaft nonunions. The median total care cost for nonunions was reported as $25,556, more than double the $11,686 required to treat a standard tibia fracture [9].

Determining fracture union is a routine part of clinical care and plays a significant role in downstream decision-making, such as advancing a patient's weight-bearing status, proceeding to hardware removal and surgical intervention in fractures determined to have delayed healing or nonunions. Considerable disagreement among orthopaedic surgeons exists regarding radiographic and clinical criteria to define fracture union, in addition to the temporal component required for diagnosis of delayed or failed union [13]. This variability also exists in clinical research with a systematic review demonstrating eleven different criteria utilized to define union [14]. Similarly, clinical trials indicate a lack of objective tools to radiographically or clinically assess fracture healing, making union as a nebulous primary outcome [15].

The determination of fracture union is a critical decision in clinical orthopaedics; however there is no standard method to evaluate clinical fracture healing. This review provides an overview of some of the challenges in assessing fracture healing, examines the modalities currently available to diagnose nonunion, and discusses preferred methods for evaluation and decision making.

Challenges

Healing is a multifactorial process affected by a host of biological factors, injury characteristics and the mechanical

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environment. This complex system can be simplified into several stages of healing, beginning with hematoma formation, followed by inflammatory response, cell proliferation and differentiation, and finally ossification with subsequent remodeling of the new bone [16]. The interaction of these biological systems is poorly understood; however, the fundamental progression of fracture healing has been elucidated in a classic work by Mckibbin [17] and further described by Einhorn [18] and many others. There are numerous variables that affect the healing process and many ways in which this progression can be altered, resulting in delayed healing or, in extreme cases, nonunion.

Various patient-related factors have been reported to alter fracture healing. Female patients of advanced age have demonstrated comparatively poor healing outcomes and a potential increase in nonunion rate. Research suggests that deceased estrogen levels and generally diminished biologic activity may be responsible for the observed trends [19]. Metabolic and endocrine abnormalities are well established etiologies of nonunions. A recent study of patients with unexplained nonunions found that 83% of participants exhibited previously undiagnosed metabolic or endocrine abnormalities after being evaluated by an endocrinologist [20]. A history of smoking, diabetes and NSAID use have also been documented to delay the healing process and increase the risk of nonunion among patients [21–24].

Certain characteristics of fractures can also influence the progression of healing. Disruption of the soft tissue envelope through either an open fracture [25] or open reduction during intramedullary nailing [24] has been shown to increase the risk of nonunion. The degree of fracture comminution has also been shown to increase the risk of nonunion in open fractures, likely due to substantial damage of the periosteum and soft tissue at the fracture site [26,27]. The presence of a fracture gap has also been indicated to increase the nonunion risk [28], however, this variable must be taken in context with the fracture type (simple versus comminuted) and fixation strategy (compression or nail, bridge or external fixator).

The mechanical environment surrounding the fracture can also affect the healing process. This is highly dependent on the fracture characteristics and the fixation technique utilized. Perren's theory of interfragmentary strain postulates that reparative tissue will develop at a fractures site in accordance to the strain tolerance of the tissue and the local strain environment between fracture fragments [98]. According to this theory, simple fracture line that is not compressed and neutralized will have a higher likelihood for nonunion relative to a fracture site exposed to a high strain environment. Some technical factors can also affect union, for example, reamed femoral nailing reports a higher union rate than unreamed femoral nailing [29].

The various patient factors, biological and mechanical components combine to influence the rate of fracture healing. Some fractures are notoriously slow to heal, while certain patient populations, such as children, heal remarkably quickly. These challenges make predicting fracture union extremely difficult and further necessitate reliable quantitative assessments of healing.

Evaluation modalities

The tools currently available to assess fracture healing can be broadly divided into four categories: (1) Imaging studies, (2) mechanical assessment, (3) serologic markers and (4) clinical examination. We will briefly discuss each of these categories as well as their current use in research and clinical practice.

Imaging studies

Radiography. Radiographic assessment remains the mainstay of fracture healing evaluation. Clinicians' familiarity with radiography, combined with the technology's widespread availability, low cost, and limited radiation exposure make this imaging modality highly appealing [13]. Unfortunately, radiographs have not been shown to be reliable or accurate when used to define union or determine the stage of healing [30–32]. In a recent study, radiographs of tibia shaft fractures treated with intramedullary nails were reviewed at the three-month follow up visit by three independent reviewers. Results showed a diagnostic accuracy of only 62% – 74%, with a sensitivity of 62% and a specificity of 77% [33]. Two radiographic scoring systems, the Radiographic Union Score for Hip (RUSH) and the Radiographic Union Score for Tibia (RUST), have been shown to increase agreement among surgeons and radiologists in assessing fracture repair [34–37]. After illustrating the limitations of older radiographic scoring systems, researchers showed that the assessment of the number of cortices bridged by callus had higher reliability in determining healing through use of these new scoring systems [38].

The RUSH score requires clinicians to first evaluate if the fracture is completely healed after initial review of the patient's radiographs. Then, the reviewer completes the RUSH checklist to assess the extent of cortical bridging, cortical visibility of fracture line, trabecular consolidation and disappearance of trabecular fracture line (Appendix A, Table 1). Bone cortices are evaluated across two different axes: anteroposterior and mediolateral. Responses are scored and added, with the overall RUSH score ranging from 10 (no healing) to 30 (complete union) [35,37]. Researchers demonstrated that the RUSH checklist was most effective at increasing agreement between radiologists and orthopaedic surgeons when used within zero to three months post-surgery, compared to six or more months post-surgery (Appendix A, Table 2). This finding was observed for both femoral neck and interochanteric fractures, with interobserver agreement reported extremely high (ICC $\geq$ 0.85) [35].

The RUST score is based on callus formation and the visibility of fracture lines at four cortices observed on anteroposterior and lateral radiographs. A minimum score of four indicates no healing and a maximum score of twelve is awarded to a healed fracture (Appendix A, Table 3). The overall interobserver agreement has been reported as high for RUST score (ICC $\geq$ 0.8).

The RUST score was recently modified (mRUST) to determine union in distal femur fractures. The mRUST scoring system further subdivides cortical assessment to consider the presence of bridging callus, whereby a score of "1" = no callus, "2" = callus present, "3" = bridging callus and "4" = remodeled bone with no visible fracture line [39]. Similar to RUST, mRUST is used to evaluate four cortices present on anteroposterior and lateral radiographs, with the total score per fracture ranging from four to sixteen. Results showed moderate interobserver agreement with slightly improved agreement in fractures treated with intramedullary nails (Appendix A, Table 4. ICC = 0.53; nails: 0.58 versus plates: 0.51). Fracture healing was also determined by the percentage of radiograph reviewers who declared union across various total RUST and mRUST scores (Appendix A, Table 5).

Since the RUST score was introduced into clinical practice, several studies have been conducted to evaluate the reliability and efficacy of the RUST score to predict nonunion. In their 2014 study, Ali et al. support the continued use of the RUST score as a reliable method of assessing nonunion fractures and improving consensus among medical care providers [40]. Radiography images of sixty-five patients with simple diaphyseal tibia fractures were independently assessed by an orthopaedic surgeon and radiologist using RUST score methodology. The patients' identity and fracture duration were withheld from the evaluating physicians. Intraclass correlation coefficients with 95% confidence intervals revealed