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ORTHOPEDIC MANAGEMENT OF FRACTURES (M KACENA AND L GERSTENFELD, SECTION EDITORS)

Epidemiology, Clinical Assessments, and Current Treatments of Nonunions

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Abstract

Purpose of Review The failure of bony union following a fracture, termed a fracture nonunion, has severe patient morbidity and economic consequences. This review describes current consensuses and future directions of investigation for determining why, detecting when, and effective treatment if this complication occurs.

Recent Findings Current nonunion investigation is emphasizing an expanded understanding of the biology of healing. This has led to assessments of the immune environment, multiple cytokines and morphogenetic factors, and the role of skeletogenic stem cells in the development of nonunion. Detecting biological markers and other objective diagnostic criteria is also a current objective of nonunion research. Treatment approaches in the near future will likely be dominated by the development of specific adjunct therapies to the nonunion surgical management, which will be informed by an expanded mechanistic understanding of nonunion biology.

Summary Current consensus among orthopedists is that improved diagnosis and treatment of nonunion hinges first on discoveries at the bench side with later translation to the clinic.

Keywords Nonunion · Fracture healing · Serum analysis · Bone graft · Bone morphogenic protein · Bone marrow aspirate concentrate

Introduction

When a fracture fails to heal, the patient, healthcare system, and economy all suffer. Fracture nonunion is associated with significant morbidity and pain for the patient as well as additional costs averaging close to $12,000 per complication in the USA, largely due to the loss of productivity that accompanies the lengthy healing course [1, 2]. Traditionally, fracture nonunion was believed to occur in 5–10% of all fractures; however, two large, recent analyses in the USA and Scotland estimate the rate more in the 2–5% range [3, 4]. The incidence of nonunion varies significantly between bones. Zura et al. analyzed 309,330 fractures at various sites and reported the highest rates of nonunion observed were in the scaphoid (15.5%), tibia and fibula (14%), and femur (13.9%). The metacarpal and radius demonstrated the lowest rates of nonunion at 1.5% and 2.1%, respectively [4].

The FDA currently defines fracture nonunion as a fracture that has failed to heal within 9 months from injury with 3 consecutive months of healing stagnation [5]. Recent evidence, however, supports shortening the failure to heal period to 6 months for a more rapid diagnosis [6]. Many clinicians disagree on when a fracture is determined a nonunion, and, therefore, the exact time point for which to distinguish delayed and arrested healing [7]. Identifying an objective way to define the transition point remains a topic of ongoing research such that nonunion can be diagnosed and treated as early as possible.

Types of Nonunion

Fracture nonunions are primarily categorized as hypertrophic or atrophic based on biological viability at the fracture site determined by radiographic analysis. Hypertrophic nonunions are described as those in which biological potential has been

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maintained and, therefore, callus is observable radiographically. These fractures are believed to fail in the healing process because of mechanical failure at the fracture site from such stressors as inadequate stability or premature weight-bearing. Radiographically, hypertrophic nonunions can be further subdivided into elephant's foot, horse's hoof, or oligotrophic based on the callus pattern. Conversely, atrophic nonunions are believed to be void of biological potential as determined by a lack of callus development. In these cases, mechanical stability is not believed to be the chief causative factor [8•]. Figure 1 depicts three separate tibial fractures of which one has healed without complication, one has gone on to hypertrophic nonunion, and the last has gone on to atrophic nonunion.

The presence of vascularity at the fracture site has traditionally been used as a marker of biologic capacity and, thus, a factor distinguishing hypertrophic from atrophic nonunions. Recent experimental evidence contradicts this, however, suggesting that adequate vascularity can persist in a believed atrophic environment [8•, 9]. Interestingly, Panteli et al. have also demonstrated that biological activity at the cellular level persists in human samples taken from nonunions that had been classified as atrophic based on classical schema [10]. These results call for revision of traditional hypertrophic vs. atrophic designation schema, or implementation of a modernized non-binary classification system such as the Non-Union Scoring System (NUSS) proposed and validated by Calori et al. [11–13]. These results also point to the deficiency of biological determinants for the progression of bone healing and primary reliance on radiological assessments.

Nonunion Etiology and Associated Factors

A Closer Look at the Fracture Site

The pathogenesis of fracture nonunion remains heavily researched but largely unexplained. Current insight points to either mechanical failure or disruption of the "bone-healing unit" as the chief causative factors [8•]. The concept of mechanical failure hinges on long-standing theories of bone tissue response to mechanical forces [8•]. In these cases, nonunions are preceded by a fracture site that is under either too much or too little, strain precipitated by such factors as inadequate implant use or application, insufficient anatomical reduction, large cortical defects, periosteal stripping, and erroneous load bearing [8•, 14–21]. Mechanical failure contributes to nonunion in the majority of cases [8•, 11].

Disruption of the bone-healing unit is believed to involve interruption of critical molecular and cellular regulators of fracture repair. At the molecular level, interruption of the signaling pathway of three specific classes of cytokines is believed to impact fracture healing [22, 23]. The first class is proinflammatory cytokines, which includes tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). TNF-α has been shown in animal studies to play a role in cartilage resorption during remodeling and to regulate mesenchymal stem cell (MSC) differentiation in a concentration-dependent fashion [14, 24, 25]. IL-6 in the early posttraumatic period was recently determined to regulate a balanced immune response and subsequent bone repair in a mouse model, and has demonstrated a positive effect on callus strength and mineralization in earlier studies [26, 27]. However, contradictory results,

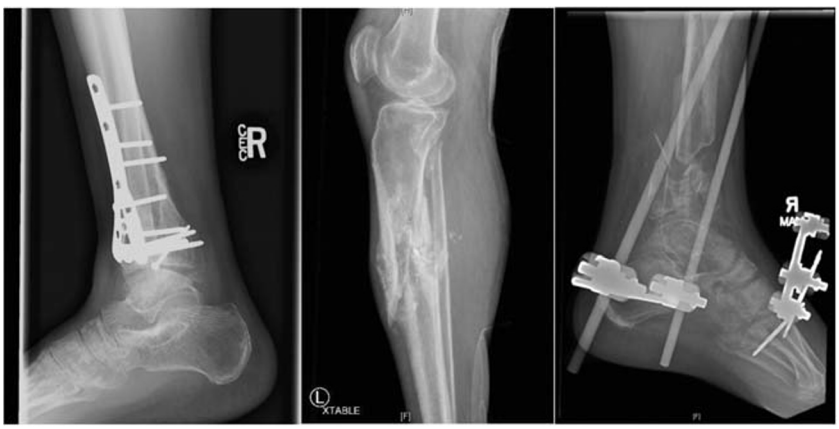

Fig. 1 Three different healing outcomes following fracture of the tibia. All images are lateral radiographs. The left image displays a distal 1/3rd tibia fracture with successful healing. The center image displays a tibial shaft fracture in which both evidence of callus as well as mechanical instability are noted. This indicates a hypertrophic nonunion. Lastly, the right image displays a distal tibial plafond fracture in which no callus is evident, indicating biologically inert boney ends and therefore atrophic nonunion

including higher IL-6 and lower IL-6 receptor serum levels in nonunion patients, convey much is still to be known about the relationship between IL-6 signaling and nonunion [28, 29].

The second class of notable bone-healing cytokines is the transforming growth factor-β (TGF-β) superfamily that includes bone morphogenic proteins (BMPs). Although the molecular mechanisms remain unknown, BMPs have a well-established role as regulators of all four phases of fracture healing as chemotactic regulators of MSC differentiation and angiogenesis [14, 30, 31]. BMP-2 and BMP-7 specifically have garnered the most research attention since they are currently on-market as biologic adjuvant therapies. Their therapeutic efficacy will be discussed in a later section of this review.

The third and final notable class of bone-healing cytokines are the metalloproteinases and angiogenic factors. These cytokines coordinate the congruous matrix degradation and angiogenesis processes of fracture healing, regulated by matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF), respectively [23]. MMP-13 and MMP-9 in particular have been shown to be critical regulators of cartilage breakdown and may even be detectable in urine as a non-invasive marker of nonunion [32, 33]. The role of VEGF in nonunion is more nuanced; it is suspected that although VEGF is important for angiogenesis at the fracture site and for union, hypervascularization in the initial healing period can be harmful [32, 34]. Continuing investigation is required to better elucidate the mechanisms by which all discussed cytokines affect healing in vivo, as well as their exact timing and at what concentration they act.

At a cellular level, the availability and adequate differentiation capacity of osteogenic cells, specifically skeletogenic stem cells (also known as MSCs), is a key component of the bone-healing unit [8•, 14]. MSCs are provided to the fracture site from a combination of periosteal, endosteal, bone marrow, and soft tissue origins and are critical progenitors for all but one cell type (osteoclasts) involved in the fracture repair process [14, 35, 36]. The significant soft tissue injury and periosteal stripping that can occur in high-energy fractures or from excessive surgical dissection can disrupt the availability of these MSCs and contribute to an inadequate supply of repair cells. These conditions can also disrupt vascular supply to the fracture site with detrimental consequences for healing [14, 37]. When applicable, the use of minimally invasive implants and implanting techniques may mitigate these disruptions and preserve the bone-healing unit.

Another factor that can disrupt the bone-healing unit is the presence of infection. Infection has demonstrated a significant association with nonunion since it can create osteolysis, a prolonged inflammatory response, and necrotic soft tissue between bone fragments [11, 14, 38–40]. Infection does not always present with classical symptoms and has been reported to be present in as low as 5% and as high as 20% of perceived aseptic nonunions [11, 41•]. Therefore, special effort should be taken to rule out infection in all cases of nonunion, especially recalcitrant ones.

Clinical Risk Factors

Nonunion development is dependent on injury factors such as fracture severity and location as well as systemic illness and medication use in the patient. These risk factors and others were examined recently in a large cohort of patients across multiple centers by Zura et al. [4]. Regarding injury risk factors, this review demonstrated that severe fractures caused by a high-energy mechanism, that were open, and that were accompanied by multiple concomitant fractures were at the highest risk for nonunion [4]. This agrees with a recent review supporting the association between higher Gustilo-Anderson classification and nonunion development in the tibia [42]. The most notable systemic illness associated with nonunion is diabetes, showing association in both clinical reviews and animal studies [4, 43]. Smoking is likely the most long-standing modifiable risk factor associated with nonunion, which has been corroborated by numerous bed and bench-side investigations [44–47]. Nicotine's vasoconstrictive effect and role as a disruptor of TNF-α signaling gives pathophysiological insight into the association [44, 48]. Interestingly, the review by Zura et al. did not find smoking to be a major risk factor in their analysis; however, this is likely a false negative due to underreporting [4].

The uses of certain antibiotics, anticoagulants, anticonvulsants, and bisphosphonates acutely have all demonstrated associations with nonunion [4, 49, 50•, 51, 52]. Regarding analgesics, acute as well as chronic use of opioids have been found to contribute to nonunion [4, 50•]. Given the trauma population's susceptibility to nonunion risk factors, a confounder(s) could explain this association; however, results thus far are a cause for concern and warrant immediate further investigation. Nonsteroidal anti-inflammatory drugs (NSAIDs) have a conflicting experimental association with nonunion despite existing dogma prohibiting their use during the fracture recovery period in the USA [45, 50•, 53, 54•]. Given the recent association between opioids and nonunion, and evidence that NSAID supplementation can decrease opioid use postoperatively, more research is called for regarding NSAID safety in the acute period [54•]. The Pain Study, a large prospective multi-center randomized controlled trial, is currently investigating this question and will provide level 1 evidence in the near future [55].

It is wise not to consider any of these risk factors in a bubble. The review by Zura et al. demonstrated that the majority of significant risk factors were much less impactful as singular actors in nonunion through a comparison of univariate and multivariate odds ratios [4]. Recent work by Mills et al. supports this idea, finding that two thirds of patients with

nonunion had more than one attributable cause [11]. Surgeons, therefore, should be sure to consider the interplay of all aforementioned risk factors when risk stratifying for nonunion.

Role of Genetics

With the increasing accessibility of genetic testing, identifying genetic predispositions for fracture nonunion has become a topic of hot research. Results thus far point to single nucleotide polymorphisms in inhibitors of BMP, as well as haplotypes of BMP-4, fibroblast growth factor receptor-1, and platelet-derived growth factor (PDGF), as potential causative agents of aseptic nonunion [15, 56–58]. Complimentary deoxyribonucleic acid array analysis has also elucidated 8 genes expressed locally at significantly higher levels in nonunion tissue when compared to fresh callus [59]. Most recently, 3 studies have also identified multiple micro-ribonucleic acids linked to both impaired and augmented fracture healing [60–62]. Although application of these results is limited by study design and current understanding of nonunion pathogenesis, it is reasonable to envision a future supplementary role of genetic testing in individualized nonunion risk determination.

Table 1 provides a summary of these factors as well as other biologic, injury associated, and patient comorbidity factors affecting the progression of bone healing.

Clinical Assessments

History and Physical Exam

Diagnosis of fracture nonunion first involves a careful history taking and physical exam. Pain/tenderness with palpation at the fracture site, pain/tenderness with weight-bearing, and/or an inability to bear weight altogether can be expected in cases of nonunion, extrapolated from the 3 accepted physical exam criteria by which a healed fracture is defined [64]. The clinical assessment also includes evaluation of movement at the fracture site, inspection for signs of infection, and assessment of lengthening of shortening of the fracture segment as well as alignment. Assessment of the patient's weight-bearing status and compliance is also important since delayed weight-bearing was recently demonstrated to be associated with delayed healing [65]. This association is likely explained by the need for an optimal stress environment to induce bone healing in accordance with Perren's strain theory [66].

Imaging

Although the physical exam can offer clues that a fracture is failing to heal, radiologic assessment is the essential element of formal nonunion diagnosis. Plain radiographs allow for assessments of callus bridging, displacement, and angulation at the fracture site, as well as implant loosening or failure hinting at a present or impending nonunion. Traditionally, radiographic determination of nonunion has been largely subjective, leading to poor reliability in determining the stage of union [67, 68]. In an effort to create more objective radiographic parameters, standardized criteria in the form of radiographic union scores for the tibia (RUST), hip (RUSH), humerus (RUSHU), and radius (RUSS) have been developed with interobserver reliability demonstrated in all scoring systems [69–73]. All four scoring systems utilize a modified version of the same base scoring system, in which the presence of callus and visible fracture line at anterior, posterior, medial, and lateral cortices is rated on a 3-point scale with higher scores correlating to union [70–73]. The RUSHU system most modifies this base criteria, applying separate scores for cortical bridging and fracture line visibility to each cortex in addition to two scores for trabecular consolidation [70]. A modified RUST (mRUST) score with a higher interobserver agreement than the traditional RUST has also been developed. The mRUST differs from RUST in that it further subdivides the middle "present callus" score of 2 in the RUST for more descriptive staging, making each cortical score out of four instead of three [74]. Figure 2 shows the mRUST system applied (Fig. 2). Validation work in animal models show that RUST and mRUST scoring systems are significantly correlated with healing time, bone mineral density, and biomechanical parameters [75–77]. The next step in widespread application of RUST, mRUST, and other union scores for nonunion involves identifying a reliable threshold score at a well-defined time point that can diagnose or even predict the complication in each bone. Recent attempts have identified a RUSH score of < 18 at 6 months after injury in the femoral neck, and a RUST score of roughly < 8 in the range of 11 to 14 weeks after injury in either the tibia or femur to distinguish a fracture that will heal from one that will progress to nonunion [78, 79]. Further research in this area is called for since identification of such a threshold score would provide an objective diagnostic and predicable value for earlier nonunion detection.

Other imaging options available for judging bone-healing progression are computed tomography (CT) scanning and ultrasound. CT scans have been posited as a more sensitive imaging study than plain radiographs for diagnosing nonunion; however, the demonstrated lack of specificity and artifact caused by implants adjacent to the fracture site limits clinical applicability [80, 81]. Alternatively, ultrasound is being considered an easily accessible, non-ionizing, and sensitive imaging technology for diagnosing nonunion. Early work by Craig et al. and Moed et al. first demonstrated ultrasound's ability to detect developing callus before it could be visualized radiographically, implying it could be used to determine the

Table 1 Biological, injury, and patient comorbidity factors affecting bone healing

Biological/molecular factors	Injury/fixation factors	Patient comorbidity factors
Adequate stem cell availability [8•,14,29,32,35]	Adequate reduction/alignment [8•,15,94]	Age [4,15,19,37]
Inflammatory state [14,22,25]	Compartment syndrome [15,19,38,63]	Alcohol use [4,15,19]
Genetic background [14,15,32,56–62]	Fracture gap (cortical defect) [15–17,19,20,38]	Diabetes [4,15,18,19,37,43]
Cytokine and morphogen expression:	Infection [11,14,15,19,38–40]	Pharmaceuticals:
TNF-α [14,23–25,32]	Mechanical instability [8•,11,15,18,19,66]	Antibiotics [4,15,19,50,52]
IL-6 [14,23,25–29,32]	Open fracture [4,15,16,18,19,38,39,42,44]	Anticoagulants [4,15,19,50,52]
BMPs [14,23,30–32]	Periosteal stripping [14,21]	Anticonvulsants [4,50]
MMPs [23,32,33]	Vascular compromise [14,15,19,37]	Bisphosphonates [4,49,50,52]
VEGF [14,23,32,34]		Chemotherapeutics [15,19]
		Opioids [4,50]
		NSAIDs [4,15,19,45,50,53,54]
		Steroids [15,19]
		Smoking/tobacco use [15,18,19,37,44–47,49]

osteogenic activity of a suspected nonunion [82, 83]. More recent results by Nicholson et al. demonstrated that at 6 weeks after injury, only 10% of patients had bridging callus on radiograph but 60% had sonographic bridging callus (SBC), of which all 60% went on to unite. Most importantly, this study showed that no SBC was present at any time point in the patients that developed nonunion [84•]. The use of contrast-enhanced ultrasound has also recently demonstrated predictive value in determining success of nonunion revision surgery in the tibia through its ability to assess perfusion at the fracture site [85]. These results, in combination with the accessibility and safety characteristic of ultrasound, suggest that this technology could be used in daily clinical practice in the near future.

Predictive Scoring

Using what is known about risk factors associated with nonunion in combination with validated imaging scoring tools, multiple predictive scoring systems have been developed. One such system integrates the RUST score, the presence of infection, and the Nonunion Risk Determination Score created by O'Halloran et al., utilizing 3 relevant paramters to stratify nonunion risk in tibia fractures [86, 87]. Another, by Zura et al., was created using a database of over 90 million participants and has demonstrated the ability to predict nonunion in 18 different bones [88••]. Overall, these scoring systems represent non-invasive, objective tools that provide the clinician and patient valuable information to help guide clinical decision-making.

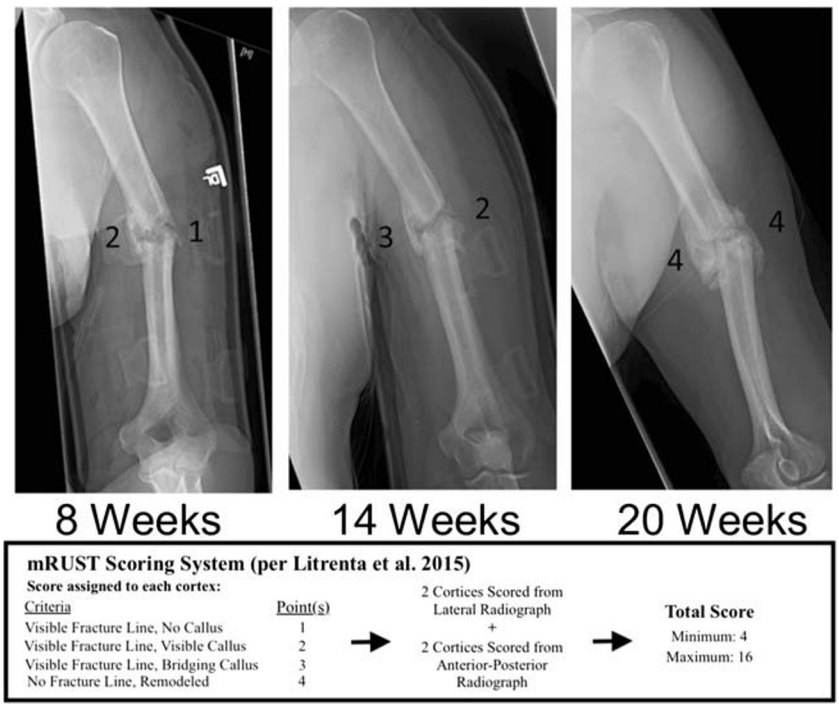

Fig. 2 Modified RUST scoring of humerus fracture lateral radiographic series. Weeks after fracture are denoted. The images include numeric scoring for each cortex based on the Modified Radiological Union Score of Tibia criteria [74]. Scoring criteria is outlined below the radiograph series. For complete mRUST scoring, both cortices on anterior-posterior radiographs would also be scored and added to the scores as seen above

Efforts should be taken to validate these scores prospectively and increase accessibility for real-time use in the clinic.

Serum Analysis

The documented circulation of signaling proteins during all phases of fracture repair posits that serological differences may exist between patients with unremarkable healing and those with nonunion. Importantly, recent proof of concept work by Hussein et al. demonstrated that changes in expression levels of various proteins involved in fracture healing were detectable through serum analysis, and identified 50 candidate proteins of particular interest [89•]. Past work identifying potential markers has demonstrated differences between alkaline phosphate, osteocalcin, and various pro-inflammatory cytokines between normal and nonunion models; small sample sizes and poor controls in these studies limit current applicability [90••, 91–93]. Properly controlled, in vivo research is called for since identification of reliable serum markers of nonunion would provide an immensely valuable, objective, and accessible test with decisive clinical applicability.

Treatment Approaches

Surgical Approaches

Surgery is often indicated for the treatment of an established nonunion. If mechanical failure is the suspected cause of the nonunion, revision, replacement, and/or augmentation of the initial construct is indicated to optimize the strain experienced within the fracture site environment to induce healing [5, 6, 8•, 49, 94]. Optimizing the mechanical environment can also involve restoring proper limb alignment, helping recover native on-axis force transmission that can improve patient function and protect implants [5]. If deep infection is noted, surgical intervention is required to irrigate and debride necrotic bone and soft tissue to create clean bony margins capable of growth (95). These cases may also require delivery of local antibiotics in the form of antibiotic nails, cement beads, and cement spacers [94, 96–98]. In the case of large cortical defects, as can occur in high-grade open injuries or in the aftermath of osteomyelitis, optimizing the mechanical environment may require the use of bone transport techniques such as application of an Ilizarov external frame [99]. The Ilizarov frame in combination with distraction of 1 mm per day following a latency period may provide adequate stimulus for bone growth in these complicated cases, preventing the need for amputation [100, 101].

In large cortical defects or nonunions deemed atrophic, bone grafting may be useful to optimize both the mechanical and biologic environment. Favorable grafts are osteogenic, osteoinductive, and osteoconductive in nature. Autograft harvested from the iliac crest (ICBG) manifests these three qualities and is the current gold standard in practice. Donor site morbidity and even associated healthcare costs have prompted the search for other options [49, 94, 102, 103]. In an effort to mitigate these drawbacks, the reamer irrigator aspirator system (RIA) was developed and has since proven to be an efficacious alternative for harvesting autograft to ICBG with decreased cost and morbidity despite questions about its yield of bone-forming cells [49, 94, 102, 104]. Allograft combined with recombinant growth factors is also an option without the drawback of host harvest [105]. Demonstration of decreased efficacy compared to autograft and associated disease transmission risks, however, limits widespread implementation [94, 103]. Of note, a recent review by Maceroli et al. found the mechanism of injury, increasing body mass, cortical defect size, flap size, and insurance status to be significantly associated with failure of the bone grafting procedure itself [106].

Current research is investigating the combination of bone marrow aspirate concentrate (BMAC) with an osteoconductive scaffold as an alternative to ICBG and RIA autograft. Thus far, BMAC has proven a reliable source of concentrated MSCs that are not only osteogenic but also osteoinductive [94, 103, 107, 108]. This is superior to both autograft and growth factor supplementation, as MSCs from BMAC are able to engage in coordinated paracrine signaling at physiological levels [94, 108]. Support for the efficacy of BMAC was recently provided by Gianakos et al. in their review of animal studies, finding superior outcomes for osteoconductive scaffolds treated with BMAC compared to osteoconductive scaffolds with no progenitor cells across all measurable markers of bone healing in the vast majority of experiments [109]. An even more recent retrospective study in humans found no difference in union rates between nonunions treated with BMAC vs. ICBG [110•]. Regarding collection method, bone marrow centrifuged to BMAC is also taken from the iliac crest; however, it has demonstrated less donor site morbidity in comparison to ICBG grafting with a researched sector rule for directing safe extraction [108, 111]. Thus, BMAC, in combination with one of the many commercially available osteoconductive scaffolds, appears to be a promising future treatment option in biologically non-viable nonunions or those with large cortical defects. It should be noted, however, that recent work in the cardiovascular field demonstrated that the benefit of stem cell–based therapies was from the acute immune response they generated rather than from specific properties of the cells themselves [112]. This consequently calls into question whether MSCs and therefore BMAC is superior to other stem cell–based therapies as promoters of healing in bone; further basic science research comparing MSCs and BMAC to cell-based controls is called for.

Commercial Biologic Adjuvants

Multiple adjuvant therapies have been developed for the purpose of augmenting the biologic capacity of an atrophic nonunion. Of these, demineralized bone matrix (DBM), BMPs, PDGF, and parathyroid hormone (PTH) therapy are the four with greatest clinical traction. DBM was the first of these therapies to be researched and introduced, building off the landmark discovery in 1965 of Marshall Urist [113]. However, a review of the literature reveals only methodologically weak studies demonstrating a benefit for DBM in healing from which clinical decisions cannot be based [94, 114]. Also deriving from Urist's experiment was the discovery of BMP's as critical osteoinductive cytokines, from which considerable research and development has led to the commercialization of both recombinant human rhBMP-2 and rhBMP-7 [102, 115]. Regarding comparison between the two types, two recent trials have demonstrated rhBMP-2 to be superior to rhBMP-7 for the indication of nonunion [116, 117]. Few trials exist, however, supporting either type's efficacy in comparison to the standard of care autologous bone graft [30, 94]. Questions surrounding dosage and delivery method, high cost, and potential complications from usage also raise concerns regarding the viability of BMP for clinical use [30, 94]. Similar to both rhBMP-2 and rhBMP-7, recombinant human-derived PDGF-BB (PDGF-BB) is commercially available and FDA approved as an adjuvant for nonunion. However, in contrast to both rhBMPs, PDGF-BB is only approved for use in the setting of foot and ankle arthrodesis nonunion for which it has demonstrated promising healing results [118]. Further work supporting its efficacy and safety in comparison to autograft and in nonunion models of other bones may expand its use. Lastly, PTH injection, available commercially as Teriparatide, has demonstrated promise as a healing adjuvant in osteoporosis and acute fracture but not yet reliably in nonunion and is not currently FDA approved for this indication [94, 119]. In summary, at current, each of these adjuvant therapy options hold immense potential value as local stimulators of fracture nonunion. However, a lack of strong, consistent level I evidence and questions about the logistics of their application continues to prevent their wholehearted adoption.

Bone Stimulation

Bone growth stimulators are an available, non-invasive, adjuvant treatment option for nonunion. Stimulator types include direct current, capacitive coupling, inductive coupling, and low-intensity pulsed ultrasound (LIPUS). A recent review by Haglin et al. summarized the research to date on all four types for the indication of nonunion, finding no consistent level I evidence to support a clinical recommendation of the use of any stimulator type [120]. This does not mean, however, that bone stimulators hold no potential treatment value. In their review, Haglin et al. acknowledged that inductive and capacitive coupling stimulators had "fair evidence" in the form of multiple level II and level III studies with consistent findings supporting their efficacy [120]. A randomized controlled trial by Schofer et al. and meta-analysis by Leighton et al. on the efficacy of LIPUS also points to LIPUS's success in the 3- to 6-month period following revision surgery for augmenting union, with Leighton et al. even going so far as to argue for their efficacy over surgical intervention [121, 122]. Even in the absence of substantial level I evidence, the indication may still exist for the use of LIPUS, inductive coupling, and capacitive coupling stimulators in light of a risk-benefit analysis. To date, no evidence links LIPUS, inductive or capacitive coupling bone stimulators to any harmful side effects; thus, these devices are low-risk, potentially maximum benefit

Table 2 Treatment approaches for nonunion

Surgical approaches	Pharma and biopharma therapies	Available devices
Mechanical environment optimization: Original hardware revision, removal, and/or replacement [5,6,8•,49,94] Ilizarov frame placement [99–101]	DBM [94,114] rhBMPs: rhBMP-2 [94,102,116,117] rhBMP-7 [94,102,115]	Bone stimulators: Direct current [97,124] Capacitive coupling [97] Inductive coupling [97,123] LIPUS [120–122]
Bone grafting: Autograft: ICBG [5,49,94,102] RIA [5,49,94,102,104] Allograft [94,105] BMAC + osteoconductive scaffold [94,103,107–109, 110•]	PDGF* [118] *only approved for use in foot and ankle arthrodesis nonunion PTH** [94,119] **Not currently FDA approved for use as nonunion therapy	
Local infection management: Irrigation and debridement [95] Local antibiotic delivery: Antibiotic nail [96,98] Antibiotic cement beads [97] Antibiotic cement spacers [94] Bioresorbable antibiotic pellets [97]		

adjuvant therapies that at worst have no effect. Therefore, a cost-benefit analysis would be a beneficial next step in addition to aforementioned level I evidence for the purposes of determining the need to elevate bone stimulators from offered to recommended in the clinic. Table 2 summarizes treatment options currently available to clinicians for fracture nonunion.

Conclusion

Fracture nonunion remains a debilitating complication characterized by high patient morbidity and economic burden. Best clinical estimates point to either mechanical failure or disruption of the "bone-healing unit" at the fracture site as the chief causative elements, although an understanding of what this means at a molecular level remains to be seen. What can be agreed upon is that the healing process involves a complex interaction of cellular signaling that is difficult to augment exogenously with commercial biologics such as rhBMPs or DBM. Zooming out from the cellular level reveals that progress has been made identifying clinical risk factors associated with nonunion and objective measures have improved with which to make a timely diagnosis. Clinical implementation of other promising diagnostic and therapeutic technologies has largely been limited by a lack of convincing evidence from reproducible and methodologically sound studies. Based on current trends, studies of this nature are likely in the near future; with them will hopefully come the evidence to support adoption of new solutions to what has been a long-standing clinical challenge.

Compliance with Ethical Standards

Conflict of Interest G. Bradley Reahl, Louis Gerstenfeld, and Michael Kain declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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