



Treatment options for aseptic tibial diaphyseal nonunion: A review of selected studies

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- In aseptic tibial diaphyseal nonunions after failed conservative treatment, the recommended treatment is a reamed intramedullary (IM) nail.
- Typically, when an aseptic tibial nonunion previously treated with an IM nail is found, it is advisable to change the previous IM nail for a larger diameter reamed and locked IM nail (the rate of success of reaming is around 90%).
- A second change after an IM nail failure is also a good option, especially if bone healing has progressed after the first change.
- Fibular osteotomy is not routinely advised; it is only recommended when it interferes with the nonunion site.
- In delayed unions before 24 weeks, IM nail dynamization can be performed as a less invasive option before deciding on a nail change.
- If there is a bone defect, a bone graft must be recommended, with the gold standard being the autologous iliac crest bone graft (AICBG).
- A reamer-irrigator-aspirator (RIA) system might also obtain a bone autograft that is comparable to AICBG.
- Although the size of the bone defect suitable to perform bone transport techniques is a controversial issue, we believe that such techniques can be considered in bone defects > 3 cm.
- Non-invasive therapies and biologic therapies could be applied in isolation for patients with high surgical risk, or could be used as adjuvants to the aforementioned surgical treatments.

Keywords: aseptic nonunion; tibial diaphysis; treatment options

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Introduction

There is no universal definition of nonunion. The Food and Drug Administration (FDA) defines nonunion as a

fracture of at least nine months' evolution that has shown no signs of bone healing on radiographs taken three months from each other.¹ The tibia is the bone in which nonunion most frequently occurs, with rates of approximately 4.6% after intramedullary (IM) nail fixation.²

Classically, three types of nonunions have been described according to their radiological appearance. Hypertrophic and atrophic are the two most common types, and synovial nonunion, which can be the evolution of the previous two, is a rare third type. The type of nonunion provides us with a clue to the possible causes that have influenced its occurrence, thus also providing valuable information on what the best treatment would be. Hypertrophic nonunions are usually due to a lack of fracture stability, thus causing excessive fracture site mobility and forming a hypertrophic bone callus.³ They are perhaps the easiest to treat, given that they are typically solved with a change to a more stable bone fixation.⁴ In atrophic nonunions there is an insufficient blood supply to the fracture site for various reasons, which prevents bone callus formation. Therefore, it is important to combine a good biological environment with mechanical stability. However, it is true that in clinical practice nonunions can be mixed with several concomitant causal factors. Kohlprath et al found a 23% rate of aseptic nonunions in open fractures of the tibia in adults.⁵ Table 1 shows the possible causes, both systemic and local, that could favour the appearance of a nonunion.⁴⁻⁶

The 'diamond concept' for the management of nonunions of long bones, as reported by Andrzejowski and Giannoudis, is a conceptual framework to achieve a successful bone repair response, which gives equal importance to mechanical stability and to the biological environment.⁶ Furthermore, it is believed that adequate bone vascularization and the physiological state of the host are essential within this framework of fracture repair. A deficit in the biological or mechanical environment, or a lack of knowledge regarding the co-morbidities of the host and a lack of vascularization can lead to nonunion. In general, the 'diamond concept' refers to the availability of osteoinductive

Table 1. Systemic and local causes that can favour the development of nonunion⁴⁻⁶

Systemic causes
Nutritional deficits
Tobacco
Diabetes mellitus
Anti-inflammatory drugs
Opioids
Chemotherapy
Anticoagulants
Benzodiazepines
Vitamin D deficiency
Alcoholism
Elevated body mass index (BMI)
Male
Osteoporosis
Peripheral vascular disease
Chronic inflammatory disease
Renal insufficiency
Advanced age
Local causes
Infection
Vascular insufficiency
Inadequate reduction, gap persistence
High energy
Open fractures
Comminuted fractures
Compartment syndrome
Tibia

mediators, osteogenic cells, an osteoconductive matrix (scaffolding), an optimal mechanical environment, adequate vascularization and management of any pre-existing comorbidity of the host. As we will explain, the various treatment modalities for tibial nonunions attempt to address, alone or in combination, one or more components of the aforementioned ‘diamond concept’. When surgical treatment is indicated, it is paramount to obtain cultures during surgery in order to rule out infection.

The purpose of this article is to review current knowledge on aseptic tibial diaphyseal nonunions and their treatment options.

Infected nonunion must be excluded: how to do it?

Usually nonunion is associated with low-grade and chronic infections which are often hard to identify.⁷ We must suspect infected nonunion when the radiographic study shows lysis, loosening, sequestering, and periostitis. Magnetic resonance imaging (MRI) is very sensitive but restricted by artifacts around the implant. Positron emission tomography–computed tomography (PET/CT) may successfully differentiate between infected nonunion, aseptic nonunion, soft tissue infection, and chronic osteomyelitis and has an approximate sensitivity of 79%, and specificity of 97%.^{8,9} Single-photon emission computed tomography (SPECT)/CT scan is another option for testing, with a small sensitivity but good specificity for

infection and non-viability of the nonunion area.¹⁰ Nonetheless, data are initial.¹¹

It is important to distinguish aseptic nonunion from infectious nonunion. This cannot be dependably forecast preoperatively. To be able to make a valid statement postoperatively, microbiological examination of smears and tissue samples even after long-run incubation and histology are needed.

Intramedullary (IM) nail after other previous treatments (surgical and conservative)

In 2019, Aldemir and Duygun reviewed 28 aseptic tibial nonunions without bone defects (15 hypertrophic and 13 atrophic), with an average time from fracture to treatment of 1.6 years.⁴ The previous treatments for these fractures had comprised four external fixators, two expandable nails, 16 plates and six conservative treatments with plaster of Paris. All had undergone a change to a reamed IM nail, with a 2-cm fibular osteotomy resection and with application of autograft obtained from reaming at the nonunion site. In addition, an extra contribution from autologous iliac crest bone graft (AICBG) and a graft from the osteotomized fibula had been added to the atrophic nonunions. Bone healing had been achieved in 100% of patients in an average of 15.5 weeks. Based on the Johner–Wrush functional scale, the results were good or excellent in 25 patients (89.2%); the average shortening was 8.36 mm. In the group with fair and poor results, the shortening was 20 mm. One case of cutaneous necrosis was solved with a rotational flap.

The same year, Kostic et al analysed 33 cases of diaphyseal aseptic tibial nonunions previously treated with an external fixator (27 cases), a plate (two cases) and with plaster of Paris (four cases).¹² All had been treated with a reamed IM nail. Open reduction was required in 25 cases to remove the plate or to make corrections to the diaphysis. In the other eight cases the reduction was closed. Fibular osteotomy was performed in all cases of fibular nonunion (78.8%). Most were locked IM nails; a distal locking screw was not implanted in four patients. Bone healing was achieved in 31 patients (93.9%). In one patient, a nail change was required to achieve bone healing, and in another patient an infection occurred requiring the removal of the nail. In three patients, the removal of the distal locks (dynamization) was required due to the absence of bone healing; bone healing was subsequently achieved for all three patients. In four patients, AICBG was required, given they were bone defects of more than 50% of the tibial circumference. Fig. 1 shows a tibial nonunion initially treated with a plate that was resolved with an IM nail (after plate removal).



Fig. 1 A 28-year-old male suffered a comminuted diaphyseal fracture of the tibia and fibula Gustilo IIIB (a). Anteroposterior (b) and lateral (c) radiographs after open reduction and bone fixation using a large fragment LCP (low compression plate), with simultaneous coverage by a latissimus dorsi flap. In (d) a plate rupture due to aseptic nonunion is observed. Anteroposterior (e) (f) and lateral (g) radiographs at 18 months after the plate was replaced by a locked reamed IM nail, in which bone healing is observed. In this case, plate fixation was chosen so as not to create a large bone defect, since the tibial fracture had multiple fragments. The external fixator was discarded because it did not stabilize the intermediate fragments, and, in association with the Plastic Surgery Department, it was possible to perform immediate coverage (fix and flap) with a latissimus dorsi free flap at the same surgical time.

Expandable nails

Expandable nails are an alternative to the classic locked nails, based on the theory of the biological benefit of

reaming, the increase in stability due to the augmentation in diameter and the extra stability that the expandability provides, without the need for locking screws.¹³

In 2009, Steinberg et al evaluated the effectiveness of an expandable nailing system to treat nonunions of femoral and tibial shafts (Fixion).¹³ Records of 24 patients (25 fractures) were retrospectively reviewed: 16 femurs, eight tibiae. During the surgery, the initial fracture fixation hardware was removed. For the placement of the expandable nail, a diaphyseal reaming of 2–3 mm less than the maximum expandable diameter of the nail was performed. The average age of the patients was 32 years for the tibia group and 49 years for the femur group. The respective intervals between trauma and reoperation were 11 months and 13 months, operating times of 60 min and 78 min, and fluoroscopy times of 21 seconds and 32 seconds. Bone debris obtained during reaming was used as a bone graft at the site of nonunion in 17 of 19 patients (13 in the femur and four in the tibia) who required grafting. Grafting was applied with a small incision at the level of the nonunion site. Thus, the need for AICBG could be reduced to only two cases (in the femur). Twenty-four (96%) of the 25 nonunions healed successfully without requiring additional procedures. In one patient, demineralized bone matrix was injected percutaneously and the lack of femoral healing was resolved. The average healing times were 23 weeks (range: 6–52) and 17 weeks (range: 6–40) in the tibia and femur groups, respectively. The results of this study demonstrated a satisfactory cure for the treatment of diaphyseal nonunions of the femur and tibia. Steinberg et al recommended using expandable nails for nonunions of the femoral and tibial shafts, and the use of bone debris obtained with reaming to reduce the use of AICBG.

PRECICE magnetic intramedullary compression nail

Fragomen et al presented a preliminary study of the PRECICE (NuVasive Specialized Orthopedics, San Diego, California, USA) magnetic intramedullary compression nail for the treatment of femoral and tibial nonunions.¹⁴ It included 14 patients with aseptic nonunions: five of the tibia and nine of the femur. The average age of the patients was 49 years; the mean number of previous surgeries was 1.9; seven nonunions were atrophic and seven were normotrophic; three were metaphyseal and 11 diaphyseal. All intramedullary PRECICE nails were distracted before implantation. Compression was applied after the procedure, until it was observed on the radiograph that the locking bolts were bending or that the nail was no longer shortened despite applying the external magnet. Bone healing was achieved in 13/14 cases. The union time was 24.5 weeks (range: 11–60). Three patients had infection (positive cultures) and were treated with intravenous antibiotics for six weeks, followed by three months of oral suppression, with no subsequent infection observed. No mechanical failures of the nails were found. Fragomen et al had concluded that the intramedullary compression

nail was successful in applying compression, preventing deformity and obtaining bone healing in all distal diaphyseal nonunions of the tibia. The signs of active compression are flexion of the locking bolts and failure of the nail to shorten. This treatment is not suitable for metaphyseal nonunions of the proximal tibia.

Prior nail dynamization

The dynamization principle is based on the fact that micro-motion at the fracture site can stimulate bone healing.² Nail dynamization can be accomplished by removing all locking screws on one side of the nail. The disadvantage of this is that instability then occurs, especially for rotation. A more stable solution is to place only one screw on one side of the nail in an oblong hole, which is then placed away from the fracture.

Litrenta et al retrospectively studied 194 cases of aseptic tibial nonunions. In 97 cases, a nail change was performed and in the other 97, only nail dynamization was performed.¹⁵ In both groups, the procedure was performed without fibular osteotomy. They found high rates of bone healing with both procedures (83% dynamization, 90% nail change), with no statistically significant differences. There were also no differences in the time from injury to surgery or in the Radiographic Union Scale in Tibia score. However, there were differences in the choice of treatment for two variables, depending on the fracture pattern: a gap > 5 mm and comminution. In these two cases, a change of nail was indicated more frequently, possibly because surgeons knew that the dynamization could lead to shortening, malrotation and a lack of reduction. In addition, the absence of a gap was a predictor of success for both procedures. Therefore, it appears that in more complex fracture patterns, the surgeon tends to make a nail change rather than just a dynamization of the nail.

According to Rupp et al, IM nail dynamization is an atraumatic, effective and economical surgical option to achieve bone healing in tibial diaphyseal fractures, particularly in delayed unions before 24 weeks after initial surgery.² Therefore, their use was advised more for cases of delayed unions than for established nonunions with longer evolution.

Nail change

As noted earlier, bone fixation with an IM nail has been the gold standard in diaphyseal fractures of long bones since the 1970s,² with a change of nail also the gold standard treatment in non-aseptic diaphyseal tibial nonunions previously treated with a nail. Good results have been reported in the literature since the 1970s, with up to 100% success in some series.

Currently, the most widespread technique is the removal of the previous nail, intramedullary reaming and the implantation of a new locked IM nail with a larger diameter. We still do not know how much the nail diameter must be increased; however, several patient-dependent factors can affect this figure: bone quality, cortical thickness and the diameter of the previous nail. In general terms, implanting a nail 2 or more millimetres wide, reaming 1 mm greater than the definitive nail, with static locking screws in a location different from the initial ones, and dynamizing it if there is no early radiological progression is recommended.¹⁶ The increase in nail size provides a mechanical benefit by adding more stability. In addition, reaming widens the isthmus, increasing the contact of the nail with the bone.¹⁶ For cases in which the previous nail was short, the length of the nail can also be increased. Another possibility is the addition of locking screws, which also increases the stability of the construct.¹⁶ Reaming provides a biological environment. Although it temporarily alters the blood supply to the endosteum, later causing a periosteal vascular reaction that stimulates bone formation,¹⁷ it also creates an intramedullary bone autograft as a result of reaming.¹⁸ Therefore, it is an effective treatment for both types of nonunions, atrophic and hypertrophic.

Regarding the need for fibular osteotomy, in the literature there are no significant differences in healing times between performing it or not. Most authors recommend it when the fibula is complete or healed, which leads to difficulty with compressing or manipulating the nonunion site, but generally not routinely. Fig. 2 shows a case of nail change without AICBG. Fig. 3 shows another case of nail change with AICBG.

Compression plate, leaving previous intramedullary nail (IM) in situ

As an alternative to the change of nail, there are authors who propose adding a compression plate and leaving the previous nail in situ. In cases of fractures in the metaphyseal–diaphyseal junction of the long bones, in which the results of the nail change tend to be poorer, some authors advocate the addition of a compression plate, leaving the previous nail in place to improve angular stability.¹⁹

The use of a compression plate while leaving the nail in situ has bone healing rates similar to those of changing the nail, and could be recommended mainly in fractures of the metaphyseal–diaphyseal junction, in fractures with angular instability, or in cases where it is impossible to remove the previously implanted nail.

Nonunions with bone defects: grafts and bone substitutes

The morbidity of the donor zone is eliminated with allografts, as well as being able to obtain numerous bone shapes and sizes (demineralized, cancellous, cortical,

osteochondral bone matrix and entire segments), something for which the use of autografts can be limited.²⁰ However, they do not have osteogenic potential, given that the cells are eliminated in their processing and have a low osteoinductive capacity. Demineralized bone matrix (DBM) is obtained from cancellous and cortical bone that is processed in a manner that decalcifies but maintains collagen and other proteins including growth factors.²¹ DBM serves as an osteoconductive scaffolding structure, and is perhaps a better option for major defects that cannot be filled using autografts.^{22,23} The use of DBM is more frequently indicated in the form of massive allografts for tumours, and less often for tibial nonunions. In comparison with autografts, DBM grafts have a higher infection rate due to contamination of the allograft.² Another disadvantage of DBM is its high economic cost and the possibility of disease transmission, although screening has reduced transmission.²⁰ There have been no reports of human immunodeficiency virus (HIV) transmission by allografts in the US since the 1990s.²

Another possibility for treating small defects are bone substitutes formed by the collagen scaffolds, hydroxyapatite and tricalcium phosphate, which are only osteoconductors.²⁰ In recent years, the association of these materials with biological therapies has been studied.²⁴

For defects of more than 2 cm we recommend the Masquelet technique, which was first described in 1986. Good results have been obtained; however, its main disadvantage is the need for two-stage surgery.²¹

Although the size of the bone defect on which to perform bone transport techniques is a controversial issue, we believe that such techniques can be considered in bone defect > 3 cm.²⁵ In fact, Harshwal et al stated that in cases where the bone gap was > 3 cm in the tibia, corticotomy and bone transport (bifocal procedure) using a mono-lateral external fixator was effective. Moreover, the nonunion was well controlled with simultaneous correction of angulation and length.²⁵

Reamer-irrigator-aspirator (RIA) system

Since the emergence of the intramedullary reaming technique to adapt thicker IM nails, as described by Küntscher in 1940,²⁶ there has been an effort to reduce the rate of fat embolism and its potential consequences. There have been several methods described over the years, but until the commercialization of the reamer-irrigator-aspirator (RIA) system (Synthes, West Chester, PA, USA), this technique was not standardized.²⁷

The published rate of complications from obtaining aspirate is up to 10% (mainly blood loss, perforation of the femoral cortex with iatrogenic fracture and prolonged local pain). However, RIA seems to be a technique for obtaining bone autografts with similar osteoinductive, osteoconductive and osteogenic capacities and lower morbidity in the donor area.²⁸

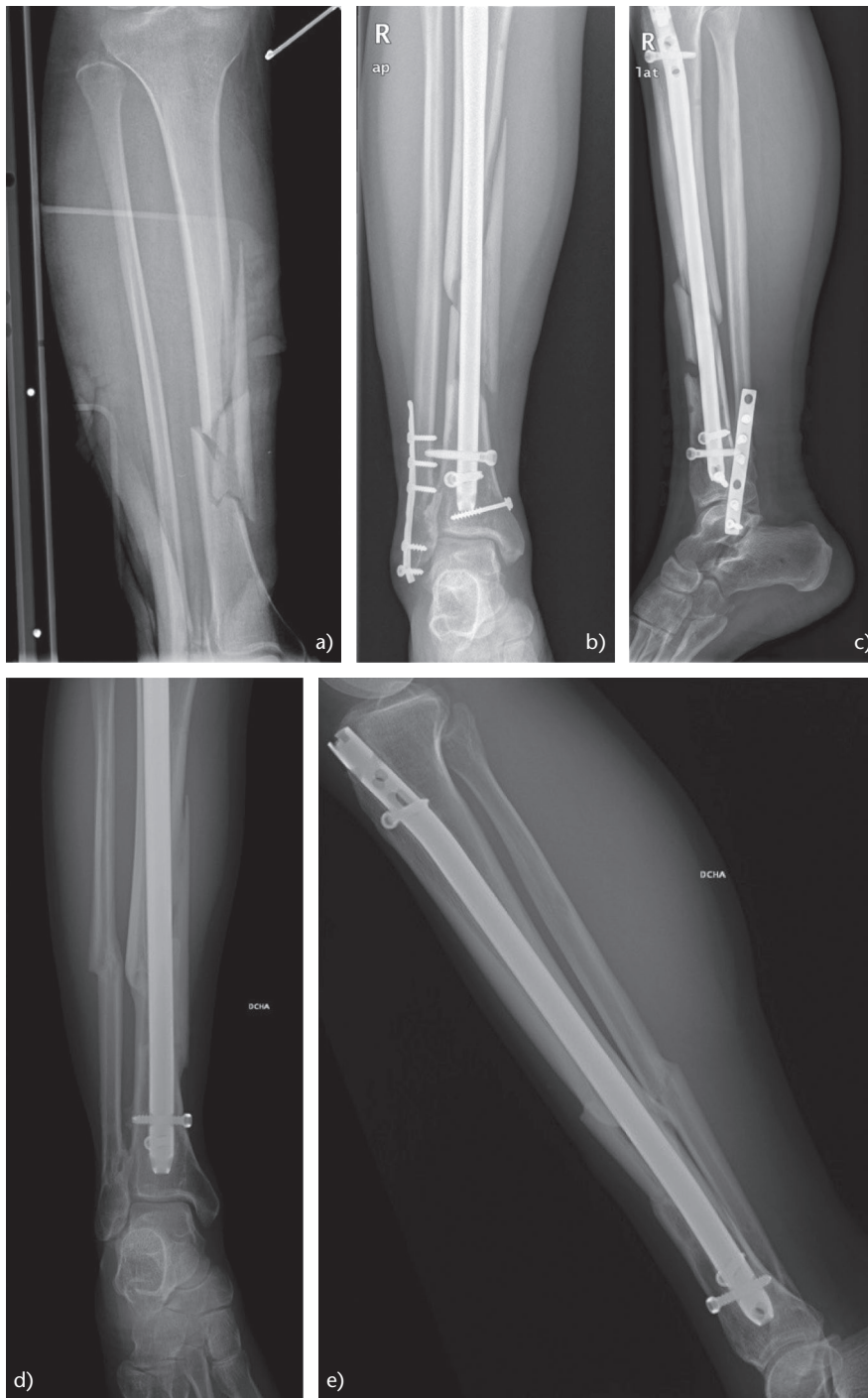


Fig. 2 A 41-year-old male suffered a comminuted diaphyseal fracture of the tibia Gustilo II (a). Anteroposterior (b) and lateral (c) radiographs at 13 months after treatment with a 10-mm diameter non-reamed intramedullary (IM) nail; note oligotrophic nonunion at the level of the tibial shaft. Anteroposterior (d) and lateral (e) radiographs at 12 months after changing the nail for a larger reamed IM nail (13 mm) with associated fibular osteotomy; note satisfactory bone healing. In the preoperative planning of this case, the clinical examination ruled out malrotation (correct thigh-foot angle). A preoperative measurement of the tibial canal at the level of the isthmus was performed, and it was found that the maximum thickness of the nail would be 13 mm, so a reaming of up to 14 mm was performed. Since the fibula was completely consolidated at the distal level, the plate was removed and a fibular osteotomy was added at the diaphyseal level.

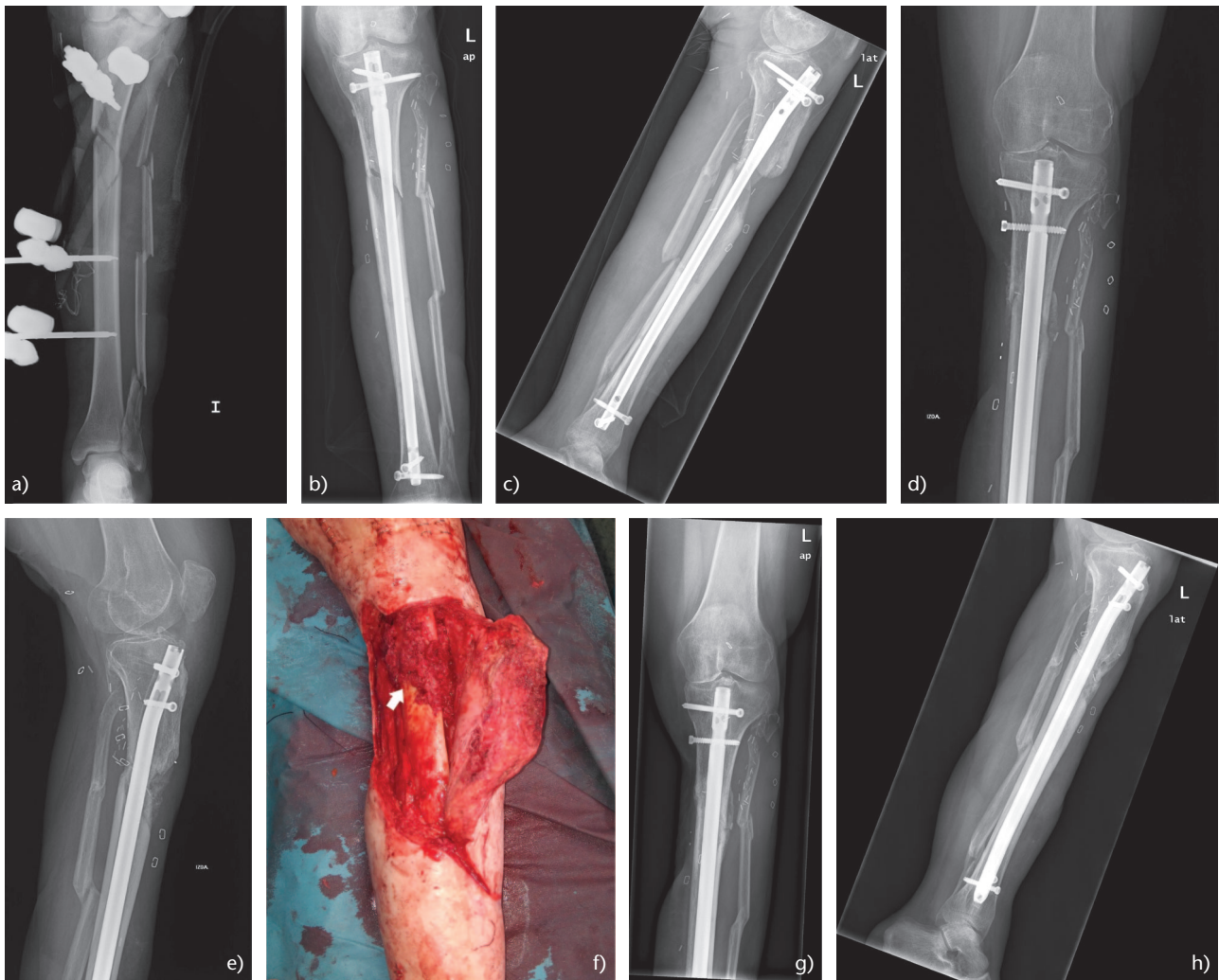


Fig. 3 A 51-year-old woman with an open Gustilo IIIB fracture in the proximal third of the tibial shaft was initially treated with an external fixator for damage control (a). Anteroposterior (b) and lateral (c) radiographs at 10 months after nailing with a non-reamed intramedullary (IM) nail 9 mm in diameter, in which nonunion is observed and a bone defect of the 50% anterior circumference of the tibia. Anteroposterior (d) and lateral (e) postsurgical radiographs after the change to a reamed nail of greater diameter (12 mm) and iliac crest autograft. In (f), an intraoperative image of the autograft implanted in the bone defect (arrow) is observed. Anteroposterior (g) and lateral (h) radiographs at nine months, in which bone healing is observed. In this case, damage control with external fixator plus initial debridement was initially performed, since this was a polytraumatized patient. In a second stage, after nine days, definitive osteosynthesis was performed with an IM nail and coverage with an anterolateral free thigh (ALT) flap. We did not add bone graft to the defect because of the possible increased risk of infection. Ten months later, lack of consolidation was observed with mobility at the fracture site, without analytical and clinical data of infection. For this reason, we decided to change the nail with the addition of bone graft, since the bone defect affected 50% of the tibial circumference. In this case the bone defect of more than 50% was given more importance than the risk of malreduction in recurvatum.

For more significant defects (> 3 cm), bone transport techniques should be considered, keeping in mind that transport techniques involve a long process, with possible psychological effects on the patient and potential complications that will require reinterventions (pin infections, nonunion and neurovascular complications).²⁹ In the tibia, the association between external and internal fixation is an effective option. An IM nail

facilitates good alignment of the tibia during transport by the external fixator and shortens the time that the patient must carry it.³

Biological therapies

Attempting to follow the diamond concept regarding the availability of osteoinductive mediators, osteogenic cells

and osteoconductive matrix (scaffolding), in addition to the optimal mechanical environment, adequate vascularization and addressing any associated comorbidity of the host, interest in certain biological therapies has emerged. There have been numerous studies that support their use, combined with the previous techniques, to provide important biological benefits.

Platelet-rich plasma (PRP)

The use of PRP in fracture healing has been investigated in many experimental studies in animals and has been shown to stimulate bone healing.³⁰ However, there is no consensus on its use for the treatment of nonunions.

Bone morphogenetic proteins (BMPs)

BMPs have some limitations, such as a lack of knowledge of their long-term effects; thus, they are not approved for children, pregnant women or patients with tumours. In addition, some complications can appear, such as initial inflammatory reaction (neuritis, swelling) and complications based on their osteoinductive properties (heterotopic calcifications).²⁰ In a 2010 review published by the Cochrane Library, it was concluded that the usefulness of BMPs in nonunions is uncertain and that there is an obvious influence of the industry in the studies that support their use.³¹

Stem cells: bone marrow aspirate

There is significant evidence for the use of bone marrow aspirate for the treatment of nonunions and defects in long bones in animals, and, since the late 1990s, numerous studies on its use in humans have also been published.³² A small percentage of mesenchymal stem cells (MSCs) is obtained in bone marrow aspirate, given these constitute approximately 0.01% of the aspirate cells. Through centrifugation the cell concentration can be increased.²⁹

Bone marrow aspirate in major defects

As percutaneous injections of bone marrow aspirate cannot fill important defects, combinations of the aspirate with bone substitutes have been proposed.^{33,34}

ORTHO-1

In 2018, Gómez-Barrena et al published the ORTHO-1 (EU-FP7-HEALTH-2009), REBORNE Project (GA: 241876).³⁵ In this report, safety and feasibility were clinically demonstrated for surgical implantation of commercially existing biphasic calcium phosphate bioceramic granules associated during surgery with autologous mesenchymal stem cells expanded from bone marrow (BM-hMSC) under good manufacturing practices, in patients with tibial nonunions.

Non-invasive therapies

Although the treatment of choice in nonunion is surgical management, this approach is not exempt from possible complications, such as infection, neurovascular injuries and implant failures that require reintervention.³⁶ Non-invasive methods have been proposed to promote fracture healing, such as electrical stimulation in the form of pulsed electromagnetic fields (PEMFs), extracorporeal shock waves (ESWs) and low-intensity pulsed ultrasound (LIPUS). Although there is some evidence in the literature for the use of these non-invasive therapies, the studies are heterogeneous and of poor quality. They could probably be applied in isolation to patients with high surgical risk and could be considered as adjuvant therapies to surgery.

Conclusions

For correct healing of fractures, the availability of osteoinductive mediators, osteogenic cells, an osteoconductive matrix (scaffolding), an optimal mechanical environment, adequate vascularization and controlling any current comorbidities of the host are paramount to success.

In the case of tibial diaphyseal nonunions after conservative treatment, the recommendation is bone fixation with a reamed IM nail, with excellent results of up to 100% bone healing. In most cases, however, a tibial nonunion previously treated with a nail is found, the most widespread treatment for fractures of long bones since the 1970s. In these cases, the change of the previous nail for a nail of larger diameter, reaming and locking yields satisfactory results of up to 100% in some series. Even a second nail change after a failed change is a good option, especially if there is some progress in bone healing in the first change. Regarding the need for associated fibular osteotomy, most authors recommend it only in cases in which the surgeon observes that it interferes with the compression of the tibial nonunion site, not as routine treatment. In cases of delayed union and before 24 weeks after the fracture, dynamization of the nail can be considered a less invasive option before deciding on a nail change. Compression plating is an uncommon option that must be reserved for special cases. Another possibility, more indicated for hypertrophic nonunions, is bone fixation with a compression plate, leaving the previous nail in situ, also with excellent results but with a frequent need for hardware removal. These excellent results are more reproducible in patients without a bone defect. For those with bone defects, most authors recommend early bone grafting. The gold standard is AICBG, which provides the three necessary properties for bone formation: osteogenesis (formation of new bone by osteoprogenitor cells), osteoconduction (scaffold for the bone to grow on) and

osteoiduction (cell migration, inflammatory cytokines and growth factors). Its biggest disadvantage is the morbidity in the donor zone; to prevent that, we can use allografts and other bone substitutes, but with them we lose osteogenesis and osteoiduction. RIA is a technique for obtaining bone autograft at least as good as the gold standard of iliac crest grafts and with similar osteoiductive, osteoconductive and osteogenic capacities, but with lower morbidity in the donor area. For major defects of more than 3 cm, bone transport techniques should be considered.

Focusing more on the biological argument of nonunions, osteoiductive options such as BMPs and osteogenic options such as stem cells have emerged in the last decade. There are numerous reports on the benefit of their use in isolation or in association with autografts or other synthetic scaffolds, with results similar to autografts while avoiding morbidity in the donor area. Long-term studies in the form of randomized controlled trials are needed to confirm this benefit, but it appears to be an interesting line of research. As noted earlier, the 'ideal graft' is the autograft, but it produces an associated morbidity. There are research lines attempting to engineer bone grafts with autograft characteristics to obtain better functional recovery and fewer complications than with autograft. That is why a combination of MSCs, synthetic scaffolding and growth factors is being studied.

Regarding non-invasive therapies (PEMFs, ESWs, and LIPUS), although there is some evidence in the literature of their benefits, the studies are heterogeneous and of poor quality. These therapies could probably be applied in isolation for patients at high surgical risk and could be considered as adjuvant therapy to surgery.

Unfortunately, the level of evidence of the studies related to biologic and non-invasive therapies is still low.

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