Treatment of Tibial Non-Unions – State of the Art and Future Implications

Léčení pakloubů tibie – současný stav a výhledy do budoucna

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SUMMARY

Although fracture healing disturbances could be decreased due to successful concepts for fracture treatment, bone healing disturbances occur in 5–10% of the cases. The anatomical region of the lower limb predisposes the tibia for bone healing disturbances. Reports about the incidence of non-unions of the tibial shaft are inhomogeneous. Different treatment strategies have been published which depend on the type of non-union as well as the history of the patient. These range from conservative approaches to complex procedures including segmental resection and bone transport. This review aimed to summarize the state of the art treatment of tibial non-unions and report about recent basic research results that may improve bone healing.

Key words: tibial non-unions, treatment strategies, bone healing.

INTRODUCTION

Although fracture healing disturbances could be decreased due to successful concepts for fracture treatment (e.g. biological osteosynthesis, MIPO techniques, advanced technical development), bone healing disturbances occur in 5–10% of the cases (19). A non-union is defined as the absence of bone healing beyond six month following a fracture, according to the historical definition (55, 67). Due to the multiple associated factors that may finally lead to the development of a non-union some authors criticised this definition as being too inaccurate because it is not ubiquitous applicable to all cases and therefore not useful in daily practise. Thus, many refinements have been proposed in literature which are mainly based on the classical definition (4, 5). Brinker et al. and McKee et al. proposed similar definitions which include the opinion of the surgeon in charge whether or not there is evidence of progress in bone healing over time (12, 45). However, this implicates a haziness due to the human factor involved. A survey in which surgeons were asked to give an assessment regarding bone healing among a representative proportion of surgeons (feedback from 444 participants) showed, that a non-union was defined between 2–12 months' post trauma (6.3 ± 2.1) (4). Interestingly, neither the age of the surgeon nor the level of training in trauma surgery had an influence on the assessment results. Another definition of non-unions was recently proposed by the ESTROT (**E**uropean **S**ociety of **T**issue **R**egeneration in **O**rthopedics and **T**raumatology): A non-union is defined as a fracture that does not heal without a further intervention – independent of the length of the previous treatment (59). However, because the assessment of the clinical and radiographic findings finally often leads to a surgical intervention, the development of a valid scoring system was subject to clinical research. Calori et al. proposed a complex non-union scoring system (NUSS) that consists of eight parameters including three main factors (bone, soft tissue, patient) (14).

The anatomical region of the lower limb with the marginal soft tissue envelope at the medial cortex predisposes the tibia for bone healing disturbances, especially when complex fracture patterns and/or relevant soft tissue injuries are present (32, 38). Reports about the incidence of non-unions of the tibial shaft are inhomogeneous due to divergent inclusion criteria (i.e. fracture classification, classification of soft tissue damage, open versus closed fractures) and the type of surgical treatment. Fong et al. published a rate of 18.2% non-unions following open and closed tibial shaft fractures (21). These numbers are similar to a review article from Coles et al. (Fig. 1) (16). Others report that fifty percent of the patients suffering a tibial fracture are in need for

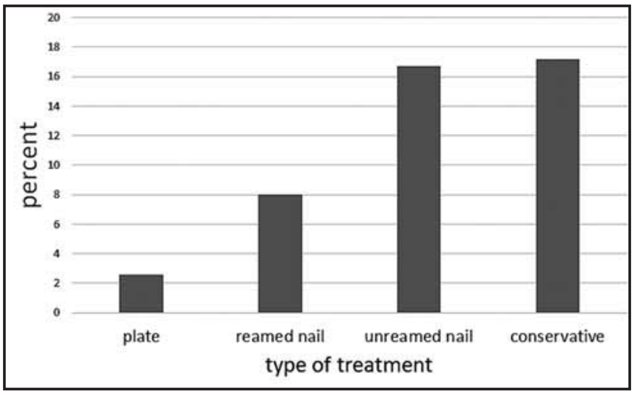

Fig. 1. The incidence of tibial non-unions depending on the type of treatment according to Coles et al. (16).

a second procedure (i.e. dynamization of the nail, bone grafting) during their treatment course to achieve bone healing (20). Different treatment strategies have been published which depend on the type of non-union as well as the history of the patient. These range from conservative approaches (e.g. ultrasound) over minimal invasive surgeries (e.g. bone grafting, application of local growth factors) to complex procedures including segmental resection and bone transport (27).

This review aimed to summarize the state of the art treatment of tibial non-unions and report about recent basic research results that may improve bone healing.

DIAGNOSTICS

Patient history

The diagnostic cascade starts with a brief history of the patient including comorbidities and medication as these could influence the further decision making process. The heretofore treatment (either conservative or surgical) has to be documented with a special focus on evidence for previous infections.

Clinical examination

The clinical examination focusses on the assessment of the surrounding soft tissue envelope, the function of the limb and the symptoms on which the patient reports (i. e. pain under load, abnormal movability, instability). Furthermore, as stated in the last paragraph findings that are suspicious for an infection of the affected region (redness, swelling, hyperthermia, fistula) have to be assessed very carefully.

X-ray

Conventional radiographs of the limb including the adjunct joints are the starting point for any further diagnostic involvement. They may serve as orientation in case of initial presentation and instabilities and deviations of the axis can be detected. However, due to the summation effect of this technique and implants in or at the surface of the bone, defects and structural disorders can be underestimated.

Computed tomography (CT), magnetic resonance imaging (MRI)

CT scans enable a detailed imaging of the affected bone. Particularly the complete or incomplete bridging of the bone can the identified. An additional MRI can be helpful to distinguish vital from avital bone masses when contrast fluid is used (49, 62). Currently, the CT scan is regarded gold standard in the evaluation of non-unions and delivers important information for the decision making process (8).

CLASSIFICATION

Several classification systems have been proposed in the past (4, 5). However, all these classifications are based on the famous principles published 1976 by Weber and Cech (67). They discriminated the non-unions upon vitality and healing potential of the bone. Three different types of non-unions are distinguished: hypervascular/hypertrophic non-unions (Fig. 2), avascular/atrophic non-unions (Fig. 3), and infected non-unions which can be hyper- or atrophic.

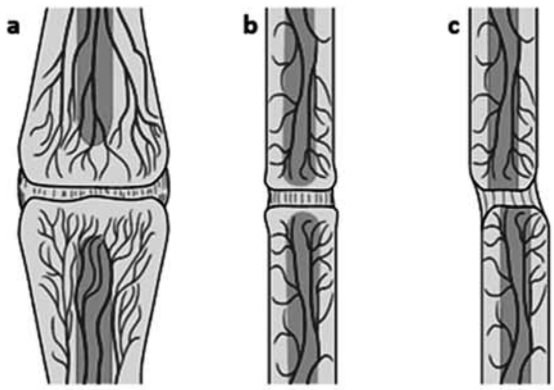

Fig. 2. Schematic illustration of the three subtypes of vascular non-unions. The elephant foot non-union (a), the horse foot non-union (b) and the oligotrophic non-union (c) are characterized by their ability to heal in a mechanical stable environment. Modified according to Weber and Cech (67).

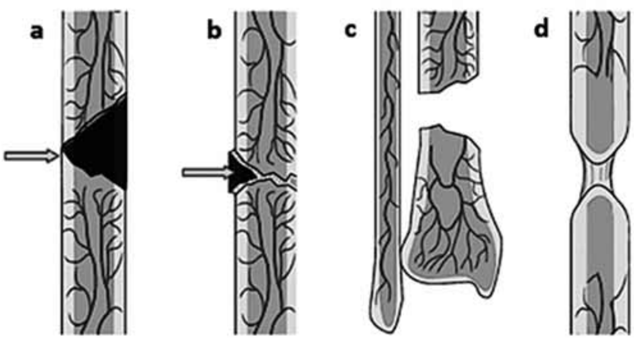

Fig. 3. Schematic illustration of the different subtypes of avascular non-unions. The torsion wedge non-union (a), the comminuted non-union (b), the defect non-union (c) and the atrophic non-union (d). They are characterized by the inability to heal without biological support (i. e. bone graft). Modified according to Weber and Cech (67).

Hypertrophic non-unions

These types of non-unions are characterized by a hypervascular or hypertrophic region at the ends of the fragments which are capable of a biologic reaction (22). Different studies demonstrated that this type of non-union has a good biological potential to heal as they have a good blood supply in the region of the fracture (22). The developing external callus is the response of the viable bone to micromotion at the fracture site. However, the amount of micromotion prevents from building up a sufficient bone mass across the fracture line (22). Thus, the underlying mechanical instability is the main factor that leads to a hypertrophic non-union. The main focus in treatment is to establish a mechanical stable situation to eliminate the motion at the fracture ends beyond a critical threshold which is compulsory for fracture healing. However, these constructs may not be too rigid as it could be shown that micromotion within distinct limits is mandatory for fracture healing (42). According to the amount of callus Weber and Cech subdivided this type of non-unions into three subtypes (67):

• “Elephant foot” non-union

These show a rich amount of callus formation which results from instability due to insufficient fixation or premature weight bearing. Because of the mechanical instability the tissue in between the fracture ends is disturbed and ossification takes only part in the peripheral area.

• “Horse foot” non-union

This subtype is slightly hypertrophic and forms only few callus. In most cases it occurs following a plate osteosynthesis which is not rigid enough to provide sufficient stability. As a result, the implant often fails due to fatigue or overloading before a sufficient bony bridging of the fracture may occur.

• “Oligotrophic” non-union

These appear without callus formation due to inappropriate reduction of the fracture, fixation in distraction or in defect situations. Although the fragment ends are viable the distance between the fragments is too large to form bridging bone matrix.

Avascular non-unions

This group consists of non-unions which are identified by inert fragments that are not capable of biological reaction. Bone scans will indicate a poor blood supply (22). A histological study on human samples, however, showed a comparable vascularization of established atrophic and hypertrophic non-unions (54). To elucidate the role of vascularization animal studies were performed supporting the importance of vascularization during the healing process and an inhibition at the beginning of the healing results in atrophic non-unions (34, 46). Atrophic non-unions occur when avital bone parts are present due to severe comminution and/or devitalisation of the fragments during surgery. Proper reduction and internal fixation or immobilisation alone will not be sufficient to achieve bone healing. These situations are subject to additional bone grafting (biological substitute) following debridement of the avital bone ends. However, large amounts of bone graft are often necessary to bridge the underlying defects. Four different subtypes can be identified:

• Torsion wedge non-union

In fractures with an intermediate fragment this fragment heals to one main fragment but not to the other. These are usually seen in fractures of the tibia that were treated by plate osteosynthesis (22).

• Comminuted non-union

The main attribute of this group is the presence of one or more intermediate fragments that appear to be necrotic. There are no signs of callus formation in radiographic imaging.

• Defect non-union

This subtype occurs in cases of severe bone loss either by the trauma itself or during treatment (i. e. debridement). The length of the defect is too large to allow sufficient bony bridging.

• Atrophic non-union

These are usually the result of the subtypes mentioned above. During the long treatment period the end of the fragment becomes atrophic with insufficient scar tissue in between.

Infected non-unions

Non-unions due to infection are the most complex situations and occur in up to 18% of the cases (11). Typically, they are associated with severe pain, impaired function and soft tissue alterations. In addition, intramedullary sequesters or fistulas are seen frequently. Treatment strategies are complex as they simultaneously aim to unite the fracture, regain function, reconstruct the soft tissue envelope and eradicate the infection (12). Furthermore, they are morphologically variable and can present in any of the above mentioned ways (37).

RISK FACTORS

In the past multiple predictive factors could be identified that impair bone healing and which may finally lead to a non-union situation (13, 52, 58). Also, a multitude of patient related factors could be identified as risk factors for the development non-unions. These include advanced age (13), malnutrition (17, 31), alcohol abuse and smoking (48, 61). Furthermore, comorbidities (e.g. Morbus Cushing (41), Diabetes mellitus (40, 52)) and medication with nonsteroidal anti-inflammatory drugs (1, 29) could be acknowledged. Recently, some authors introduced a genetic predisposition as a significant risk factor for non-unions into the discussion (18). Beside these systemic factors, a wide range of local factors have been recognized yet, that obviously impair bone healing beyond a point where sufficient fracture healing is possible (Table 1). Within the local factors the type and quality of the initial surgical treatment seems to play a major role (58).

THERAPY

Generally, all treatment strategies aim for union of the bone defect including restoration of the axis and length to regain previous function of the extremity. The fundamental requisite to achieve this goal is a sufficient soft tissue envelope that is free of infection.

Diamond concept

The complex pathophysiological interactions which are necessary to achieve bony union can be divided into basic components which are of essential significance: mechanical environment, osteogenic cells, osteoconductive scaffolds, and osteoinductive growth factors (25, 26). Giannoudis et al. summarized the most important interactions of these factors in the so-called "Diamond concept" (Fig. 4). The application of the diamond concept leads to an optimized combination of biological and biomechanical factors (49, 59). This allows the surgeon to individually develop an optimized treatment pathway based on the diagnostic results and the brief review of the patient s history by adding the individual missing mechanical and/or biological factors.

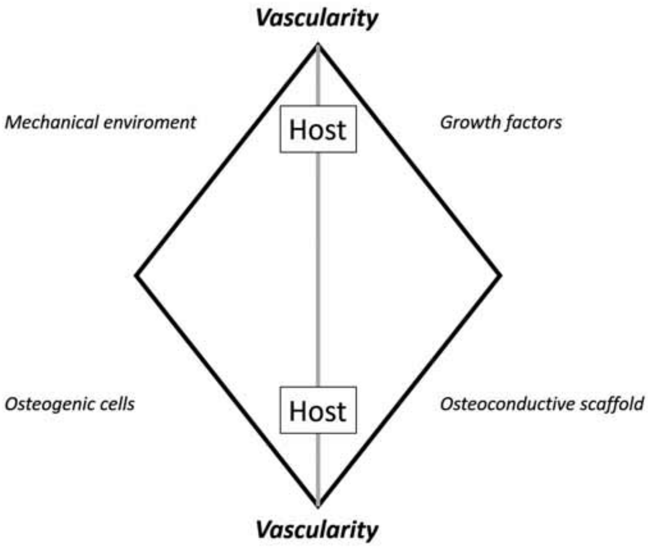

Fig. 4. The „Diamond concept" of fracture healing interactions modified according to Giannoudis et al. (26, 27).

Bone defect filling

Autograft is considered to be gold standard because of its osteogenic, osteoinductive and osteoconductive qualities (50). Most often it is harvested at the iliac crest because it can be either used as tricortical wedge which provides good stability or as cancellous bone of optimal consistence. However, data demonstrate that bone grafting is accompanied by significant morbidity, prolonged operative time and hospital stay. Furthermore, its availability is limited and the biological activity of the mesenchymal stem cells decreases as the donor ages (6). Another option to gain cancellous bone is the RIA (**R**eamer-**I**rrigator-**A**spirator, DePuy Synthes) method. Following a percutaneous approach to the femur or the tibia, this system allows to harvest up to 80 cm^3 autologous bone (59).

Table 1. Local risk factors for the development of a posttraumatic non-union

Fracture related	Treatment related
degree of closed/open soft tissue damage	missing fragment contact following reduction (> 3 mm)
fracture morphology	mechanical instability
compartment syndrome	infection
previous fracture at the same bone	open reduction

Bone morphogenetic proteins (BMPs)

Besides numerous surgical options the stimulation of bone healing by osteoinductive growth factors moved into the focus of research. Within the group of growth factors bone morphogenetic proteins (BMPs) have been shown to positively influence bone healing (6). In 1965 Urist described bone formation after implantation of demineralized bone (66) and in the late 1980th the osteoinductive proteins responsible for bone formation were named BMPs (70). Since that more than 20 subtypes have been identified (39). Via complex pathways these proteins play different roles in the embryogenesis and maintenance of virtually all tissues and organs. Regarding bone healing they influence endothelial and osteogenic cells, therefore stimulating both: vessel and bone formation (57). Since their introduction various clinical and experimental studies have been accomplished (6). To date, only BMP-2 and BMP-7 are approved for the treatment of open tibial shaft fractures or tibial non-unions, respectively. It could be shown, that the combination of autologous bone graft and growth factors has a synergistic effect on bone healing which is superior compared to single application (28). Furthermore, there is some evidence, that growth factors positively influence bone healing in cases of persisting non-unions (24, 47).

Non-surgical treatment

A conservative approach in the treatment of tibial non-unions is only indicated in the early stage of the patient s course. A stepwise but continuous increase of load until full weight bearing is one of the most often used treatment option. However, mechanical stability and the ability of the bone to regenerate are assumptions. There is some evidence that additional low energy ultrasound can positively influence bone healing (35, 51, 56). The group of Heckman et al. found a significant faster fracture healing using ultrasound in a clinical randomized, double-blind evaluation of 67 tibial shaft fractures (35). Nolte et al. included 29 non-union cases and achieved bone healing in 86% of the cases with a mean treatment time of 22 weeks (51). In concordance with these authors and our own clinical experience the ultrasound therapy can be useful in cases of non-infected stable osteosyntheses where bone healing is delayed.

Surgical treatment

The recent understanding of the physiological processes governing the fracture healing process involves numerous mediators as well as elements at the cellular and molecular level that interact with each other and thus exert an effect in association with physiological and biomechanical principles (26). Although not fully understood, the interaction of the above mentioned parameters is believed to constitute intricate pathways that finally provide bone healing. However, the up-to-date consensus additionally considers mechanical stability being a mandatory factor to create an optimized environment for bone fracture repair (25, 26, 42). In summary, a successful treatment depends on a brief assessment of the patient s history and the diagnostic results available. Based on these facts the type of non-union has to be defined while the different treatment modalities depend on this evaluation.

Hypertrophic non-unions

Historically, a wide range of treatment modalities have been proposed in literature (53). Some authors advocate exchange nailing while removing the previously implanted nail and inserting a larger diameter nail following additional reaming (50). Other procedures that have been recommended are dynamization of the nail (71), plating following nail removal (3) or bone grafting (50). According to the Diamond concept hypertrophic non-unions need an optimized mechanical environment. Therefore, the revision procedure should aim to increase the biomechanical stability of the osteosynthetic construct. The easiest procedure is still the dynamization of the intramedullary implant followed by full weight bearing. However, in cases when dynamization represents no option, the nail exchange including reaming of the intramedullary canal is the preferred procedure (Fig. 5) (23, 68).

Atrophic non-unions

These are characterized by an insufficient bone regeneration as mentioned above. Referring to the Diamond concept an additional biological activation of the bone regeneration is necessary (Fig. 6) (47, 49). However, the most important initial step in the surgical treatment of atrophic non-unions is the radical debridement of all avital and necrotic material followed by a stable osteosynthesis and augmentation of the resulting defect (69). To optimize the biomechanical environment and to correct existing deviations of the axis implant removal followed by a new osteosynthesis is often inevitable (59). Reconstruction of the defect is facilitated using bone graft. Additionally, growth factors can be used to enhance the outcome. However, in cases of infection or low grade infection one-stage-procedures are obsolete. Therefore, in cases where the intraoperative surgical site is suspicious for infection, a two-stage-procedure should be aimed for.

Infected non-unions

This type of non-unions has the worst outcome and the most complex treatment course (Fig. 7) (10). In many cases large segmental bone defects (> 2 cm) result following debridement and they need special techniques to reconstruct. Here, bone reconstruction can be achieved by using the Masquelet s technique (43). In this two stage procedure the resulting bone defect is filled with bone cement during the first operation. After 6–8 weeks during the second surgical procedure the membrane which developed around the bone cement is carefully opened and the bone cement is extracted. Now, the biological reconstruction using bone graft (e. g. iliac crest or RIA) is performed and the membrane closed afterwards (59). When the defect size exhibits 6 cm segmental bone transport using the Ilizarov method (36) or vascularized bone transfer are the preferred methods of treatment (65).

Fig. 5. Patient (51 years, male) presented with a painful hypertrophic non-union of the tibia combined with a varus deformity (a). According to the diamond concept mechanical instability lead to this non-union. Due to the accompanying varus deformity a modified open wedge osteotomy in the non-union plane was performed followed by reamed nailing of the tibia to enhance stability (b). As second procedure dynamization of the nail was done six weeks thereafter. The patient was able to walk pain free under full weight bearing seven months following the correction osteotomy (c).

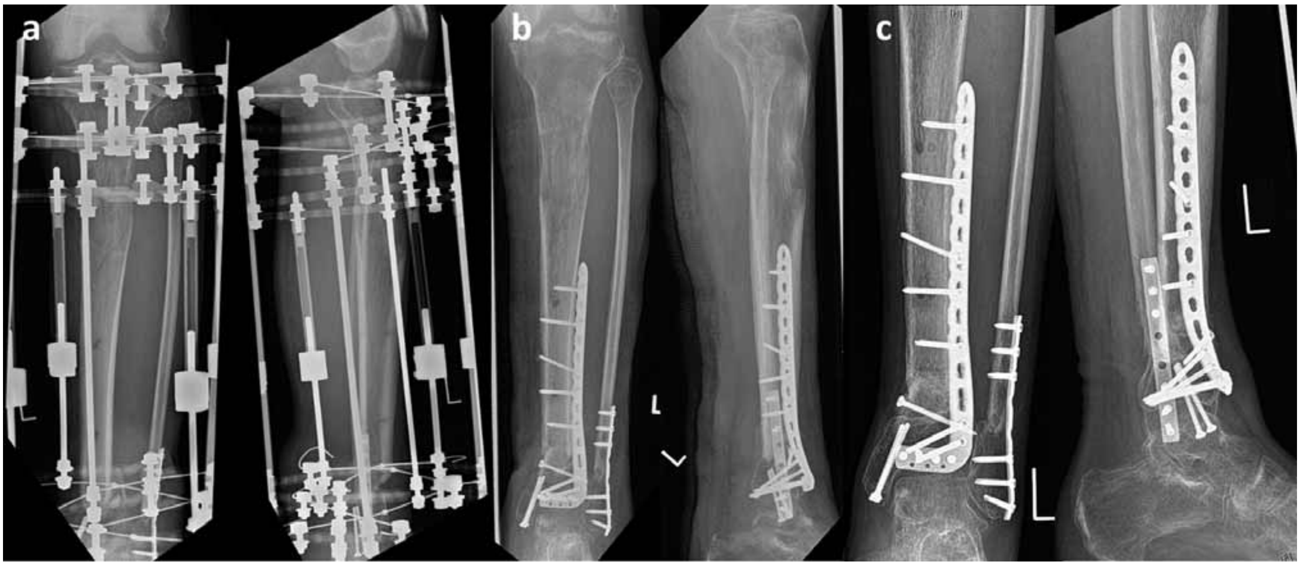

Fig. 6. 46-year-old male following high velocity trauma. Initial treatment of this grade IIIB open segmental fracture was a primary bone transport via the proximal fracture to bridge the defect of the distal fracture. The patient developed an atrophic non-union at the docking site (a). In a second procedure, bone grafting combined with BMP and internal plate fixation was performed (b). Bone healing was achieved within six months (c).

RECENT RESEARCH

BMPs have been shown to increase the success of bone healing in non-unions cases. However, because of their short half-life and the dose related effect, the local concentration of BMPs while application is far beyond the natural concentration in the bone (15). At the moment, BMPs are used in combination with a collagen sponge or matrix and approximately 50% of the factors are released within the first days after implantation (64). The development of optimized drug delivery systems might allow a reduction of the dosage in combination with a prolonged release (60). But also gene transfer has become a focus in basic research. In a rat model a stable BMP expression for ten days following transfection could be shown (63). Besides gene transfer, the application of bisphosphonates has been focussed. Using bisphosphonates an accelerated fracture healing in an animal model was shown (30). However, due to different study designs, applied substances and doses the results published are not consistent (2, 7, 33, 44). The basic principle of these substances is either a pro-anabolic (i. e. BMPs) or

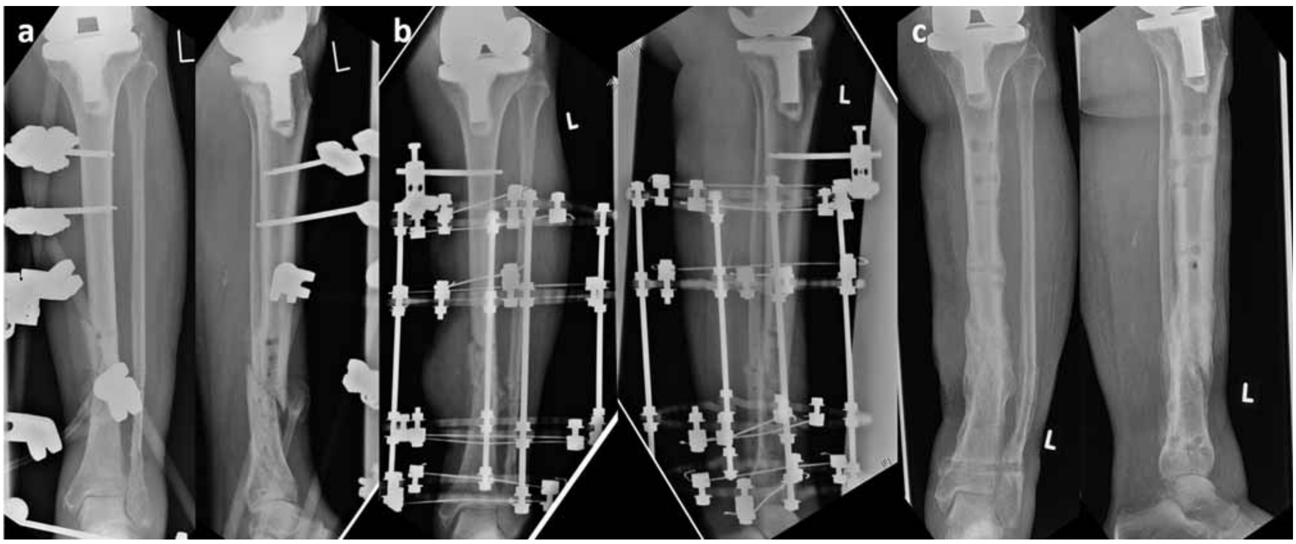

Fig. 7. 71-year-old female was transferred to our centre with an infected non-union of the tibia following a periprosthetic fracture (type V.4 C according unified classification system) which was initially treated by plating. The patient underwent implant removal and several soft tissue debridements prior to the transfer (a). In our centre the patient underwent serial debridements of the soft tissues and the bone and was stabilized with a hybrid external fixator according to Ilizarov (b). The soft tissue defect could be reconstructed using a distally based sural artery neurocutaneous flap. One year after referral to our centre patient was able to perform full weight bearing with an intact soft tissue envelope free of infection (c).

mainly anti-catabolic (i. e. bisphosphonates) mode of action. The group of Bosemark et al. combined these effects and could demonstrate that the fractures had a significant better mechanical strength six weeks following the trauma (9). Furthermore, the volume of callus produced was significantly bigger than in the control group (9).

Although these alternative treatment options and the results seem so far to be promising, these techniques have to proof their safety first in order to be implemented in the clinical use in order to have an effect in terms of preventing non-unions to develop.

CONCLUSION

Tibial non-unions remain one of the most severe complications following fractures of the tibia. They are accompanied by a significant impact on patient s quality of life and functionality of the affected limb. Based on valid classifications and the diamond concept for understanding the fundamental requirements of successful bone healing, treatment strategies have been established. However, the success of the surgical treatment of tibial non-unions remains uncertain and the course of the patient still is not easy to predict, since multiple variables concerning fracture/non-union morphology and risk factor profiles have to be individually assessed. Literature data demonstrate that algorithm based treatment strategies ament the outcome of affected patients in terms of bone healing and functionality of the limb. Nevertheless, every patient has to be analysed individually and the patient with all his expectations and preservations has to be involved in the planning of the surgical strategy in order to achieve optimal results and to keep the frustration on both sides as low as possible.

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