Reconstruction of Large Diaphyseal Defects of the Femur and the Tibia with Autologous Bone

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Abstract
Post-traumatic segmental bone defects of the femur and the tibia above the critical size require special attention because conventional bone grafts result in high rates of nonunion. The biological and biomechanical aspects of this challenging surgery, as well as ongoing refinements to achieve mechanically stable bone healing with correct bone alignment are reviewed. Choosing the best appropriate method is mainly dependent on both the location and etiology of the bone defect. Three patients with successful bone reconstruction using two-stage reconstruction with cancellous bone graft, double-barrel free vascularized fibula transfer and distraction osteogenesis are described. Advantages and disadvantages of these methods are discussed in accordance with recent literature.

Key Words
Critical size defect · Femur · Tibia · Bone transplantation · Open fracture · Bone tumor · Bone infection

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Introduction

Progress in managing soft tissue defects and stabilizing bone as well as clear schemes for eradicating bone infection have contributed to increasing limb preservation following severe open fracture and post-traumatic bone infection. Segmental bone defects resulting from debridement or local control of infection are challenging, especially at the lower extremity, where bone shortening is not a valuable option. Massive cancellous bone autograft of segmental bone defects of the femur and the tibia exceeding the critical size of 5–7 cm result in high rate of nonunion [1, 2]. Recent advances in reconstruction of large segmental bone defects have mainly arisen from refinements of classical techniques [3]. Biological and biomechanical considerations are also important for guiding the surgeon in the selection of both the best bone stabilization and an appropriate autologous bone grafting method to achieve bone healing in the shortest time. Here, we describe current options, including two-stage reconstruction with nonvascularized cancellous bone autograft, double-barrel free vascularized fibula transfer, and distraction osteogenesis.

Biological and Biomechanical Issues Related to Bone Defects of the Femur and the Tibia

Independent of the origin of the bone pathology, several issues are commonly encountered when managing a large diaphyseal defect in the lower extremity. Stabilizing the femur or the tibia with a bridging osteosynthesis is not an easy task, because there are conflicts of interest between requirements for the host bone and the transplanted bone. Bone osteosynthesis must be stable because of the strong load and muscle mass acting on the bone, especially over the femur, and the need for the hardware to carry all mechanical constraints up to complete bone healing [4]. On the other hand, too much stability will stress shield the transplanted bone, favoring its resorption and delaying bone union [5]. Nails allow early weight bearing, but the hardware reduces the room left for the subsequent bone graft. External fixation has obvious advantages in the case of bone infection, decreasing the risk of infection recurrence. In an aseptic situation, however,

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external fixation is less attractive, as pin track infection and patient acceptance may become a problem after several months. Plate osteosynthesis is probably the best option in the case of a large segmental bone defect of the femur and the tibia in an aseptic environment. On the other hand, modern monolateral external fixation is our reference method when treating an infected nonunion. Specific issues are discussed in more detail according to the origin of the segmental bone defect.

Primary and Secondary Care of Fractures with Bony Defects

High-energy injuries like motorcycle accidents create severe soft tissue lesions, including injuries to the muscle, avulsion of the periosteum and contamination of the wound, all of which contribute to bone devascularization and increased risk of infection. Taking care of the bone defect is part of a global strategy to prevent infection and allow both soft tissue and bone to heal. Shortening the leg to allow bone contact and then re-lengthening it later using distraction osteogenesis is a rarely performed approach, but it must be kept in mind as a salvage procedure [6]. However, taking care of a severe open tibia fracture usually involves combining thorough debridement (including removal of all devascularized tissues), stabilizing the bone, and covering the bone and hardware with healthy soft tissue. Primary stabilization of the fracture with a nail or a plate is favored when both bone and hardware can be easily covered by tension-free soft-tissue mobilization or a reliable pedicled flap [7]. This option is also valuable when a free flap is required, and can be performed within a few days by the specialist (i.e., before colonization of the surgical site with skin flora) [8, 9]. This delay may be extended using vacuum dressing [10], but no data on how long the coverage can be safely delayed are available [11]. A second option consists of using an immediate external fixation as an awaiting bone stabilization procedure and then to proceed with ORIF when both general and local situations have improved. However, there is controversy over the increased risk of infection resulting from the use of a nail or ORIF following external fixation [12–14]. The third option consists of using the external fixation as a definitive bone stabilization method. This has the major advantage that repeat bone and soft tissue debridements can be performed up to the time of definitive wound coverage, and that the risk of bone infection is decreased because internal osteosynthesis is not used. The use of modern monolateral external fixation with static and dynamic compression capabilities and hydroxyapatite-coated pins makes this option a valuable alternative to internal fixation because it allows early partial weight bearing, and both pin track infection and loosening rates are reduced [15, 16]. Also, the management of a soft tissue defect is easier with monolateral external fixation than with a ring fixator, which may impair the harvesting of a local flap.

Conversely, soft tissue lesions in open fracture of the femur have little impact on the choice of method used for bone stabilization, because the muscle surrounding the bone can usually be used to cover both bone and hardware. Damage control surgery is favored in polytrauma patients because it is quick and straightforward and allows the focus to be initially directed to life-threatening injuries [17], but the majority of patients with femur fractures are treated directly with a nail or by ORIF.

In the context of open fractures of the tibia and the femur, immediate reconstruction of a bony defect above the critical size is risked because of the higher infection rate [18]. Also, the use of an immediate massive cancellous bone graft reduces options later, because less graft material will be available in the case of delayed union or nonunion. Therefore, delaying bone reconstruction up to the time of complete soft tissue healing is the preferred approach.

Infected Nonunion

Bone defects and bone infections are two difficult issues. A combination of them is one of the worst problems encountered in orthopedic surgery and traumatology. Treating bone infections requires a combination of surgery and appropriate systemic antibiotics for several weeks to months. Many approaches, like the Papineau method, have been proposed to treat infected nonunion of the long bones using only marginal bone debridement [19]. However, it was not uncommon for such approaches to result in recurrent open drainage despite bone healing due to remaining bone infection [1]. ''Oncological'' debridement is now mandatory in order to treat chronic bone infection [20]. Current concepts that use a two-stage approach allow the treatment of the bone defect to be postponed until the bone infection has been eradicated, and this delay is used to prepare an optimal environment for the future bone graft [21]. Vascularized soft tissue transfer has provided a major advance in the management of infected nonunion, because the improved local blood supply favors both antibiotic delivery and bone healing [22]. Initial surgery involves soft tissue and bone debridement, external fixation, filling the bony defect with a gentamycin- or vancomycin-impregnated cement spacer, and reconstruction of the soft tissue with a muscle flap and skin graft. Second-stage surgery, performed at least six weeks later, consists of removing the cement spacer and reconstructing the bone with nonvascularized cancellous bone chips placed within the membrane formed at the former cement interface [21].

Biological and Biomechanical Issues in Bone Reconstruction Above the Critical Size

Properties of Autologous Bone Grafts

Both mechanical and biological properties of autologous bone grafts differ widely according to their origin (Table 1). Nonvascularized cortical bone grafts provide good structural support, but very few osteoblasts are present, and both the osteoinduction and osteoconduction of the cortical bone is poor. This becomes obvious when the in vivo behaviour of nonvascularized fibula transfer is compared to vascularized fibula transfer, with the former behaving like an allograft [23]. Conversely, although cancellous bone has no mechanical resistance and therefore must be combined with a solid for bridging osteosynthesis, cancellous bone osteoblasts resist transplantation well, and both osteoconduction and induction of cancellous bone is important because it contains bone matrix and mesenchymal stem cells that release growth factors. On the other hand, vascularized bone transfer provides mechanical stability and immediate vascular connections allow some cell survival. Nonetheless, osteoconduction and osteoinduction differ widely according to the structure of the transplanted bone: the iliac crest and ribs are rapidly integrated, while fibula transfer requires more time because of its cortical structure. However, when reconstructing the long bone, the most commonly used vascularized bone graft is the fibula because of the length available, easy fixation, mechanical resistance and low donor site morbidity [24].

Table 1. Comparison between nonvascularized and vascularized autologous bone grafts.

	Nonvascularized bone graft		Vascularized bone graft
	Cancellous bone	Cortical bone	
Osteoprogenitor cells	+++	–	+
Osteoconduction	+++	+	+
Osteoinduction	++	+/–	+
Structural support	–	+++	++

Remodeling of the Bone Graft

Resorption of the bone grafts used to bridge a segmental defect above 6 cm has been widely documented in patients. Bone graft remodeling is regulated by signaling pathways that control both bone formation and resorption. The terms ''anabolic'' and ''catabolic'' bone responses – which describe the pathways that control the formation of new bone matrix and the resorption of damaged bone, respectively – are now preferred, as they better describe the underlying mechanisms of bone healing and their disorders [25]. The balance between these two activities depends on several factors, including age, metabolism, local blood supply, bone structure, the presence or absence of a bone defect, and mechanical considerations. The anabolic and catabolic responses in bone and bone graft are also influenced by several substances, some of which have a dual role [26]. The bone morphogenetic proteins (BMPs), for example, which stimulate bone formation through the recruitment and differentiation of mesenchymal progenitor cells into osteoblasts, also stimulate osteoclasts, and can therefore contribute to bone resorption. On the other hand, biphosphonates inhibit osteoclast functions. Other growth factors may also directly or indirectly influence bone formation through recruitment, stimulation or inhibition of cells, or by improving bone vascularization [27]. There are still several issues regarding the basic scheme for reconstructing bone defects, as well as uncertainties over the mechanisms of particular methods (for a review, see [28]). This is especially true of the two-stage reconstruction method. This method was first empirically used in infected nonunion of the tibia with defects above the critical size [29]. Why the use of two-stage cancellous bone grafting permits bone healing in situations where one-stage reconstruction is very likely to fail is unclear. There is experimental evidence for the production of vascular endothelial growth factor, transforming growth factor-β1, and BMP-2 in the spacer-induced membrane [30]. However, how and to what degree these factors contribute to successful bone healing is unknown, and attempts to compare the induced membrane potential to the osteogenic properties of the periosteum have proven inconclusive.

Strategies for Bone Reconstruction of Large Diaphyseal Defects

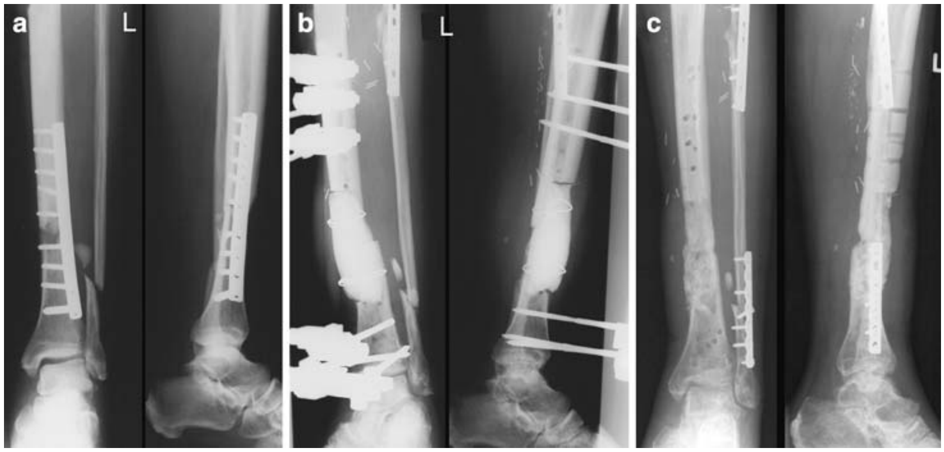
Patient A: Double-Barrel Fibula for Reconstruction of the Femur

A 16-year-old teenager underwent an isolated Gustilo IIIA open fracture of the left femur at the mid-diaphyseal level (Figure 1a). Initial surgery consisted of debridement, irrigation and wound closure with drainage, and stabilization with external fixation (Figure 1b). General antibiotics consisting of amoxycillin/clavulanic acid and metronidazole were given. This was followed two weeks later by ORIF with a 4.5 mm plate (Figure 1c). A deep infection with *Serratia marcescens*, *Enterococcus* and *Clostridium* occurred. It was treated by thorough debridement, the infected bone was resected, a cement spacer was placed in the bone defect, and the femur was stabilized again with a 4.5 mm plate. General antibiotics consisting of amoxycillin, metronidazole and clindamycin were given. Ten surgeries, including five debridements, irrigation and spacer changes and five changes of both the spacer and the plate were subsequently performed over a period of four months to control the infection. This resulted in a 10 cm segmental defect of the femur, which was filled with cement (Figure 1d). The femur was subsequently reconstructed with a double-barrel ipsilateral vascularized fibula with lateroterminal vascular anastomoses with the femoral artery and termino-terminal anastomoses with the vena saphena magna (Figure 1e). A postoperative hematoma of the thigh was evacuated 2 days later. The patient received amoxycillin and metronidazole for three months. Partial weight bearing was allowed at three months and full weight bearing at six. At 1.5 years follow up, the patient was free of pain and could salsa dance (her favorite recreational activity) (Figure 1f).

Patient B: Two-Stage Reconstruction of the Tibia

A 59-year-old man underwent a motorcycle accident in Thailand and suffered multiple fractures of the lower left extremity, including an open fracture Gustilo II of the medial/distal third of the tibia and closed fractures of the distal femur and the calcaneum. ORIFs of the femur and the tibia (Figure 2a) were initially performed. Both the femoral and calcaneal fractures healed uneventfully. A deep infection of the tibia with methicillin-sensitive *Staphylococcus aureus* was treated by removing the plate and infected tissues and stabilizing the tibia with external fixation. Further surgeries consisted of serial debridements resulting in an 8 cm defect of the tibia and an 80 cm^2 defect of the soft tissue exposing the bone. A two-stage reconstruction was performed. The first stage involved thorough debridement of both bone and soft tissue, filling the

Figures 1a to 1f. The Gustilo IIIA open fracture of the femur (a) was initially treated with external fixation (b). An ORIF was performed two weeks later (c) and was complicated by a deep infection. The serial bone debridements resulted in a 10 cm segmental defect of the femur which was filled with a cement spacer (d). The defect was bridged with a double-barrel free vascularized fibula transfer harvested from the same side. Both fibular fragments underwent inlay placement away from the plate to avoid stress shielding of the bony transplants (e). At one year follow up, both fibular fragments had healed, resulting in a bone bridge with a width similar to that of the recipient bone (f).



Figures 2a to 2c. The Gustilo II open fracture of the tibia was initially treated with ORIF (a). The resulting osteomyelitis was treated with hardware removal, soft tissue and bone debridements, and bone stabilization with external fixation. The first-stage reconstruction involved filling the defect with gentamycin-impregnated cement, and covering both bone and cement defect with a serratus anterior free-muscle flap and a skin graft (b). Three months later, the cement spacer was removed, respecting the membrane formed at its interface, and the defect was filled with cancellous bone graft from the iliac crests. At eight months of follow up, the bone was completely healed and the external fixation was removed (c).

bone with gentamycin-impregnated cement, and covering the defect with a serratus free-muscle flap and thin skin graft (Figure 2b). The patient subsequently received general amoxicillin and clavulanic acid for three months. The second-stage surgery was then performed: the cement spacer was removed, respecting the membrane formed at its interface, and the bone defect was filled with cancellous bone from both posterior iliac crests. Both fibula fractures were stabilized with plates. Partial weight bearing was allowed at four months and full weight bearing at seven months. The external fixation was removed at eight months of follow up (Figure 2c). At one year of follow up the patient was free of pain with full weight bearing and could walk at least 30 min.

Patient C: Bone Transport in Pseudarthrosis of the Tibia

At one year of age, anterior bowing of the lower left leg was noted when the patient, a boy, started to walk (Figure 3a). The child was referred to a general district hospital where the diagnosis was suspected osteosarcoma. A surgical biopsy was performed. A pathologic fracture at the former biopsy level occurred (Figure 3b). The tibia was stabilized by ORIF and a cancellous bone graft was performed (Figure 3c). The diagnosis of congenital pseudarthrosis of the tibia was recognized because the facture did not heal (Figure 3d). Subsequently, the patient was referred to our clinic and a resection reconstruction of the pseudarthrotic tibia was performed when the boy was three years old (Figure 3e). After having resected the pseudarthrosis and sclerotic bone, a segmental bone transport was performed using a mini-fragment frame (Synthes®), allowing complete bone healing of the tibia (Figure 3f). A proximal tibial extension osteotomy was performed at the age of seven and an autologous bone graft and plating of the fibula when he was 13 (Figure 3g). Clinical and radiological assessments at the age of 15 showed unrestricted functions of the knee and foot and correct bone alignment (Figure 3h). The patient declined any further leg lengthening to correct the remaining leg shortening. He practices sport activities without impairment.

Discussion

Reconstructing large segmental diaphyseal defects of the femur and the tibia usually requires several surgeries, and full bone healing is always a long process. Current options exclusively use autologous bone because none of the currently available bone substitutes have the biological potential to bridge defects above the critical size [31]. An efficient bone graft should provide an osteoconductive matrix, allowing bone ingrowth; osteoinductive factors and osteogenic cells, both inducing bone growth and repair; and structural support, contributing to the primary stabilization of the reconstructed bone. Bridging a segmental bone defect is part of a global strategy that takes into account the patient's physiological stage and expectations, the etiology of the bone defect and its specific requirements,

Figures 3a to 3h. Anterior bowing of the tibia was noted when the patient, a boy, was one year old (a). A fracture occurred at the site of the former bone biopsy (b). It was treated by ORIF and cancellous bone graft (c), resulting in nonunion (d). A bone transport was performed at the age of three (e), which allowed complete healing of the tibia pseudarthrosis (f). The remaining fibula pseudarthrosis was plated and grafted at the age of 13 (g). At the age of 15, the former congenital tibia pseudarthrosis area was unrecognizable (h).

and the presence of soft tissue damage or vascular compromise. This article presents our ongoing strategies based on our own experiences in reconstructing large post-traumatic segmental defects of the femur and the tibia, as well as a review of the literature. We presented clinical cases with staged reconstruction with cancellous bone, double-barrel free vascularized fibula transfer, and the Ilizarov method of distraction osteogenesis (for other options, see also [3]). Although none of these techniques is new, their respective indications and some refinements have been developed over the last few years (Table 2).

Two-stage reconstruction using a cement spacer and subsequently a cancellous bone graft is an easy technique with low risk. It is, however, unclear as to why this technique gives better results than the one-stage can-

Table 2. Advantages and disadvantages of the different options for reconstruction with autologous bone of large diaphyseal defects of the tibia and the femur.

	Two-stage reconstruction	Free vascularized double-barrel fibula transfer	Distraction osteogenesis
Main indication	Segmental defect of the tibia	Segmental defect of the femur	Segmental defects of the femur and the tibia
Donor site morbidity	+ (free flap)	+ (free fibula)	–
Local complication rate	+/–	+/–	+
Time to healing	6–8 months	6–8 months	6–12 months

cellous bone graft, as reported [21]. Experimental studies may help us to understand the underlying mechanisms of bone healing, as they show that the induced membrane contains growth factors that are important for the bone healing. However, among these, the BMPs can also have adverse effects since they stimulate osteoclasts, and anyway, there is no evidence that these factors are available to the bone graft. Other factors may also contribute to the success of this method. The first stage involves improving the local vascularity through soft tissue reconstruction, which in turn can improve the bone graft neovascularization [32]. Also, the soft tissue reconstruction permits a large cement spacer to be placed under the flap so that the subsequent bone graft can be oversized. Indeed, a partial resorption of the cancellous bone should be less detrimental to the mechanical stability of the bone bridge. Infection recurrence is reduced in infected nonunion because the bone reconstruction is only performed after controlling the bone infection with debridement, soft tissue reconstruction, and both locally released and general antibiotics. This method is a good approach for reconstructing a large segmental defect of the tibia, but may be less efficient when reconstructing the femur [24]. In the case of a large segmental defect of the tibia, stabilization of the fibula is always important, because it contributes to skeletal stability.

Free vascularized fibula transfer is well indicated for the reconstruction of a large segmental defect of the femur, but is less efficient when reconstructing the tibia [33]. The double-barrel technique is useful in patients that have achieved their skeletal maturation, due to the limited hypertrophy of the transplanted bone. Inlay placement of the fibula improves compression of the transplant, yielding higher union rates compared to onlay placement [34]. However, this technique is demanding, and the length of the fibula that can be harvested is limited. Of course, the extent of the fibula available depends on the whole bone size. It is preferable not to harvest the head of the fibula because of the insertion of the lateral ligament complex. Similarly, distal harvesting must preserve the last 5–7 cm of the bone to avoid ankle instability. Refinements of this technique include harvesting of the fibula based on the tibialis anterior vessels [35–37]. This allows the simultaneous transfer of the proximal fibula growth plate, which is not vascularized by the fibular vessels. Transplanting the proximal growth plate allows further growth of the bone transplant and is particularly useful when treating a young child with a growth plate defect following an injury or a surgical resection. However, this technique is very demanding, because the close proximity of the deep peroneal nerve and the tibialis anterior vessels makes the transplant harvest very difficult due to the risk of inducing a peroneal nerve lesion. Another refinement is to harvest the fibula with part of the soleus muscle, with both tissues being vascularized by the peroneal vessels [38]. This composite free flap, as well as others, like the serratus anterior with ribs, the latissimus dorsi with scapula, or the vascularized iliac crests with a flap based on the branches of the lateral circumflex femoral arteries, is also used in the one-stage reconstruction of combined soft tissue and bone defects [39–41].

Ilizarov methods of bone reconstruction combine the three concepts of bone lengthening, distraction osteogenesis and external ring fixation (for a systematic review, see [42]). Although donor site morbidity is absent, union rates and the occurrence of complications depend on the surgeon's experience, necessitating a learning curve [43]. The risk of inducing a bone malalignment during a simple distraction osteogenesis using a complex frame, like the original external ring fixator with transfixing wires, stimulated the development of alternative methods using half pin modification and monolateral external fixation with rail [44, 45]. The occurrence of malalignment during bone transport is further reduced using intramedullary nailing or a bilateral frame [46]. Other refinements concern the fixation of the intermediate bone segment with intramedullary cable wire to reduce the soft tissue injury caused by the pins during the bone transport and the adjunct of the bone graft around the docking site [46, 47]. It is also essential to respect the periosteum at the osteotomy site because of its major osteogenic potential. Reconstruction of the soft tissue with a flap is advised prior to distraction osteogenesis in the case of scarred soft tissue or in the management of open fracture of the tibia with combined soft tissue and bone defects [48, 49]. Distraction osteogenesis is particularly well suited to the tibia if the defect is very proximal or distal and in the case of leg length discrepancies [50].

Taking care of factors that may adversely affect bone and soft tissue healing and the functional outcome is an integral part of the management of patients with large segmental bone defects. Correct patient information, repeated assessment, treatment of psychological distress, physiotherapy to prevent joint stiffness, and cessation of smoking (with appropriate pharmacological substitution) are essential in such challenging situations. Understanding the underlying concepts of the different options available for reconstructing large segmental bone defects allows us to combinine them in new ways; for example into a two-stage reconstruction using a free vascularized fibula for the second stage. The use of a cement spacer to fill out a bone defect in a first-stage surgery is useful in any septic context to reduce infection recurrence. A cement spacer is easier to remove than antibiotic-impregnated beads, and although its reduced surface with respect to beads may reduce the release of antibiotics, there is evidence that the membrane formed at the spacer interface has osteogenic potential. The extension of indications of two-stage reconstruction to the primary care of open fractures with large bone defects should be also considered.

Currently available options allow us to take care of almost any segmental defect of the femur and the tibia in children and adults, but future developments using mesenchymal stem cell therapy, growth factors and pharmacological adjuncts in combination with bone grafts will probably further improve healing rates, decrease morbidity, and reduce time to healing in patients with large defects of the long bones.

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