



REVIEW ARTICLE

Chinese Association of Orthopaedic Surgeons (CAOS) clinical guideline for the treatment of diabetic foot ulcers using tibial cortex transverse transport technique (version 2020)



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ARTICLE INFO

Keywords:

Clinical guideline

Diabetic foot ulcers

Tibial transverse transport technique

Tissue regeneration

SUMMARY

Ilizarov discovered the phenomenon of rich vascular network formation during distraction osteogenesis for limb regeneration and functional reconstruction. The tension-stress rule could activate and enhance the regenerative potentials of living tissues, leading to growth or regeneration of muscles, fascia, blood vessels, and nerves simultaneously. Orthopaedic surgeons in China applied the tibial cortex transverse transport (TTT) technique to reconstruct limb microcirculation, to treat lower extremity microvascular lesions and diabetic foot ulcers since 2001. Clinical studies from China demonstrated that the TTT technique could effectively regenerate the microvascular network in the lower limbs of diabetic patients, promote ulcer healing and reduce the amputation rate. As a novel treatment for severe Diabetic Foot Ulcers (DFU), the TTT technique may be adopted in different countries to benefit DFU patients worldwide. This guideline is initiated by the Chinese Association of Orthopaedic Surgeons (CAOS) TTT Technique for Diabetes Foot Taskforce Group. This guideline provides clear recommendations for indications, contraindications, principles for surgical procedures, preoperative and postoperative management, which maximize the success rate for TTT surgery in treatment of severe DFU.

The translational potential of this article: This guideline provides clear recommendations for indications, contraindications, principles for surgical procedures, preoperative and postoperative management, which maximize the success rate for TTT surgery in severe DFU treatment. This guideline serves as a starting reference for those who are interested or about to carry out TTT surgery. As an alternative novel treatment for severe DFU, we hope that the TTT technique may be adopted in different countries soon to benefit DFU patients worldwide.

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<https://doi.org/10.1016/j.jot.2020.05.003>

Received 8 March 2020; Received in revised form 16 May 2020; Accepted 20 May 2020

Available online 28 June 2020

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Background

Diabetic foot ulcers (DFU) are typically chronic skin ulcers associated with deep tissue destruction around the foot and ankle region with varying degrees of lower extremity vasculopathy and neuropathy [1,2]. DFU is associated with a high rate of morbidity, disability, mortality and psycho-social cost. The global prevalence of diabetes is about 6.3%, ranging from 1.5 to 16.6% in different countries [3,4]. Severe DFU is often complicated by skin infection, osteomyelitis and gangrene. Major limb amputation is a common treatment to manage severe chronic DFU. Currently, 90% of patients suffered from the diabetic foot with Wagner III or above will eventually require an amputation [5,6]. A recent nation-wide study in China showed that 45% of the diabetic foot patients are Wagner III and above, and the amputation rate is between 18 and 28% [7]. The mortality rate of DFU patients was up to 11% [8]. A survey found that the 5-year mortality rate of DFU was 32.7% in Tianjin, China [9]. The treatment cost for DUF was up to \$727 billion USD in the United States and \$110 billion USD in China in 2017 [10].

Although endovascular procedures and vascular bypass surgery are the preferred options for ischemia foot ulcers [1,2], 40% of DFU patients with severe limb ischemia cannot meet the requirements for these options. Therefore, amputation is usually considered to be the best choice for many DFU patients. However, the post-amputation 5-year mortality rate was about 25–50% [5,6]. For patients managed by conventional treatments, the recurrence rate is about 40% within 1 year, 60% and 65% within 3 and 5 years, respectively [11]. Therefore, new treatments are greatly needed to promote the healing of DFU and improve the limb salvage rates.

The TTT technique is based on Ilizarov's "law of tension-stress" for limb regeneration and functional reconstruction. The principle is that when appropriate tension is applied to living tissues, it promotes cell division and differentiation of adult stem cells like that in the fetal tissues development and lead to tissue regeneration. Bone has great regenerative potential and plasticity, under proper tension stress, bone tissues together with the surrounding skeletal muscles, fascia, vessels and nerves can grow simultaneously, this process is termed as distraction osteogenesis (DO) or distraction histogenesis [12,13]. In various experimental and clinical studies of DO, it was well established that there is a formation of rich microvascular networks before osteogenesis. Angiography confirmed the microcirculation regeneration and increase of local blood flow in DO [14]. Despite discovering the phenomenon of vascular network regeneration during DO, Ilizarov did not purposefully apply this technique to treat avascular diseases. In recent years, DO technology has been applied to the field of vascular surgery with some promising results, many animal experiments confirmed that DO promotes capillary and vascular network regeneration [15–17], and the bone transport technique can significantly improve the microcirculation and soft tissue wound healing [18]. Tension-stress principle activates and enhances the regenerative potentials of living tissues. The DO technique thus provides a new alternative for treating avascular diseases.

Qu Long was the first in China to report the use of tibial cortex transverse transport (TTT) technique to treat lower extremity vascular lesions in 2001 [19]. Since then, the TTT technique has been gradually and experimentally applied for the treatment of severe DFU (Wagner III or above) to promote wound healing [18]. A recent 3-year retrospective study involving over 100 cases of severe DFU in China confirmed that the TTT technique significantly reduced the amputation rate, with the wound healing and limb salvage rates both over 95%. The 1-year recurrence rate of DFU after TTT surgery treatment was lower than 10% [18]. During and after TTT treatment, the patients reported immediate pain relief, a feeling of warmth in the diseased limb, and quantitative angiography confirmed the formation of rich neo-vascular networks in the diseased limb or ischemic areas [18]. The followings are the possible biological mechanisms:

- (1) The corticotomy in the tibia shaft immediately reduces the intramedullary pressure, improving the microcirculation of small vessels in the medullary cavity, including arterial blood supply

and venous drainage. Most of the patients reported pain relief and raising of the limb skin temperature within 24 h after TTT surgery.

- (2) During the cortex bone chip movement, the tension-stress mechanical stimuli promote formation of neo-vascular networks, gradually improving the distal circulation (including the arterial, venous and lymphatic circulation networks) and promote the re-formation of collateral circulations in the affected limbs. In a recent study [20], it was found that the long bones of vertebrates and humans have a closed blood circulation system called "trans-cortical vessels" (TCVs). These TCVs are tiny holes with a diameter of only 10 μm , and blood vessels travel in these tiny holes (60% of TCVs are arteries and 40% are veins). Cells that enter the bone marrow through arterial TCVs can immediately leave through venous TCVs, thus ensuring the rapid release of cells in the bone marrow. The study also found that numbers of TCVs can be altered by some drugs and osteoclasts activities in the bone [20]. We speculate that the TTT technique may lead to a rapid increase in TCVs numbers, strengthen the circulation and metabolism within the surrounding tissues, and the TCVs may be possible directions for future research on the mechanisms of TTT technique.
- (3) There are increasing clinical evidences suggesting that TTT technique may mobilize stem cells systemically, especially promoting recruitment and migration of mesenchymal stem cells towards to damaged tissues, mediating the local inflammatory responses, improving the local microenvironment to facilitate tissue repair/regeneration. However, the studies of biological mechanisms for the TTT technique are still lacking, thus future investigations using animal models and clinical studies are warranted.

Despite the lack of mechanistic studies, the TTT technique may be a promising new treatment for severe DFU. In order to promote and study this method, it is necessary to provide a practical guideline for using TTT technique in the management of severe DFU. The Chinese Association of Orthopaedic Surgeons (CAOS), formed a taskforce team called "China TTT Technique for DFU Management Group" in May 2019 to invite experts in orthopedics, endocrinology, DFU care specialists and evidence-based medicine experts to jointly establish a Committee to write up this clinical guideline of treating severe DFU using TTT technique.

Pathology of DFU

Diabetic vascular lesion is one of the most crucial pathogenesis of DFU. It is characterized by extensive lesions, especially the main vessel calcification and stenosis, which lead to the ulcers, disability and mortality [1,2]. Multi-center studies found that patients with lower extremity vascular diseases accounted for 47.5% among all DFU patients in Europe in 2008 [21] and 59% in China in 2012 [22]. Primary-care physicians and diabetic patients usually have a low degree of awareness of diabetic vascular lesions. Microvascular lesions increased blood viscosity and blood flow disorder, which are the pathological basis of DFU outcome. The causes for microvascular lesions may include metabolic disorders, hyperglycemia, hyperlipidemia, high glycoprotein and other pathogenic factors, leading to atherosclerosis, stenosis or obstruction of the vascular lumen, capillary endothelium injuries. The diabetic patients likely suffer more severe lower limb ischemia with the foot neuropathy. DFU is usually attributed to peripheral neuropathic denervation and sensory abnormalities, resulting in infected wound ulceration such as rahagades, empyrosis or abrasions, which are difficult to heal. The pathology of DFU consists of peripheral vascular disease, peripheral neuropathy and local infection. The peripheral vascular disease and neuropathy lead to ulceration and gangrene-inducing infection, that further aggravate tissue damage in a vicious cycle.

Clinical features and classification of DFU

The clinical features of diabetic foot are classified into two major types or both. One is characterized by acute infection, which often

rapidly spread along the tendon sheath, superficial fascia, myofascial space, and toe fascia through small skin defect, usually with infection of gram-positive bacteria combined with anaerobiont. The microbiological profile of diabetic foot infections often demonstrates complex polymicrobial infection. Gram-positive aerobic bacteria were the dominant, comprising 68% of all isolates, the most frequently seen bacteria was *Staphylococcus*, which accounted for about one-third of all isolates, and next in occurrence were species of enterococcus, streptococcus, and corynebacterium [23]. The frequency of anaerobes recovered from diabetic foot ulcer infections is about 25–45%, but their roles in infection were unclear [23]. The patterns of population diversity observed in the DFU samples support the concept of functional equivalent pathogroups (FEP), in that individual members of bacteria may not cause too much harm but when they coaggregate or consort together into a FEP the synergistic effect provides the functional equivalence of well-known pathogens, such as *Staphylococcus aureus*, to maintain chronic biofilm infections [24]. This type ulcer spreads rapidly, and may cause sepsis and life-threatening conditions that lead to amputation. Another type ulcer is characterized by chronic ischemia skin ulceration, hardly healed wound or gangrene, owing to the poor blood supply to the limb, the main features are ischemic and chronic necrosis.

There are many methods for classifying DFU. The most common ones are Wagner Classification, TEXAS Classification, and IWGDF/IDSA Classification [1–3]. Wagner Classification: Wagner level 0: intact skin; Wagner I: superficial ulcer of the skin or subcutaneous tissue; Wagner II: ulcers extend into tendon, bone, or capsule; Wagner III: deep ulcer with osteomyelitis, or abscess; Wagner IV: partial foot gangrene; Wagner V: whole foot gangrene.

Wagner Classification, TEXAS Classification and IWGDF/IDSA Classification focus on ulcer wounds, infection and ischemic conditions, respectively. Combined with the above classification criteria, we think that it is necessary to determine the peripheral vascular lesions, as well as the systemic illness. In order to facilitate the clinical application of TTT, we have used a Comprehensive Classification of Diabetic Foot (Table 1). As a supplement to Wagner Classification and TEXAS Classification, this new classification could use to guide treatment for different DFU conditions.

Conventional standard treatments

Principles of basic medical treatment for diabetes

The principles mainly include blood glucose and pressure control; blood lipids reduction; microcirculation improvement; nerves nutrition and improvement of systemic conditions.

1. Blood glucose control: Generally, based on the high-protein diet and blood glucose monitoring, insulin therapy is used to control blood glucose, which can improve the general condition. Fasting blood

glucose shall be maintained at < 7.8 mmol/L; postprandial blood glucose <10 mmol/L.

2. Blood pressure and lipid control: the target systolic pressure is < 140 mmHg; diastolic pressure <80 mmHg. Young patients without complications could be controlled to <130 mmHg. ACEI (Angiotensin-converting enzyme inhibitor) and ARB (Angiotensin receptor blockers) are the preferred drugs. TC < 4.5 mmol/L; TG < 1.7 mmol/L; LDL <2.6 mmol/L (without coronary disease); LDL <1.8 mmol/L (with coronary disease); HDL > 1.0 mmol/L (male); HDL > 1.3 mmol/L (female); Reducing LDL with statins is the key target.
3. For patients with kidney disease, malnutrition, and hyperproteinemia, nutrition supplement therapy is needed to correct hyperproteinemia, anemia and electrolyte imbalance. Besides, diuretics or ACEI are recommended for the treatment of foot edema.
4. Microcirculation, nerves condition should be improved. Some patients with diabetic lower limb ischemia in the hyper-coagulable state should take Aspirin to prevent thrombosis, and use Kaishi or Ginaton to improve microcirculation. For patients with peripheral neuropathy, alpha-lipoic acid and Mecobalamin are used to improve these symptoms.

Principles of debridement for DFU

Principles of debridement: debride timely and not to expand the wound; ensure adequate drainage. Their main purpose is to remove the infected tissues and to cut off the vicious cycle of sepsis.

1. Debride as soon as possible after hospitalization. The black and yellow necrotic tissues should be removed.
2. If the necrotic toes have to be amputated, the joint cartilages shall retain, because the cartilage surface can protect the subchondral bone, and the necrotic cartilage will be drained naturally.
3. Treatment of infected lumens: Debride and leave the wound open, change dressing daily. Vacuum sealing drainage (VSD) treatment is not suitable for the active bleeding wound. After the necrotic tissues being removed and no secondary infected necrosis, VSD may be applied.
4. The principle of dressing change after debridement: The dressings shall be changed daily; the wounds shall be washed with Furacilin solution (0.2 mg/mL or 0.02%), or 1% iodophor and saline water. To prevent damaging granulation tissues, hydrogen peroxide is not recommended. Antibiotics could be used locally or systemically for a short duration according to the bacterial culture results. After the wound infection is controlled, bFGF or other biological agents may be applied to the fresh granulation tissues to promote skin healing.

Protocols for TTT surgery

Basic requirements

The TTT surgery shall be performed by orthopaedic surgeons in a hospital with an Orthopaedic ward, and preferably with support of vascular surgeons and endocrinologists. The surgeons should understand the principles of TTT technique, the indications and contraindications of this technique, and thoroughly studied this consensus. It is better for the surgeons to participate in the training course of the TTT technique run by individuals or institutions authorized by The China TTT Diabetic Foot Ulcer Group.

Indications and contraindications for TTT surgery

Indications

The TTT technique is a surgical treatment, it is mainly for the management of complicated, chronic and severe diabetic foot wounds. Therefore, patients with severe diabetic foot ulcers are the main

Table 1
Comprehensive classification of diabetic foot ulcer.

Grading	Clinical features	Treatment principles
Type I	Dry gangrene, no infection or lower extremity artery occlusion	Debridement; dressing change; TTT technique
Type II	Combined with an infected ulcer or wet gangrene	Debridement; dressing change; intravenous antibiotics; TTT technique
Type III	Combined with one or more organ damages or failures	TTT technique based on improved heart and kidney function; debridement and dressing change
Type IV	Combined with occlusion of the main artery of the lower extremity (DF+ASO)	TTT technique after received percutaneous lower extremity vessel angioplasty and (or) percutaneous lower extremity vessel intervention until no postoperative occlusion.

indication of TTT surgery. Inclusion criteria are:

- (1) Diabetic foot with Wagner III and above, or with TEXAS Class 3B and above. The diabetic foot which received debridement, dressing change, VSD therapy or standard medical therapy over 2 months with no obvious improvement.
- (2) Diabetic foot classified as Type I (with dry gangrene) in comprehensive classification (as shown in Table 1), or worsen after receiving VSD therapy, dressing change or standard medical treatment for more than 2 months.
- (3) Diabetic foot combined with type II, III, or IV (comprehensive classification) or type II with moderate grade in IWGDF/IDSA classification or sepsis.
- (4) Meeting the conditions above, the patient refuses or cannot undergo vascular bypass surgery.
- (5) Meeting the conditions above, after vascular surgery, the arterial flow is enhanced as shown by ultrasound Doppler, CTA, MRA or DSA. The vascular condition must have the followings: (a) The superficial femoral and iliac artery remains open; (b) At least one of anterior or posterior tibial artery, or iliac artery remains open; (c) ABI (Ankle-brachial index) < 0.40 or ankle artery pressure < 50 mmHg or toe artery pressure < 30 mmHg in the resting state. Other general examinations: haemoglobin, albumin, blood lipids, neutrophils as well as heart, lung, kidney and liver functions are in the normal range. Systemic nutritional status assessment should be in the normal range. The patient is mentally stable, willing to cooperate with the treatment and sign the pre-operative informed consent.

Contraindications

- (1) Patients with mental illness who cannot cooperate with the doctor during treatment.
- (2) Patients diagnosed with other uncontrollable severe diabetic complications by endocrinologists.
- (3) Patients are intolerant of anesthesia owing to cardiovascular complications or renal failure in the past 3 months.

- (4) The superficial femoral or radial artery is obstructed, or no arterial branches (anterior and posterior tibial artery, or peroneal artery) supply beyond the ankle joint.

The protocols of TTT surgery

In the past, the TTT surgery was performed with a large cortical bone window on the tibia (15 cm long x 2 cm wide), with a bulky fixator, which has the risk of postoperative skin necrosis, tibia fracture and inconvenience. The new TTT surgery is now performed with mini-incisions and a small cortical bone window (5 cm long x 1.5 cm wide) on the tibia, with a specially-designed fixator for cortical bone chip transverse transport. The surgical protocols recommended are as following: (please note that different surgeons can improve the surgical procedure according to this principle, please refer to the flow diagram of surgery Fig. 1):

The minimal invasive TTT surgery is performed a specially-designed frame for mini-incision cortical bone chip transverse transport. The recommended surgical protocols are as follows:

- (a) Epidural anesthesia or general anesthesia without using a limb tourniquet.
- (b) The corticotomy site shall be 5 cm below the tibial tuberosity on the medial tibia.
- (c) A metal guide plate with 2 holes at the center (5 cm × 1.5 cm as shown in Fig. 2A) is inserted into the medial aspect of the tibia by two pins, using the special TTT fixator (for example: BFIX™, Transverse Bone Transport System, China Patent 201610722035.5, Aike Shanghai Medical Instrument Co. Ltd, www.bfix.cn/) as a guide to ensure the other two anchor half-pins for the external fixator are in the center line of the tibiae shaft.
- (d) Several 1 cm (1 cm apart) skin incisions are made perpendicular to the guide plate at all sides as shown in Fig. 2 A and B.
- (e) The corticotomy is created using a custom-made 3-hole drill guide (each hole has a diameter of 3.0 mm), through multiple drill holes along the guide plate as shown in Fig. 2 B. Use low speed drill (the lowest speed possible) and saline irrigation to cool down and minimize the thermal-injury.

- ① Surgery is performed under the epidural anaesthesia or general anaesthesia without using a tourniquet.
- ② A 3~5 cm curved incision is made in the medial side of 5 cm distal to the tibial tuberosity.
- ③ The tissue is isolated until the superficial periosteum.
- ④ A 50 mm × 15 mm bone flap is made.
- ⑤ Two 2.5 mm holes are made in the flap and two distracting pins are applied.
- ⑥ Parallel the distracting pins, two 4.5 mm fixating pins are applied into the proximal and distal end, respectively.
- ⑦ The cortex is sliced off by osteotomy.
- ⑧ the tibial transverse transport fixator is installed.

Five days after surgery, transversely distract outward the bone flap 1mm/d, divided into 4 times to complete. After that, the condition is maintained for 3 days and then push the flap back 1mm/d, divided into 2 times to complete (accordion technique).

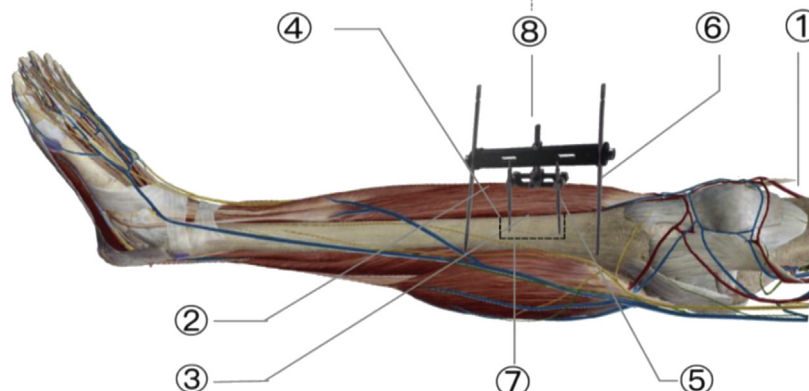


Fig. 1. Illustrations of TTT surgery key steps.



Fig. 2. A. The guide plate is secured in place by the two half-pins penetrated through one side of the tibial cortex. Several 1-cm cuts are then made perpendicular to the guide plate at all sides. B. Illustration to show how the drill jig is used to drill multiple holes around the guide plate. The drilling jig has 3 connecting holes, each hole has a diameter of 3 mm. C. Radiograph before the transverse transport starts, showing the position of the two anchor pins (through two cortices) and the two pins at the corticotomy site (through one cortex). D. Lateral view to show the external fixator position when the surgery is completed, arrows show that all the 1-cm skin cuts have been closed with one single suture each. E. The dressing after the TTT surgery. The entire wound area shall be covered with two large self-adhesive thick gauzes, all pain holes should be covered as shown. These above figures and some figure legends were selected, modified and quoted from the original figures and legends published in Journal of Orthopaedic Translation 25 (2020): 28–32 [25], with authors' consents and permission.

- (f) Check the central pins position via fluoroscopy (Fig. 2 C). Then insert the two anchor pins (3.5 mm in diameter) to keep the fixator in place and tighten all the pins and position the fixator well for patient's comfort (Fig. 2 D).
- (g) The multiple drill holes are joined together using a small, thin and sharp osteotome, taking care not to fracture to cortical bone chip to turn the fixator upwards, ensure the bone chip is moving up (Fig. 2 C and D).
- (h) Finally, the subcutaneous tissues and skins are sutured and bandaged as shown in Fig. 2 E. There will be bleeding from the tibial corticotomy site, and the dressings/bandages should be changed 4 h after the surgery, and then daily.
- (i) For the patients with a stable condition, they can be performed TTT surgery first and then debridement of the wounds with open drainage. For severe DFU patients, a through debridement shall be done earlier to avoid toxemia, and the TTT surgery may be performed 2–3 weeks later.

Postoperative management

- (1) Prophylactic antibiotics may be used for 1–3 days on and after the surgery. If the wound is drained well, antibiotics may not be necessary.
- (2) Five days after surgery, transversely move the bone chip outward at a speed of 0.5 mm/12 h, for 10 days. X-ray shall be taken 5 days after to check the bone chip position. After 10 days, stop moving the bar for 3 days and then compress the bone chip back at the same speed for 10 days, and confirm with x-ray to make sure the bone chip is back to the correct position.
- (3) 2 weeks after the bone chip is back to the original position, the fixator can be removed. The operated limb shall be protected by small splints or braces for another 6–8 weeks. The patient can weight bear the limb but has to prevent fall during this period.
- (4) During the whole period, the pin holes should be cleaned with 75% alcohol daily.
- (5) Debridement and change of dressing: secondary necrosis may occur after the first debridement, which may involve skin, fascia, muscle, tendon and bone tissues, therefore, repeated debridement may be needed by surgical, ultrasonic or chemical means. After

surgery, the dressings shall be changed daily; the wounds shall be washed with Furacilin solution (0.2 mg/mL or 0.02%), or 1% iodophor and saline water. To prevent damaging the granulation tissues, hydrogen peroxide shall not be used.

- (6) Management of edema (if any): the affected limb should be raised up slightly to prevent limb edema. If edema preexisted or occurs after TTT surgery, Aescufen forte, Spironolactone or Hydrochlorothiazide and Furosemide may be used (consulting to specialist physicians if needed).
- (7) Postoperative exercise (including active and passive exercise) is recommended. Please consult physiotherapists for the appropriate exercise for each case. For the cured patients, they should be educated for foot care to prevent ulcer recurrence.

Efficacy assessments

- (1) Walking distance: to measure the walking distance (meter) in unit time (e.g. 3 min). This measurement is objective and easy, which may be done once a week.
- (2) Size of the ulcer (wound): the ulcer size should be measured and recorded. It is recommended to take a pre- and postoperative photo of the wound in a standard position with a ruler placed near the wound for reference. It should be recorded every week for at least 6 weeks, to monitor the dynamic change of wound healing.
- (3) Percutaneous oxygen pressure at the toes: this directly indicates the oxygen perfusion level in tissues. The patient should rest in room temperature for at least 30 min before the oxygen pressure measurement, which may be done once a week.
- (4) Ankle-brachial index (ABI) and toe-brachial index (TBI) in resting-state: It is a simple, convenient and effective evaluation index, but it will not be improved significantly in the short time. ABI should be monitored every 2 weeks before and during treatment for 6 weeks. ABI range: 1–1.3 (normal); 0.5–0.9 (mild ischemia); <0.4 (severe ischemia).
- (5) Laser Doppler for blood flow: As one of the gold standards for evaluating the blood supply to the lower limbs, it is a sensitive and non-invasive examination. This can be measured once a week.
- (6) Digital subtraction angiography (DSA): This is an invasive procedure, it can accurately access the angiogenesis based on a

grading system: Grade 0: no angiogenesis; Grade I: slight angiogenesis without vascular network formed; Grade II: medium angiogenesis connected into vascular networks; Grade III: abundant angiogenesis connected into networks, forming rich bypass vascular cycles. DSA may be measured before the surgery, 2 weeks after surgery and before the fixator removal, respectively.

- (7) Follow-up observation: It is recommended to make a follow-up visit at the first, third, sixth and twelfth months after TTT surgery, respectively, to check the progress of wound healing and recurrence rate.

Conclusions

This guideline is initiated by the Chinese Association of Orthopaedic Surgeons (CAOS) TTT Technique for Diabetes Foot Taskforce Group. Clinicians in China first proposed the concept of using TTT technique to treat severe diabetic foot ulcers (Wagner III and above) and have successfully conducted more than 1000 cases. Performed along with routine debridement and dressing change, TTT technique can significantly enhance diabetic ulcer healing, increase the limb salvage rate and reduce the DFU recurrence rate. However, the TTT technique was not 100% effective for severe DFU treatment and there were reports/feedbacks of complications such as skin necrosis, fracture and non-responses. Many of these complications are attributed to lack of clear clinical guidance and training for the correct surgical protocols and postoperative management. The TTT surgery should be performed with a minimally invasive fashion through small skin incisions, corticotomy by customized guide plate, drill jig and purposely-designed fixator, to ensure standard surgical procedure and postoperative management. This guideline provides clear recommendations for indications, contraindications, principles for surgical procedures, preoperative and postoperative management, which maximize the success rate for TTT surgery in severe DFU treatment. With this guideline, clinical trials involving multiple centers should be conducted to verify the efficacy and the underlying biological mechanisms. As an alternative novel treatment for severe DFU, we hope that the TTT technique may be adopted in different countries soon to benefit DFU patients worldwide. This guideline serves as a starting reference for those who are interested or about to carry out TTT surgery. In the meanwhile, we also hope to receive feedback and criticism from the peers to further improve this guideline.

Conflict of Interest

The authors have no conflicts of interest to disclose in relation to this article. This clinical guideline was published in Chinese first in *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* (Chinese Journal of Reparative and Reconstructive Surgery) in August 2020 [25], this English edition was published with slight modifications from the published Chinese version, with full permission granted from the (Chinese) Journal of Reparative and Reconstructive Surgery (*Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*).

Acknowledgement

This project was funded by the Scientific Research Project (19PJ056) of the Sichuan Provincial Health Committee, PR China. The Department of Orthopaedics and Joint Surgery, The First Affiliated Hospital of Guangxi Medical University, PR China; The Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, SRA PR China

are acknowledged for providing staff, resource and financial support for this project.

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