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Original Article

Efficacy and safety of unilateral tibial cortex transverse transport on bilateral diabetic foot ulcers: A propensity score matching study

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ABSTRACT

Background: Tibial Cortex Transverse Transport (TTT) has been demonstrated to be an effective treatment for unilateral diabetic foot ulcers (UDFUs). However, this retrospective study was designed to compare the efficacy and safety of unilateral TTT on bilateral diabetic foot ulcers (BDFUs).

Methods: This retrospective study included a review of patients with TTT treated from January 2017 to August 2019, Propensity Score Matching (PSM) was performed to compare patients with BDFUs to those with UDFUs. Ulcer healing, recurrence, and major amputation rates were evaluated at 1-year follow-up. Changes in foot vessels were assessed in the BDFUs group using computed tomography angiography (CTA).

Results: A total of 140 patients with DFUs (106 UDFUs and 34 BDFUs) were included in the study. UDFUs and BDFUs were matched in a 1:1 ratio (34 in each group) using PSM. No significant difference was observed at 1-year-follow-up [91.2% (31/34) vs. 76.5% (26/34), OR 0.315 (95% CI 0.08 to 1.31), $P = 0.10$] and 6-month-follow-up [70.6% (24/34) vs. 50.0% (17/34), OR 0.85 (95% CI 0.15 to 1.13), $P = 0.08$] in two groups. Significant differences in rates of major amputation and recurrence between the groups ($P > 0.05$) were not observed. The BDFUs group appeared more angiogenesis of the foot by CTA after 8 weeks of operation.

Conclusion: Results of this study suggest that severe BDFUs can be effectively treated by unilateral TTT. TTT is easy to operate and effective, which may be a good alternative for treating severe BDFUs.

The translational potential of this article: In previous retrospective clinical studies, TTT has demonstrated promising clinical outcomes in the management of diabetic foot ulcers. In this current study, we aim to investigate the potential use of TTT in treating distant tissue defects by evaluating the limited availability and safety of TTT for the management of bilateral diabetic foot. While additional basic and clinical research is necessary to fully elucidate the underlying mechanisms, our study offers insight into the potential therapeutic use of TTT for this condition.

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1. Introduction

Diabetic foot ulcers (DFUs) are a severe and persistent complication of Diabetes Mellitus, with a global prevalence estimated at 6.3% [1]. The severe consequences of DFUs include non-healing ulcers, osteomyelitis, amputation, and even death, which cause severe threats to human health and a tremendous healthcare burden [2,3]. Approximately 77% of DFUs heal within one year with appropriate surgical treatment, including debridement, negative pressure wound therapy, and even lower extremity revascularization [4–6]. However, the recurrence rate of ulcers within one year is as high as 40% and even 8.5% of patients with diabetic foot had bilateral diabetic foot ulcers (BDFUs) [7,8].

In previous studies, the authors developed a new technique named Tibial Cortex Transverse Transport (TTT) and applied it to the treatment of severe and recalcitrant DFUs. The results showed a higher wound healing rate, greater extremity salvage, and a lower recurrence rate in the TTT treatment group compared to other treatments. Postoperative radiographic studies also revealed a significant increase in neovascularization and perfusion in the treated extremities [9,10].

In a retrospective study, about 8.5% of patients with DFUs were found to have BDFUs [8]. BDFUs not only increase the cost of treatment, but also make it more difficult to treat. In some studies, minor BDFUs were healed using glucose modulation, oral or injectable antibiotics, and topical wound medications [11,12]. However, for severe DFUs, antibiotic therapy and glycemic control therapy alone have limited effect, and approximately 20% of patients with moderate or severe diabetic foot infections still suffer amputations [13]. Another case study reported using *Hypericum perforatum* and *Azadirachta indica* to treat BDFUs [14]. Although it has sound therapeutic effects, studies with larger clinical samples are lacking, and its efficacy and safety remain to be verified. Previous studies on treating BDFUs did not have a holistic treatment plan but treated them separately as unilateral ulcers. It would be a groundbreaking research development if a treatment could be found to treat BDFUs in a single session.

Observing several patients with BDFUs who underwent unilateral TTT and achieved successful healing, the authors conducted a retrospective comparative study to evaluate the efficacy of TTT on BDFUs.

2. Patients and methods

2.1. Patient selection

The study reviewed 167 patients from January 2017 to December 2019 (ulcers penetrating the tendon, capsule, bone or joint with infection and/or ischemia) [15]. All patients with DFUs were treated with TTT (patients with BDFUs were treated with unilateral TTT), performed by the same surgeon. The Institutional Review Board approved the study of the First Affiliated Hospital of Guangxi Medical University.

2.2. Patient inclusion and exclusion criteria

Inclusion criteria included patients >18 years of age; with a diagnosis of diabetes mellitus and non-healing or recurrent ulcers in the lower extremities for at least two months; ulcers were classified as Texas University grades 2B to 3D; received a 1-year follow-up; previous non-surgical treatments included wound care, diabetes management and negative pressure wound therapy; previous surgical procedures included debridement, revascularization, and local or free flap transplantation. Exclusion criteria included patients with acute myocardial infarction and cerebrovascular accident, severe liver and kidney dysfunction, and severe lung infection or heart failure in the past three months; Treatment with cortical steroids, anti-inflammatory drugs, or chemotherapy; active Charcot's arthropathy of the foot; severe peripheral vascular disease (popliteal arteries with occlusion >80%); and those who died of other diseases before the end of the follow-up.

2.3. Clinical and imaging evaluation

Ulcer (location, duration, complications, etc) were recorded in our database. The severity of the ulcers was assessed using the University of Texas Wound Classification System [15]. In case of suspicion of wound infection, wound secretions were obtained for culture to determine the causative organism and its antibiotic susceptibility. Bone probe tests were performed on infected open ulcers, and plain radiographs of the foot were taken to detect diabetic foot osteomyelitis [16]. Based on the drug sensitivity analysis results, the antibiotic to which the patient was sensitive, was selected for oral or intravenous administration. Lower

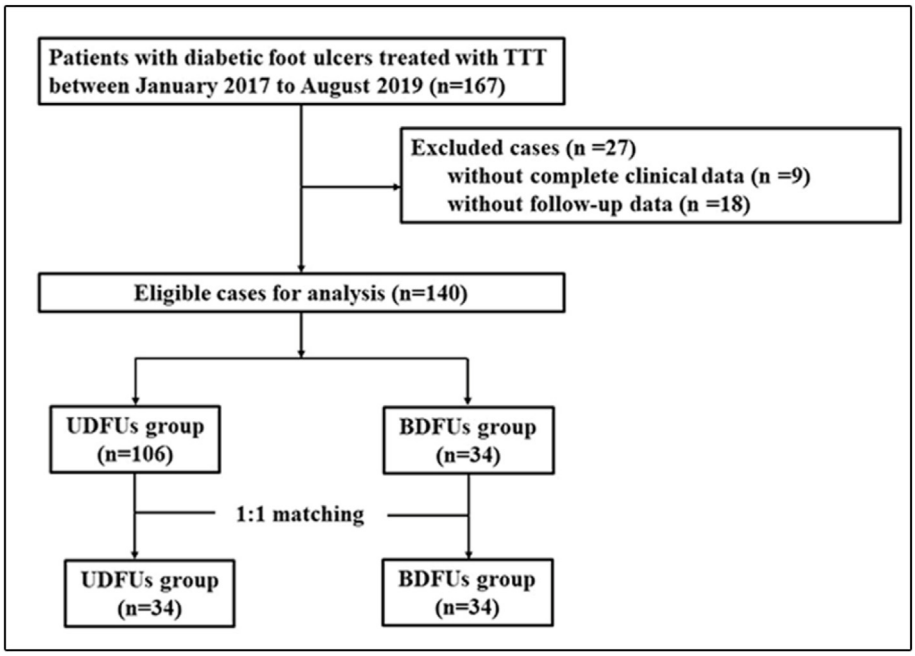

Fig. 1. Flowchart of the process of patient selection. (UDFUs = unilateral diabetic foot ulcers, BDFUs = bilateral diabetic foot ulcers).

extremity peripheral artery disease is defined as the absence of palpable dorsalis pedis and posterior tibial artery and/or ankle index <0.9 [17]. Computed tomography angiography (CTA) was used to assess the vascular status of the lower extremities. In case patients had severe arterial stenosis (>50% of diameter reduction) [18] and occlusion caused by atherosclerosis, they were referred to a vascular surgeon for further evaluation and, if necessary, revascularization was performed.

2.4. Surgical techniques

As previously reported, TTT surgery was performed according to the standard protocol and by the same surgeon [9,19,20]. After nerve-blocking anesthesia, two straight skin incisions of 1 cm in length were made at 4 cm below the tibial tubercle. Longitudinal skin incision was made along the long axis of tibia, and blunt dissection was used for subcutaneous soft tissue structures. After drilling multiple holes along the rectangle on the tibial cortex, corticotomy was performed at a length of 5 cm, and a width of 1.5 cm. After osteotomy, two 4 mm diameter nails were inserted into the osteotomized cortex for distraction, and another two 5 mm diameter external fixation nails were parallelly inserted into both the distal and proximal ends of the surgical area. Subsequently, an external fixation frame was installed to form a stable construct for tibial cortex transport (Fig. 2). After the external fixator assembly, aggressive debridement was performed according to the international guidelines [21–23]. Negative-pressure wound therapy was applied according to wound depths and sizes. The wound was left open without skin grafts or flaps in both groups.

2.5. Post operarative protocols

Dressing change daily in the early stage of wound healing, and every other day in the later stage when the wound exudes less. Regulation of blood glucose, correction of hypoproteinemia and electrolyte disturbances, maintenance of renal function and application of drugs to improve microcirculation are applied throughout the treatment process. X-rays were taken on postoperative day 1 to determine the position of the osteotomy block and screws. After a 4-day latency period, TTT was initiated and adjusted by 1 mm per day, completed in three sessions. The patients were subsequently discharged and instructed to complete the tibial cortex transport at home, i.e., 14 days of medial transport followed

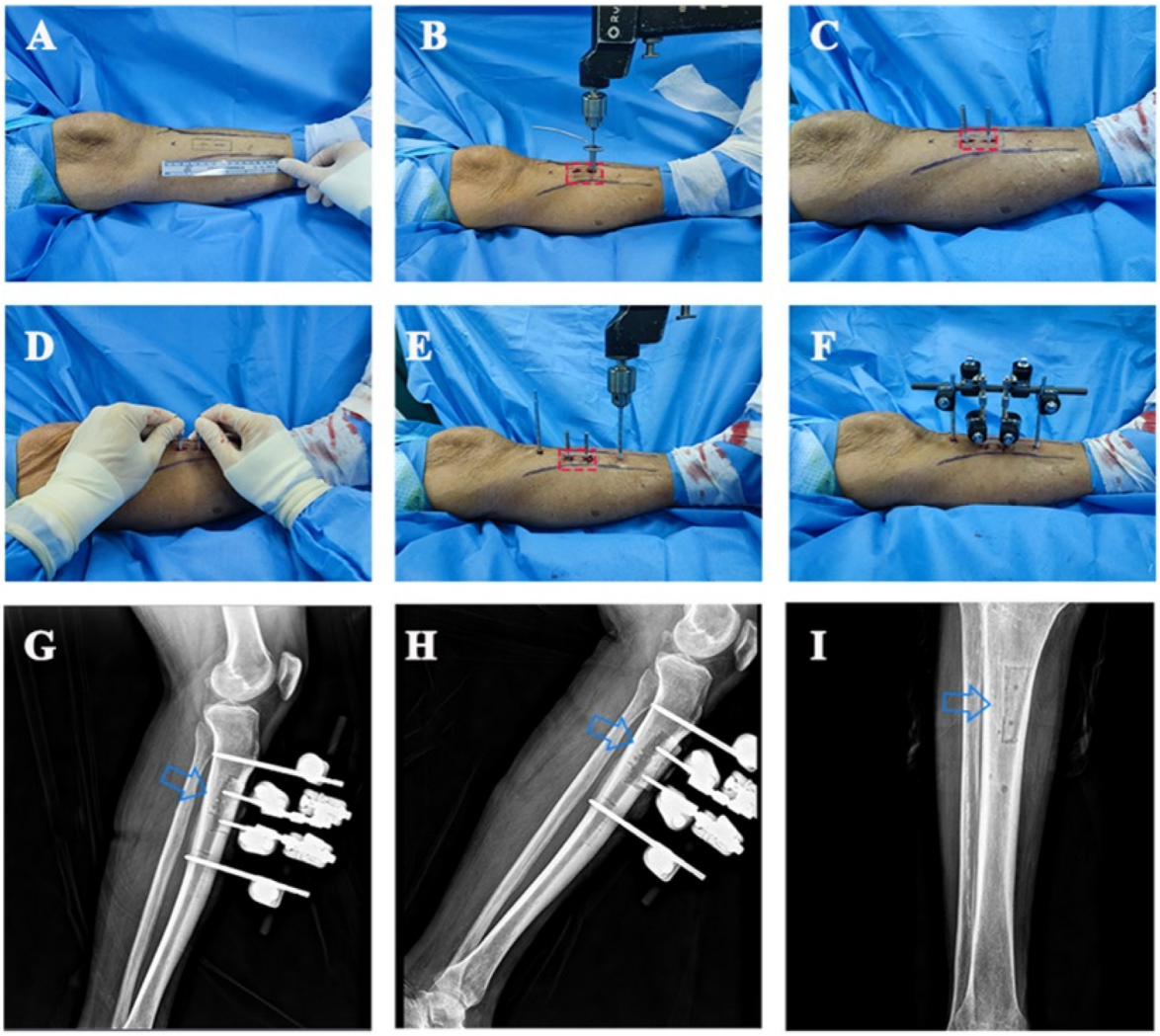

Fig. 2. Fig. 2 demonstrates the procedures involved in TTT surgery. A: The positions of corticotomy and nailing are shown with marks. B–C: Corticotomy (1.5 cm × 5 cm) is performed, and two 4 mm diameter nails are inserted in the osteotomized cortex for distraction. D–F: The cortex is completely separated, and two 5 mm diameter nails are inserted on both sides of the cortex. The components are assembled into a completed bone distraction device. G: The position of the corticotomy and external fixation frame is confirmed on lateral X-Ray 1 day after surgery. H: After two weeks of medial distraction, the cortex fragment distracts in the opposite direction. I: This is followed by a 2-week lateral transfer to restore the cortex to its original position, after which the external fixation frame is removed. (The red dashed box shows the location of the osteotomy). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

by 14 days of lateral transport. Radiographs were used to confirm cortex transport at 2 and 4 weeks after the initiation of tibial cortex transport (Fig. 2). In the outpatient department, the external fixator was removed after four weeks of tibial cortex transport, and a second CTA was performed. After removing the external frame for four weeks, x-rays were performed to confirm that the cortex had returned to its original position.

2.6. Follow up

A 12-week postoperative evaluation and dressing change was conducted for all patients in the outpatient department. In case of unhealed ulcers, the patients were instructed to change the dressing at home. Patients avoid weight bearing on the affected limb until the ulcer has completely healed and are allowed to walk with crutches. Follow-up was then performed at monthly intervals until 1-year follow-up was completed.

2.7. ELISA

Patient's peripheral blood samples were collected at the first admission (pre-Op) and the end of TTT (post-Op), respectively, and serum was isolated for testing. Angiogenesis-related cytokines vascular endothelial growth factor (VEGF) and stromal cell-derived factor-1 (SDF-1) obtained from patients' serum were quantified using enzyme-linked immunosorbent assay kits (ELISA, R&D Systems). Three copies of each patient's serum were tested at each point of time.

2.8. Outcomes

The primary outcomes included the proportion of ulcers that healed at six months and one year, the rate of extremity salvage, and the proportion of patients in whom ulcers recurred. Ulcer healing was defined as complete epithelialization maintained for two weeks without drainage [24]. Recurrent ulcers were defined as the appearance of new ulcers in patients with a history of foot ulcers since the previous foot ulcers, regardless of their location and timing. A secondary outcome was CT angiographic changes in the small lower extremity arteries in the BDFUs group. The pro-angiogenic-related factors SDF-1 and VEGF were measured quantitatively using ELISA.

2.9. Statistical methods

To minimize the effect of confounding factors and potential bias between UDFUs and BDFUs groups, propensity scores were calculated using logistic regression with 1:1 patient matching, using the nearest neighbor matching method without replacement. A caliper radius with a standard deviation of 0.2 was set to prevent poor matching. The variables of the matching model included age, sex, hemoglobin A1c (HbA1c), duration of diabetes, duration of ulcer and comorbidities. The balance of baseline covariates between groups was evaluated by the standardized mean differences (SMD).

Data were compared between groups using a *t*-test for normally distributed variables, Mann–Whitney U-test for nonparametric variables, and the chi-square test or Fisher's exact test (if the expected count was <5 for any unexpected cells) for categorical data as appropriate. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as numbers and percentages. In case the data did not obey a normal distribution, the median (P50) was used. The statistical analyses of propensity score matching (PSM) were performed with the statistical software package R (http://www.R-project.org, The R Foundation). All statistical analyses were performed with SPSS 25.0 software (SPSS Inc, Chicago, Illinois, USA); significance was set at $P < 0.05$.

3. Result

3.1. Patient selection and matching

A total of 167 patients met the inclusion criteria in this study. After excluding cases due to missing data (n = 27), 140 patients were included for analysis (Fig. 1). The entire cohort consisted of 56 women and 84 men with a median age of 62 (range 46–82) years. All patients with DFUs underwent TTT (patients in the BDFUs group were treated with unilateral TTT) and debridement. After PSM was performed, 34 patients from each group comprised the matched cohort (Table 1). A significant difference in age, sex, HbA1c, duration of diabetes mellitus and ulcers, ulcer area, and complications was not observed ($P > 0.05$). The quality of PSM was assessed as balanced in two groups (all SMD<0.2) (Table 1).

Table 1
Patient demographic and clinical data.

	UDFUs(n = 34)	BDFUs(n = 34)		SMD	P-value
		TTT side	Contralateral side		
Age (years)	64.5 ± 10.5	64.6 ± 9.8		0.009	0.97
Male sex, % (n)	26 (76.5)	30(88.2)		0.01	0.2
Coronary heart disease, n (%)	4(11.8)	5(14.7)			1.0
Chronic kidney failure, n (%)	10(29.4)	5(14.7)			0.14
Peripheral arterial disease, n (%)	23(67.6)	22(64.7)		0.07	0.8
HbA1c (%)	9.0 ± 2.0	9.0 ± 2.3		0.004	0.99
Duration of diabetes mellitus (years)	9.5	4.5		0.05	0.52
Duration of ulcers (months)	3.6	3		0.036	0.12
Ulcer area (cm^2)	18.5	24	13		0.19
University of Texas wound classification system, n (%)					0.63
2B	6(17.6)	10(29.4)	10(29.4)		
2C	2(5.9)	1(2.9)	2(5.9)		
2D	7(20.6)	2(5.9)	5(14.7)		
3B	6(17.6)	4(11.8)	7(20.6)		
3C	1(2.9)	3(8.8)	2(5.9)		
3D	12(35.3)	14(41.2)	8(23.5)		
Prior treatment, n (%)					
Debridements	7(20.6)	6(17.6)	2(5.9)		0.19
Negative-pressure wound therapy	1(2.9)	1(2.9)	0(0.0)		1.0
Current treatment, n (%)					
Debridements	34(1.0)	34(1.0)	34(1.0)		—
Negative-pressure wound therapy	6(17.6)	2(5.9)	1(2.9)		0.14

Data are presented as n (%) or the mean ± SD; UDFUs = unilateral diabetic foot ulcers; BDFUs = bilateral diabetic foot ulcers; SDM = standardized mean differences

3.2. Healing

The wound healing rates of UDFUs groups showed no significant difference at 1-year-follow-up than BDFUs groups [91.2% (31/34) vs. 76.5% (26/34), OR 0.315 (95% CI 0.08 to 1.31), P = 0.10]. By six months, the significant difference in the two groups was still not observed [70.6% (24/34) vs. 50.0% (17/34), OR 0.85 (95% CI 0.15 to 1.13), P = 0.08] (Table 2, Fig. 3, Fig. 4, Fig. 5). A significant difference in amputation (P = 0.24) and ulcer recurrence (P = 0.49) between the two groups was not found at 1-year follow-up (Table 2).

3.3. Imaging and laboratory tests

In the BDFUs group, patients were found to have increased vascularization in the bilateral ulcer area and foot using CTA, at eight weeks postoperatively (Fig. 7). The serum VEGF and SDF-1 levels were significantly increased one month after TTT. Baseline preoperative serum VEGF levels (233.88 ± 23.25 pg/ml) increased to (432.42 ± 79.97 pg/ml) postoperatively (P < 0.05). Similarly, mean serum levels of SDF-1 increased from (69.54 ± 15.81 pg/ml) preoperatively to (160.69 ± 20.05 pg/ml) postoperatively (P < 0.05) (Fig. 6).

4. Discussion

BDFUs pose significant treatment challenges, with a reported 8.5% of DFUs patients presenting with bilateral wounds [8]. Several case studies have explored treatments for BDFUs, including oral/intravenous antibiotics, hypoglycemic agents, local stem cell injections, and herbal remedies. However, the efficacy and safety of these treatments are not well established. Furthermore, these patients had a lower wound severity (Wagner grade I or II, with a diameter of ≤1 cm). More than half of diabetic ulcers become infected, and about 20% of moderate or severe diabetic foot infections result in some degree of amputation [7] and there is a need for more comprehensive approaches to treating BDFUs.

In this study, we divided patients that received TTT into UDFUs or BDFUs groups at a 1:1 ratio with PSM. We found great healing, low major amputation, and recurrence rates in both groups. Simultaneously, CTA also demonstrated increased vascularization in the bilateral foot. Finally, we saw increases in two blood markers, SDF-1 and VEGF, that are involved in promoting healing. These results suggest that TTT can be used to treat both UDFUs and BDFUs.

We found that patients in the UDFUs group had a 1-year healing rate of 91.3%, with no major amputations or recurrences [9]. This result is

Table 2
Outcomes of TTT for unilateral and bilateral diabetic foot ulcers.

Outcome parameters	UDFUs(n = 34)	BDFUs(n = 34)	Odds ratio (95% CI)	P-value
Ulcers healed by 1 year, n (%)	31(91.2)	26(76.5)	0.315 (0.08–1.31)	0.10
Ulcers healed by 6 months, n (%)	24(70.6)	17(50.0)	0.85 (0.15–1.13)	0.08
Major amputation, n (%)	0	3 (8.8)	1.10 (0.99–1.22)	0.24
Ulcer recurrences, n (%)	0	2 (5.9)	1.06 (0.98–1.16)	0.49

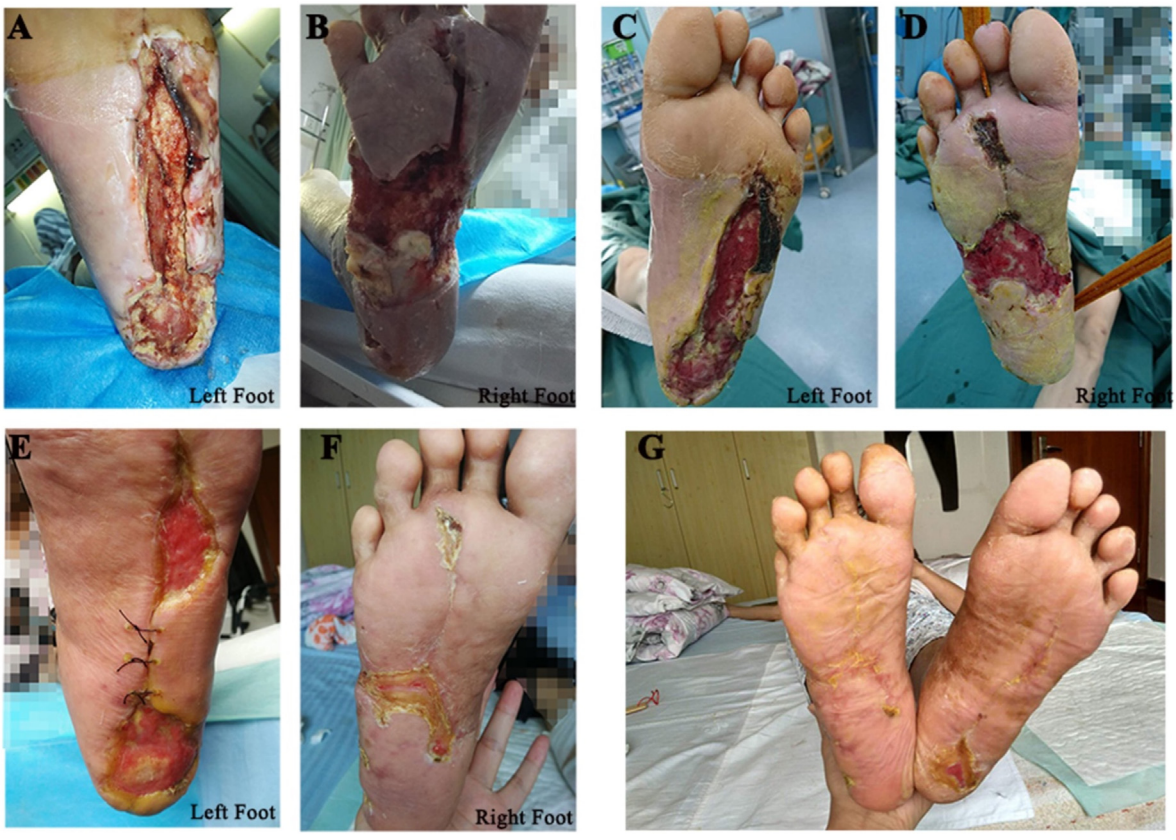

Fig. 3. Fig. 3 demonstrates the effect of TTT on a 60-year-old woman with severe and refractory plantar DFUs on both feet. A–B: The foot ulcer was inflamed with tissue necrosis before TTT surgery. C–D: One month after surgery, granulation tissue completely covered the wound, indicating the initial healing process. E–F: Two months after surgery, the wound was further reduced and had healed well, suggesting the progression of the healing process. G: Four months after surgery, the ulcers were completely healed, indicating the effectiveness of TTT in promoting ulcer healing.

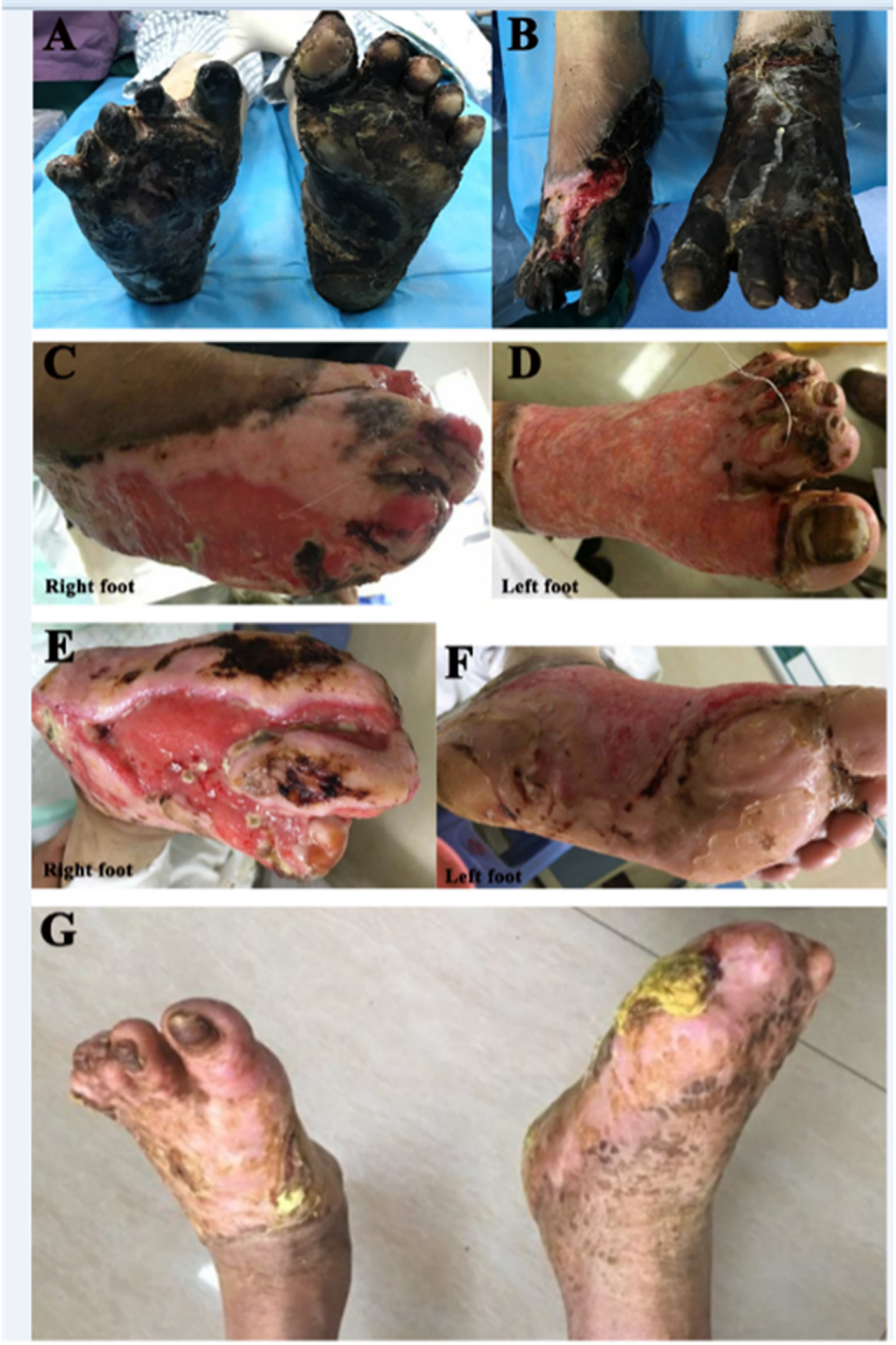

Fig. 4. Fig. 4 demonstrates the effect of TTT on a 57-year-old man with a diabetic ulcer located on the entire foot bilaterally. A–B: Preoperatively, skin and toe necrosis were visible on both sides of the foot. C–F: At 3 weeks postoperatively, the necrotic tissue was removed, and fresh granulation tissue was visible, indicating the initial healing process. G: Four weeks after surgery, the ulcers were completely healed, demonstrating the effectiveness of TTT in promoting ulcer healing.

consistent with previous studies. On the other hand, the healing rate for the BDFUs group was 50% at 6 months and 76.5% at one year, with three major amputations and two recurrences. These data indicate that healing was somewhat worse in the BDFUs group than in the UDFUs group; although, these differences were not statistically significant ($P < 0.05$). Possible reasons for this are more severe combinations of vascular disease and infection in patients with BDFUs. Diabetic peripheral neuropathy and peripheral arterial disease are the main risk factors for the formation of DFUs. Patients with BDFUs imply that damage to peripheral nerves in the foot and ischemia in the lower extremities is more severe [7]. These reasons may have contributed to the differences in healing time, major amputation rate, and ulcer recurrence rate between the two groups. However, despite these challenges, our results show that the TTT technique was still effective in treating DFUs, even in patients with multiple co-morbidities such as coronary heart disease, chronic renal failure (Fig. 5), and peripheral arterial disease.

The mechanism behind TTT, a transverse bone distraction technique that promotes revascularization of the foot in patients with DFUs, is similar to distraction osteogenesis (DO) in its ability to induce angiogenesis and neovascularization in surrounding tissues [25–29]. Our previous studies have shown that TTT increases foot revascularization three months after the procedure and results in a large amount of new granulation tissue [9,10,19]. In this study, TTT is performed on one side of the calf, promoting neovascularization on both sides of the foot and

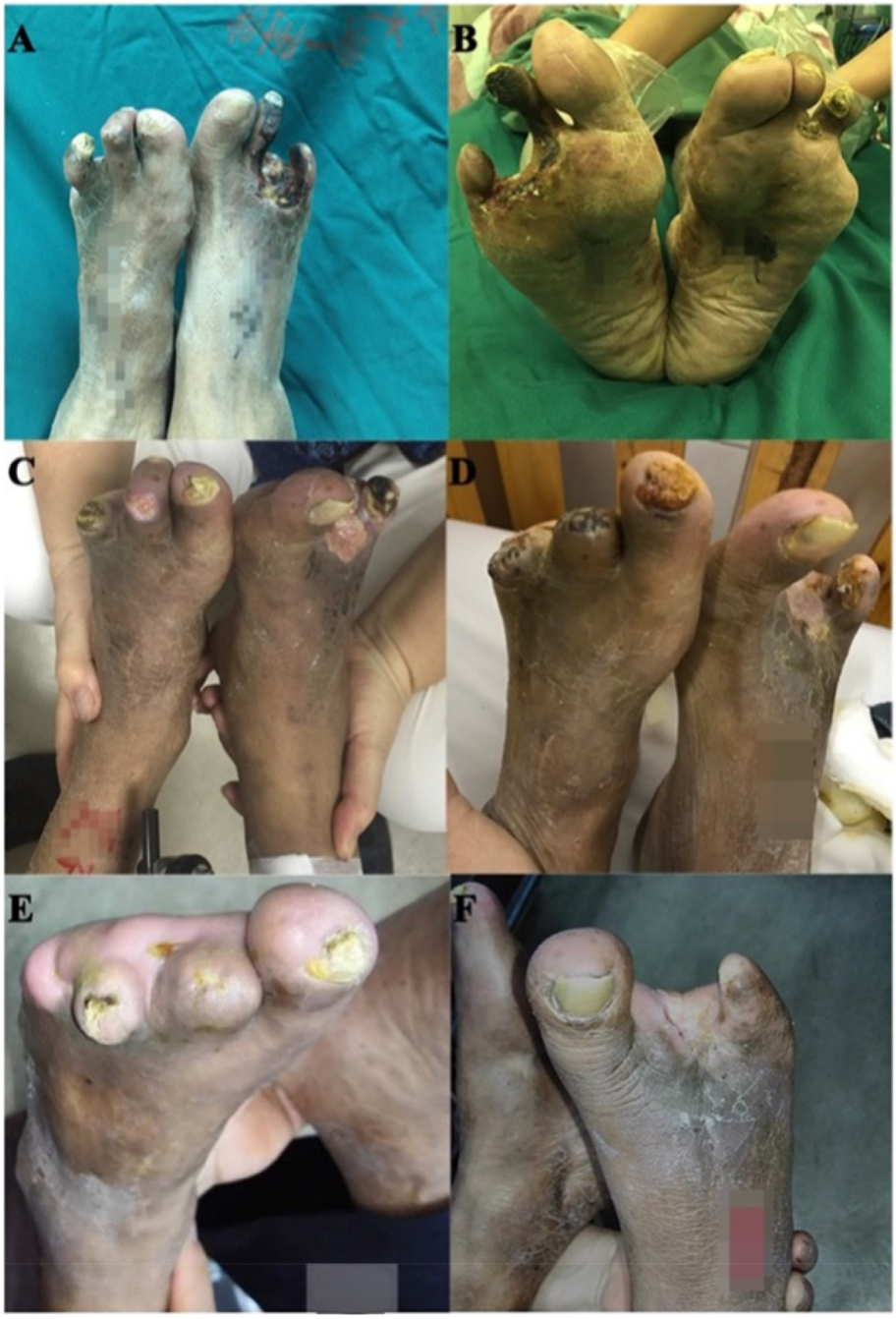

Fig. 5. Fig. 5 illustrates the effect of TTT on a 62-year-old man with diabetes for 8 years and uremia, who had diabetic foot ulcers located on both toes. A–B: Both foot ulcers are Texas grade 3D, both feet have undergone toe amputation and gangrene of the toes and skin is visible. C–D: One and two months after surgery, respectively, granulation tissue is visible, and the wound is gradually healing. E–F: Four months after surgery, the ulcers were completely healed, indicating the efficacy of TTT in promoting ulcer healing. These images provide a visual representation of the clinical improvements that can be achieved with TTT treatment in severe diabetic foot ulcers.

healing bilateral ulcers(Fig. 7). The increased blood flow due to bone distraction is thought to be a crucial factor. The exact molecular mechanism behind TTT has not been fully investigated, but previous studies have shown that TTT increases the expression of pro-angiogenic factors VEGF and SDF-1 [30]. VEGF plays a direct role in regulating endothelial cells and promoting angiogenesis, while SDF-1 binds to endothelial progenitor cells (EPCs) and bone marrow mesenchymal stem cells (BMSCs) in the bone marrow, causing them to differentiate into endothelial cells and promoting pro-angiogenic effects [31–33]. Elevated SDF-1 expression during TTT stimulates increased VEGF levels, leading to angiogenesis. Our study found elevated levels of VEGF and SDF-1 in the blood one month after TTT, consistent with previous findings. The systemic increase in pro-angiogenic factors and mobilization of endothelial progenitor cells may also explain why TTT is effective in promoting the healing of BDFUs (Fig. 8). Further research is needed to fully understand the underlying mechanisms of TTT.

Local inflammation plays a crucial role in the healing process of diabetic ulcers. However, the high-glucose environment disrupts the physiological cascade of wound healing, leading to impaired macrophage polarization from the pro-inflammatory (M1) phenotype to the anti-inflammatory (M2) phenotype [34]. This disruption results in the accumulation of M1-type macrophages within the wound, releasing pro-inflammatory cytokines that induce oxidative stress and cellular damage, thus prolonging the inflammatory phase [35]. Numerous studies have emphasized the significance of macrophage polarization in the healing of DFUs [35–37].

In a study by Yang et al., it was observed that TTT therapy could enhance local inflammation resolution and promote ulcer healing by facilitating the polarization of M1 macrophages towards the M2 phenotype [38]. Similarly, in our previous research, we demonstrated that TTT

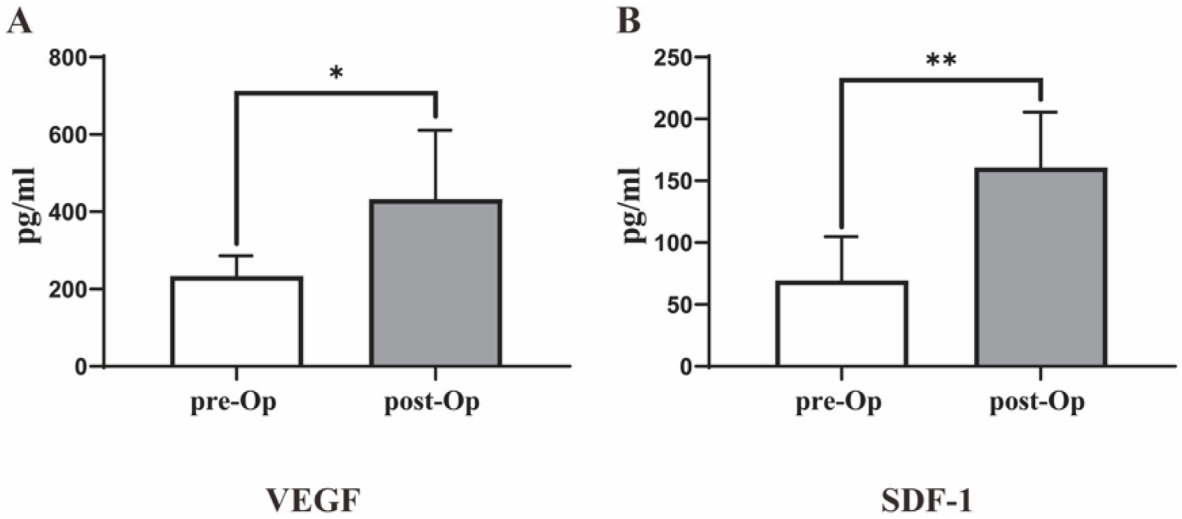

Fig. 6. Fig. 6 shows the plasma levels of VEGF and SDF-1 before and after TTT surgery. A: The levels of VEGF increased significantly after surgery. B: Similarly, the levels of SDF-1 also increased significantly after surgery. (*p < 0.05, **p < 0.01).

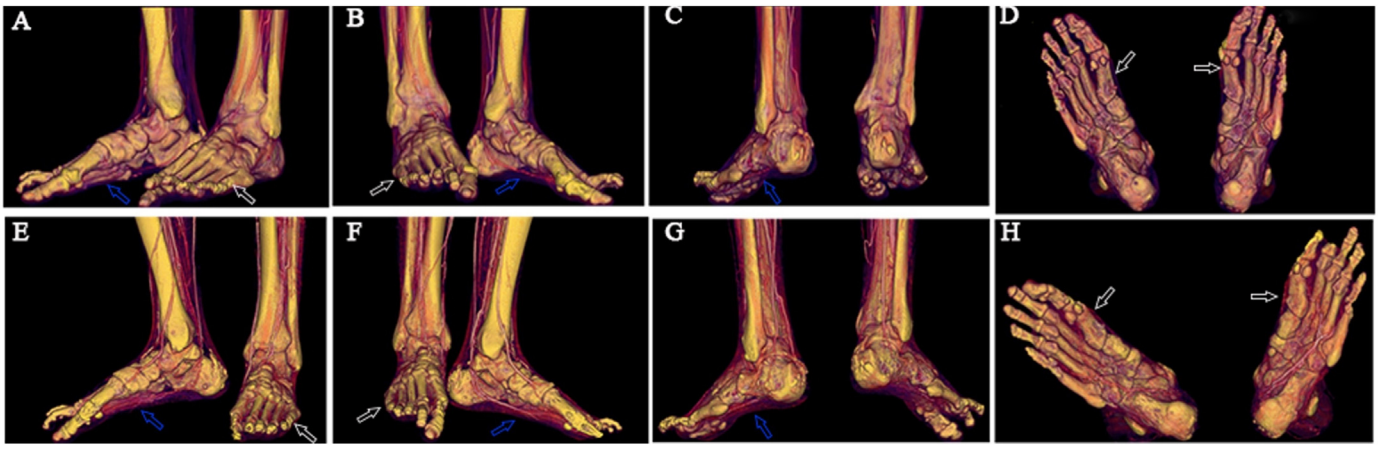

Fig. 7. Fig. 7 shows the CTA results of a patient with BDFUs treated with TTT. The CTA images were taken eight weeks after surgery, and small vessels at the planta (blue arrows) and toes (white arrows) of both feet were more visible than preoperatively. (A-D:pre-operative, E-H:8 weeks after TTT).(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

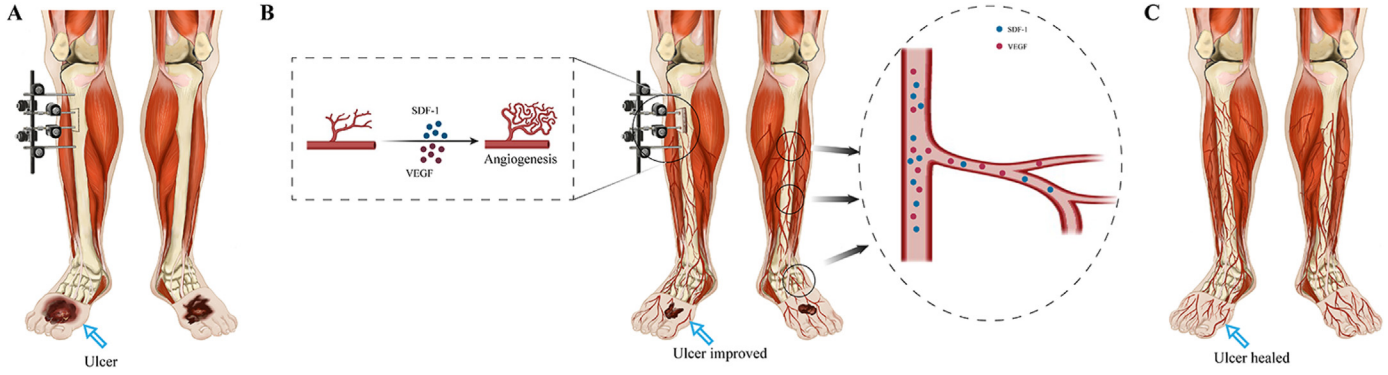

Fig. 8. The potential mechanism of TTT. Fig. 8 illustrates how TTT can promote the healing of diabetic foot ulcers. A: TTT surgery involves osteocorticotomy of the right proximal tibia and the installation of an external fixation frame. BDFUs are then debrided. B: The bone distraction process increases the levels of SDF-1 and VEGF in the peripheral circulation, leading to neovascularization in both feet and gradual improvement of the ulcers. C: After the external fixing frame is removed, the corticotomized cortex unites with increased vascularization, and complete healing of the ulcer is achieved.

treatment promoted the polarization of M2 macrophages in the wounds of diabetic foot patients, leading to reduced chronic inflammation and improved ulcer healing [39]. Moreover, TTT treatment of severe diabetic foot cases accompanied by systemic inflammatory response syndrome

(SIRS) resulted in systemic inflammation improvement and enhanced ulcer healing [40]. Consequently, we propose that one of the mechanisms by which TTT promotes the healing of DFUs is by improving the inflammatory status through immunomodulation , but this still requires more research to confirm.

This study was challenged by several factors, such as a lack of randomization and the potential for selection bias, that may compromise the validity of the findings. However, we attempted to reduce the selection bias through the use of PSM. Despite this, a future randomized trial would be needed to confirm our findings. Additionally, this was a retrospective study and computed tomography perfusion was not performed on the patients, which could limit our understanding of the association between TTT and angiogenesis, perfusion spec, and diabetic foot ululation. The study would be necessary to further investigate these associations. The hypothesis that TTT promotes angiogenesis through elevated expression of VEGF and SDF-1 was based on a limited detection of these two factors and did not account for the potential role of other pro-angiogenic factors. Furthermore, the mobilization of EPCs was not assayed, and the hypothesis that TTT promotes such mobilization still requires further experimental validation. The small sample size of the study (n = 34) may also contribute to some bias and future studies with larger sample sizes would help eliminate this.

5. Conclusion

In conclusion, our findings indicate that treating BDFUs with unilateral TTT is effective in promoting healing and is comparable to treating UDFUs. The increase in pro-angiogenic factors VEGF and SDF-1 in the blood may play a role in the healing process. However, further research is necessary to refine the treatment protocol and better understand the underlying mechanisms.

Authors' contributions

All authors contributed to the article and approved the submitted version.Wencong Qing, and Xinyu Nie performed the data collection, experiments, graph production and manuscript writing. Hongjie Su, Yi Ding, Lihuan He, Kaibing Liu, Jun Hou, Kaixiang Pan, and Liexun He performed the data compilation and graph production and assist in writing manuscripts, Sijie Yang, Lisha Li, Shenghui Yang Xiao Peng, and Jinming Zhao helped perform the analysis through constructive discussions. Jack Guan, Xiaocong Kuang, and Qikai Hua contributed to the conception and design of the study.

Ethics approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (approval no. 2022-E389-01).

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare that they have no competing interests.

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