ORIGINAL ARTICLE

INFLUENCE OF CLINICAL PRESENTATION OF DIABETIC PATIENTS WITH CHRONIC LIMB THREATENING ISCHEMIA SUBMITTED TO DISTAL REVASCULARIZATION

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Abstract

Objective: *The purpose of this article was to evaluate the clinical impact of diabetic foot ulcer (DFU) severity in patients with chronic limb-threatening ischemia (CLTI) who underwent distal open revascularization.*

Methods: *This study included a single-center retrospective analysis of diabetic patients with CLTI who underwent distal revascularization between January 2012 and December 2019. The sample was divided into two groups according to DFU severity; group 1 was defined if observed Wound grade ≥ 2 and Infection grade ≥ 1 and group 2 was defined if observed Wound grade < 2 and Infection grade < 1, according to Wound, Ischemia, and foot Infection (WIfI) classification.*

The primary endpoint was achieving freedom from CLTI at 1 year. Secondary endpoints encompassed the recurrence of CLTI, limb salvage, amputation-free survival, overall survival, and primary patency over a 4-year follow-up period.

Results: *A total of 258 distal bypasses were performed in diabetic patients with CLTI. Among these, 95 patients had infected major foot lesions (group 1), while the remaining 163 limbs comprised group 2. Group 1 patients were slightly younger, with a median age of 72 years (IQR 14), compared to 74 years (IQR 14) in group 2 (p=0.045).*

Most of the patients achieved freedom from CLTI at 12 months (82%), with no significant differences between groups (HR 0.75, CI 0.53-1.04, p=0.084; aHR 0.77, CI 0.54-1.08, p=0.130). At 4 years of follow-up, recurrence rates of CLTI and limb salvage were no different between groups (HR 0.68, CI 0.34-1.35, p=0.266; aHR 0.71, CI 0.34-1.48, p=0.355 and HR 1.18, CI 0.63-2.24, p=0.591; aHR 1.81, CI 0.80-4.11, p=0.155, respectively). Survival-related end points were not different between groups, except when adjusted for baseline characteristics and graft type (survival: HR 1.50, CI 0.96-2.33, p=0.072; aHR 2.49, CI 1.54-4.05, p<0.001; amputation-free survival: HR 1.37, CI 0.97-1.92, p=0.071; aHR 2.03, CI 1.40-2.93, p<0.001).

Conclusion: *The present study emphasizes the value of distal revascularization in limb salvage of patients with diabetic foot, independently of the DFU severity. However, these results suggest a lower survival in patients with infected major foot lesions. Further studies are needed to assert these findings.*

Keywords: *diabetes; CLTI; distal revascularization; infrapopliteal; infragenicular; bypass; diabetic foot ulcer.*

INTRODUCTION

Diabetes is nowadays considered a global epidemic. The number of adults living with diabetes quadruplicated since 1980, which has resulted in an inevitable increase in diabetes-related complications, such as diabetic foot ulcers (DFU) [1]. DFU are a common and serious complication intimately correlated with minor and major amputation, being the most common cause of non-traumatic lower limb amputation [2, 3]. In fact, 15-20% of DFU will ultimately require amputation [4].

Atherosclerotic peripheral arterial disease (PAD) is one of the main causes of chronic foot ulceration in diabetic patients. Chronic limb threatening ischemia (CLTI), formerly known as critical limb ischemia, is the terminal stage of PAD when rest

pain or lower limb tissue loss is observed for more than 2 weeks[5]. It is associated with a significant impact on the quality of life of patients and, ultimately, with high rates of morbidity and mortality[6]. CLTI remains a tremendous challenge in vascular care, particularly when associated with diabetes. The pattern of arterial disease in these patients is mostly infragenicular and particularly extensive, which translates into complex arterial revascularizations. Open surgery is the first choice to treat CLTI when a single segment of the great saphenous vein is available [7,8]. In the absence of an adequate venous conduit, endovascular treatment can be an alternative. However, the evidence of the outcomes of these techniques is short and predominantly limited to focal disease [7]. A recently published study, BEST-CLI trial, suggested that, when lacking an adequate venous conduit, open revascularization with alternative conduits can be an option to endovascular approach [8].

This study aimed to evaluate the clinical impact of the severity of diabetic foot ulcers in patients with CLTI submitted to distal open revascularization.

METHODS AND MATERIALS

Patient selection and data collection

A single-center retrospective analysis was conducted on all patients with DFU and CLTI who underwent distal bypasses between January 2012 and December 2019. Baseline demographic characteristics, comorbidities, procedural details, and follow-up data were collected from medical records. Informed consent was obtained from all patients prior to surgery. This study was approved by the institutional review board, reference number 0112/2023_MJH/MP/NO.

Classification system and definition of groups

The Wound, Ischemia, and foot Infection (WIfI) classification system provides an objective categorization for threatened lower extremities, based on three risk factors (wound extent, degree of ischemia, and extent of foot infection) combined to obtain a WIfI clinical stage [9]. In the present study, all threatened limbs were classified according to wound and infection grade. A 4-grade scale is employed for each parameter (Wound grade: 0 = ischemic rest pain, 1 = minor tissue loss, 2 =major tissue loss, 3 = extensive tissue loss; Infection grade: 0 = none, 1 = mild, 2 = moderate, 3 = severe) 10. Infected major foot lesions, defined as Wound grade ≥ 2 and Infection grade ≥ 1, were labeled as group 1; the rest of the patients formed group 2.

Periprocedural approach

All patients underwent a comprehensive clinical assessment and wound grading, followed by a duplex ultrasound (DUS) examination to assess lower limb perfusion, analyzing distal waveforms to assess the anatomical pattern of each limb. Preoperative angiography was also performed, except when contraindicated.

Lipid-lowering medication and antithrombotic therapy were prescribed - acetylsalicylic acid (ASA), if venous bypass, and therapeutic anticoagulation, if prosthetic graft.

After the procedure, graft surveillance was conducted at 1, 3, and 6 months, followed by annual assessments thereafter, comprising physical examinations and DUS. Patients experiencing failure to heal or displaying new signs or symptoms of CLTI underwent immediate reevaluation.

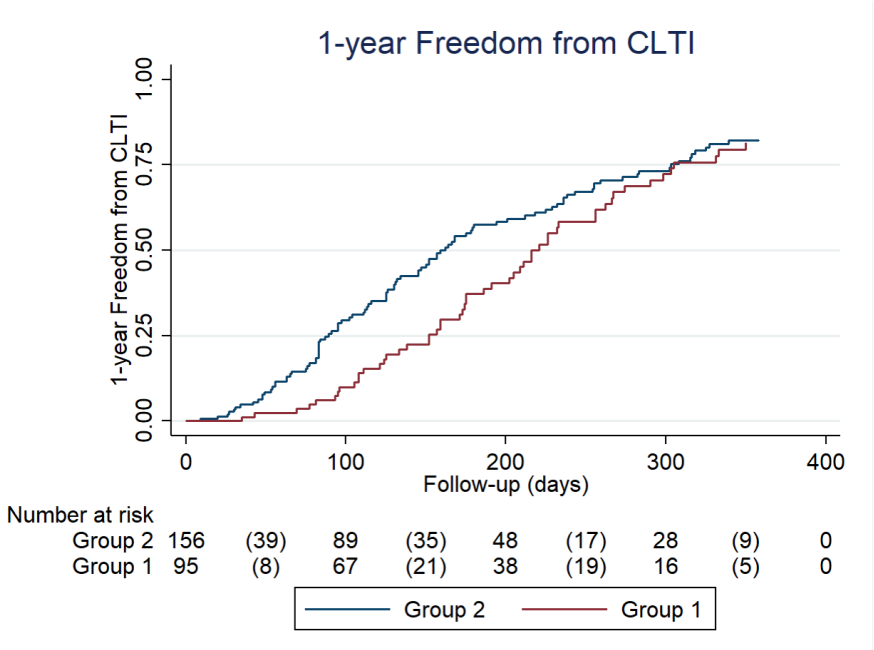

Figure 1 *Kaplan-Meier curves depicting 1-year freedom from CLTI stratified by groups.*

Table 1 **Clinical characteristics**

Characteristics	Distal bypasses			
	Group 1 (n=95)	Group 2 (n=163)	Total (n=258)	p value
Basic demographics				
Male gender	71 (75%)	111 (68%)	182 (71%)	0.162
Age, yearsΩ	72 (14)	74 (14)	73 (15)	0.045
BMI, kg/m2 Ω	26 (5)	26 (6)	26 (5)	0.847
Smoking status				
Current smoker	5 (5%)	27 (17%)	32 (12%)	0.005
Former smoker	19 (20%)	36 (22%)	55 (21%)	0.409
History of smoking	24 (25%)	63 (39%)	87 (34%)	0.019
Comorbidity				
Hypertension	91 (96%)	156 (96%)	247 (96%)	0.622
Dyslipidaemia	78 (82%	130 (80%)	208 (81%)	0.386
CAD	29 (31%)	62 (38%)	91 (35%)	0.139
CKD (eGFR<60 mL/min/1.73m2) *	40 (42%)	66 (40%)	106 (41%)	0.450
ESRD requiring dialysis	24 (15%)	11 (12%)	35 (14%)	0.304
Previous lower limb revascularization				
Contralateral	21 (22%)	42 (26%)	63 (24%)	0.307
Ipsilateral	16 (17%)	27 (17%)	43 (17%)	0.542
ASA				0.180
2	4 (4%)	14 (9%)	18 (7%)	
3	80 (84%)	121 (74%)	201 (78%)	
4	11 (12%)	28 (17%)	39 (15%)	
WIfI	-			
Wound class				
1	-	91 (56%)	91 (35%)	
2	77 (81%)	59 (36%)	136 (53%)	
3	18 (19%)	13 (8%)	31 (12%)	
Foot infection class				
0	-	134 (82%)	134 (52%)	
1	38 (40%)	14 (9%)	52 (20%)	
2	53 (56%)	15 (9%)	68 (26%)	
3	4 (4%)	0 (0%)	4 (2%)	
GLASS Stages	N=78	N=131	N=209	0.896
I	6 (8%)	9 (7%)	15 (7%)	
II	9 (12%)	18 (14%)	27 (13%)	
III	63 (81%)	104 (79%)	167 (80%)	
Graft type				0.034
Prosthetic graft	27 (28%)	66 (40%)	93 (36%)	
Venous graft	68 (72%)	97 (60%)	165 (64%)	

* Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73m2. Ω Continuous variables were presented as median with interquartile range from 25th to 75th percentile.
Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; ASA, American Society of Anesthesiologists physical status classification system; GLASS, Global Anatomic Staging System.

Clinical end points and variable definitions

The primary endpoint was achieving freedom from CLTI within one year. Secondary endpoints encompassed CLTI recurrence, amputation-free survival, limb salvage, and overall survival over a four-year follow-up period. Amputation-free survival (AFS) was defined as patients remaining alive without major amputation of the index limb. One-year freedom from CLTI was considered attained if patients achieved amputation-free survival with complete wound healing and absence of ischemic rest pain within 12 months, a timeframe assumed to be linked to the index revascularization. Recurrence of CLTI encompassed patients who initially achieved freedom from CLTI but subsequently experienced ischemic rest pain or developed a new wound within the four-year timeframe. Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73m^2, according to CKD-EPI.

Statistical analysis

Statistical analysis was conducted using Stata 12.1 (StataCorp®, Lakeway Drive, College Station, Texas, USA). Results were reported as a median with an interquartile range from the 25th to 75th percentile (IQR), and as absolute numbers with corresponding percentage values. For univariate analysis, the Mann-Whitney U test compared continuous variables across different groups, while Fisher's exact test analyzed categorical variables. Time-to-event endpoints were illustrated with Kaplan-Meier estimates and compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CIs) were estimated through univariate Cox analysis. Adjusted hazard ratios (aHR) were determined using a multivariate Cox proportional-hazards model, which was adjusted for predetermined baseline characteristics (gender, age, history of smoking, coronary arterial disease, hypertension, end-stage chronic disease under dialysis), along with all covariables exhibiting a p-value < 0.05 in univariate analysis. The proportional hazards assumption was assessed using Schoenfeld residuals. Statistical significance was defined as a two-tailed p-value < 0.05.

RESULTS

A total of 227 diabetic patients with CLTI were submitted to 258 distal bypasses, 95 of them with infected major foot lesions (group 1). Prosthetic graft was used as an alternative to venous conduit in 36% (93/258) of the limbs. Overall median age was 73 years (IQR 15), with group 1 being marginally younger than group 2, with 72 years (IQR 14) vs. 74 years (IQR 14), p=0.045, respectively. Fourteen percent (35/258) of the sample had end-stage kidney disease requiring dialysis and 35% (91/258) had coronary artery disease. Status of current smoker and history of smoking were less prevalent in group 1, with 5% (5/95) vs. 17% (27/163), p=0.005 and 25% (24/95) vs. 39% (63/163), p=0.019, respectively. Prosthetic graft was less frequently an option in group 1, with 28% (27/95) vs. 40% (66/163), p= 0.034. Patient characteristics and clinical data are summarized in Table I.

Overall, most of the patients achieved freedom from CLTI at 12 months (82%), with no significant differences between groups (HR 0.75, CI 0.53-1.04, p=0.084 and aHR 0.77, CI 0.54-1.08, p=0.130) (Figure 1). Recurrence rates of CLTI were no different between groups (HR 0.68, CI 0.34-1.35, p=0.266 and aHR 0.71, CI 0.34-1.48, p=0.355), with overall rates of 9%, 15% and 30% at 1, 2 and 4 years of follow-up.

Overall, limb salvage achieved about 80% at 4 years of follow-up, without significant difference between groups (HR 1.18, CI 0.63-2.24, p=0.591 and aHR 1.81, CI 0.80-4.11, p=0.155). At 4 years of follow-up, survival-related end points were no different between group 1 and group 2, except when adjusted for predetermined baseline characteristics and graft type (overall survival: HR 1.50, CI 0.96-2.33, p=0.072 and aHR 2.49, CI 1.54-4.05, p<0.001; amputation-free survival: HR 1.37, CI 0.97-1.92, p=0.071 and aHR 2.03, CI 1.40-2.93, p<0.001). Primary patency rates were not different between groups at 4 years of follow-up (HR 0.98, CI 0.61-1.59, p=0.935 and aHR 1.28, CI 0.76-2.14, p=0.356). Primary and secondary end points are summarized in Table II.

DISCUSSION

In this retrospective trial, we found no significant differences between groups in all limb-specific end points, including the primary end point freedom from CLTI.

Literature has demonstrated increased healing time and high amputation rates related to complex foot lesions[11-14]. However, endovascular intervention was the predominant treatment approach in these studies [11-14]. Endovascular technology evolved substantially in the last decades, but treatment of infrapopliteal arteries remains a challenge, with reasonable outcomes only limited to focal arterial lesions. It must be emphasized that most diabetic patients with CLTI exhibit extensive and complex obstructive lesions in the infrapopliteal sector. In the present study, 80% of the population was classified with GLASS stage III (the highest level for anatomical pattern complexity based on the Global Anatomic Staging System) [7]. It is well established that surgical bypass is the gold standard to treat CLTI when an adequate great saphenous vein is available. But based on the latest evidence from BEST-CLI trial [15], surgical bypass with prosthetic grafts may be an alternative to an endovascular approach when lacking an adequate venous conduit.

Hicks et al and Weaver et al showed that WIfI classification can be a predictor of diabetic foot wound healing[10,11,13]. However, we must be careful when evaluating wound severity using WIfI stages since it is not only determined by wound and infection grades, but also by ischemia parameters. As an example, mild foot lesions (i.e., modest wound and infection grades) can achieve high WIfI stages if observed high ischemia grades.

In the present study, we obtained a significant difference between groups for survival-related end points when adjusted with predetermined baseline characteristics and graft type. This statistical find is apparent only after 6 months

Table 2 **Bypass-related and clinical outcomes after revascularization**

Outcome and time point	Group 1 (n=95)	Group 2 (n=163)	Total (n=258)	p value*
Limb-specific end points				
1- year Freedom from CLTI	81%	82%	82%	0.082
Recurrence of CLTI †				0.263
1 year	8%	10%	9%	
2 years	8%	19%	15%	
3 years	15%	25%	22%	
4 years	27%	31%	30%	
Limb salvage				0.592
1 year	85%	86%	86%	
2 years	81%	85%	84%	
3 years	78%	82%	81%	
4 years	75%	79%	78%	
Survival-related end points				
Survival (n=227)				0.070
1 year	77%	83%	81%	
2 years	63%	74%	70%	
3 years	61%	67%	65%	
4 years	45%	60%	55%	
Amputation-Free Survival				0.070
1 year	64%	72%	69%	
2 years	52%	63%	59%	
3 years	46%	55%	52%	
4 years	35%	47%	43%	
Bypass-related end points				
Primary patency				0.935
1 year	73%	81%	78%	
2 years	71%	68%	68%	
3 years	65%	63%	63%	
4 years	61%	55%	56%	

*p value determined with log rank test comparing both groups. Total of 244 cases (61 with ePTFE graft and 183 with venous graft) that is the total number of cases that was previously free from CLTI.

of follow-up, which suggests not to be related to postoperative period. However, it remains to be answered if a primary major amputation would change positively the survival-related end points.

The therapeutic goal for DFU with a significant underlying PAD is to improve distal blood flow. Revascularization will improve oxygen and nutrient supply and the delivery of antibiotics to the infected ulcers. This study suggests that patients with DFU and CLTI submitted to distal bypasses have comparable limb-specific outcomes independently of the wound severity. As such, it is highly recommended to discuss all DFU with a multidisciplinary team, including vascular surgery.

We recognize some limitations in our study. It is a single-center retrospective trial, which may introduce inherent biases and limit generalizability; the number of patients included in the study is limited; the multiple comparisons performed in the statistical analysis can increase the risk of type I error; and the study focuses solely on patients who underwent surgical bypass, lacking a comparative endovascular group for analysis;.

CONCLUSION

Wound severity does not seem to affect limb-specific outcomes of patients with CLTI and diabetes submitted to distal bypasses. As such, all diabetic foot lesions should be considered for discussion in a multidisciplinary team in order to analyze possible arterial revascularization.

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