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Outcomes of Three Years of Teamwork on Critical Limb Ischemia in Patients With Diabetes and Foot Lesions

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Abstract

To evaluate the outcomes of a multidisciplinary team working on diabetic foot (DF) patients with critical limb ischemia (CLI) in a specialized center, the authors retrospectively traced all the patients admitted in their department in 3 consecutive years with a diagnosis of CLI. From January 2006 to December 2008, 245 consecutive DF patients with CLI according the TransAtlantic interSociety Consensus II criteria were included in the study. Treatment strategy was decided by a team of diabetologists, inteventional radiologists, and vascular surgeons. Technical and clinical success, mortality, and ulcer recurrence were evaluated at 6 months and at a mean follow-up of 19.5 ± 13.4 months. Percutaneous transluminal angioplasty (PTA) was performed in 189 (77%) patients, whereas medical treatment, open surgical revascularization (OSR), and primary amputation were performed in 44 (18.3%), 11 (4.3%), and 1 (0.5%) patients, respectively. Revascularization was successful in 227/233 (97.4%) patients. At follow-up, the overall clinical success rate was 60.4%; it was significantly ($P = .001$) higher after revascularization (75.9%) compared with medical treatment (48.3%). During follow-up, surgical interventions in the foot were 1.5 ± 0.4 in those treated with PTA, 1.6 ± 0.5 in those treated with OSR, and 0.3 ± 0.8 in those receiving medical therapy ($P < .05$ compared with the others). Ulcer recurrence occurred in 29 (11.8%) patients: 4 (1.6%) in PTA, 2 (0.8%) in OSR, and 23 (9.4%) in the medical therapy group ($P < .05$). Major amputation rate was 9.3%, being significantly ($P = .04$) lower after revascularization (5.2%) compared with medical therapy alone (13.8%). Cumulative mortality rate was 10.6%. In conclusion, this study confirms the positive role of a PTA-first approach for revascularizing the complex cases of DF with CLI in a teamwork management strategy.

Keywords

critical limb ischemia, diabetes, diabetic foot, revascularization, teamwork

The increasing incidence of diabetes worldwide creates a problem of health care, both for the disease per se and for its chronic complications.[1]

Complications at the lower limb (LLC) are, among those related to diabetes, the most prevalent and relevant, both from clinical and social points of view: diabetes is now the major cause of nontraumatic amputation of the lower extremities (LEA), and the trend is positive because of the increasing prevalence of diabetes and the longer life expectancy of patients.[2]

Critical limb ischemia (CLI) plays a crucial role in determining the fate of the patients with LLC, since it exposes them to a risk of amputation, which is almost 60 times higher than that of nonischemic patients.[3]

Until recent times patients with CLI unavoidably ended with an LEA after a long clinical course characterized by rest pain, often not easily controlled by analgesics; foot infections; necrosis; and gangrene.[4-6]

Besides this local extremely severe prognosis, a higher mortality rate due to severe comorbidities was registered in many studies, which provided evidence to show how CLI in

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diabetic patients was actually a marker of cardiovascular morbidity and mortality.[7,8]

Revascularization, once only accomplished by open surgery, now even endovascular, associated with aggressive surgical debridement and antibiotic therapy, did change the prognosis of our patients, restoring districtual blood flow in the leg and in the foot and controlling infections, thus stopping the progression of disease and reducing the number of patients undergoing LEA.[9-11]

Despite the increasing evidence that it is crucial to save legs and lives of patients, the indications and contraindications to revascularization and the choice of open versus endovascular arterial reconstruction are still debated, and there is a lack of consensus due to the scarce evidence in the literature.[12]

Therefore, there is little information on which kind of approach is safer and more effective to revascularize diabetic patients with CLI, and even more relevant, the decision-making process of if and how to revascularize largely depends on personal experience rather than on objective considerations, also in relation to the complexity of the cases.[13]

Teamwork has been indicated as a solution to overcome the difficulties related to the choice of any type of revascularization; in the guidelines for the management of diabetic foot (DF) released by the International Working Group on Diabetic Foot (IWGDF), the multidisciplinary team approach is expressly indicated as the method of choice in all the aspects of the management of DF, both in the diagnostic and therapeutic phases.[14]

In our center, since 1991 a team on DF has been established, managed by diabetologists, involving both vascular surgeons and interventional radiologists, sharing the cases, and working together in an integrated way.

Each patient admitted for CLI undergoes a collegial evaluation to decide case by case the most appropriate therapeutic option among the following: amputation, medical therapy, surgical or endovascular revascularization. After the decision, patients are managed and followed-up by the same team, which also provides general medical management and local therapy in case of presence of active lesions in the foot.

To evaluate the performances of such an approach, we retrospectively analyzed the results of 3 years of activity on diabetic patients admitted for CLI.

Patients and Methods

We retrospectively evaluated all the patients admitted in the ward of our department from January 2006 to December 2008 and with the diagnosis of CLI according to the definition of the TransAtlantic interSociety Consensus (TASC II—ie, rest pain and/or throphic lesions with $TcPO_2 < 30$ mm Hg or ankle pressure <50 mm Hg).[15]

Patients were traced via the hospital general electronic database, and their files, containing details of radiological exams and interventional procedures, were sorted out.

The data obtained were cross-checked with the patients' record files stored in our department archive, and with the electronic databases of both the cath lab of the imaging department and the operating room registry, in order to validate them and sort out the number and type of interventional procedures carried out.

Patients were selected for the study according to the following inclusion criteria: type 1 or type 2 diabetes mellitus, admission for CLI, and clinical management and discharge by our department. Patients were excluded in case of acute ischemia, if the cause of CLI was not related to diabetes mellitus, or in case of a life expectancy less than 1 year due to a cause not related to diabetes. Patients admitted in our department with the diagnosis of CLI, but who were transferred to other departments (ie, intensive care unit) before being treated, and then managed by others, were excluded as well.

According to the indications of the International Consensus on Diabetic Foot Guidelines,[16] patients underwent clinical assessment focused on local conditions (anamnestic or actual rest pain, presence and grading of foot lesions, ankle-brachial pressure index [ABPI], transcutaneous oxygen tension [$TcPO_2$], Duplex scanning of lower extremity arteries) and systemic (cardiovascular, renal, and metabolic) conditions before being submitted to the collegial evaluation for the indications to revascularization.

Although each case was evaluated on a single basis, the criteria adopted for deciding which option to pursue were the following: percutaneous transluminal angioplasty (PTA) was considered the first-line option whenever possible, open surgical reconstruction (OSR) was the second option, medical therapy was considered in case neither PTA nor OSR was feasible, and primary major amputation was indicated when none of the above was feasible.

The motivations that led to select the different therapeutic options were recorded in the patients' files and were codified as local, when the conditions that informed the judgment were related to the arterial or foot status (ie, the extension and localization of arterial lesions or the severity of foot ulceration or necrosis); systemic, when the prominent determiner of clinical strategies was related to the presence and severity of comorbidities (ie, heart failure [HF], renal failure [RF], hemodyalisis [HD], sepsis [S]); and mixed, when both local and systemic conditions were present.

Revascularizations were aimed at restoring direct blood flow to the ischemic foot, and their effectiveness was checked by duplex scanning and $TcPO_2$ within 1 week from the procedure; PTAs were carried out by interventional radiologists (AC, IB, PP, and RC), with both endoluminal and subintimal techniques; and OSRs were performed by vascular surgeons (MF, RB, DA, and ADC) and encompassed endo-atherectomy and arterial by-passes, according to the

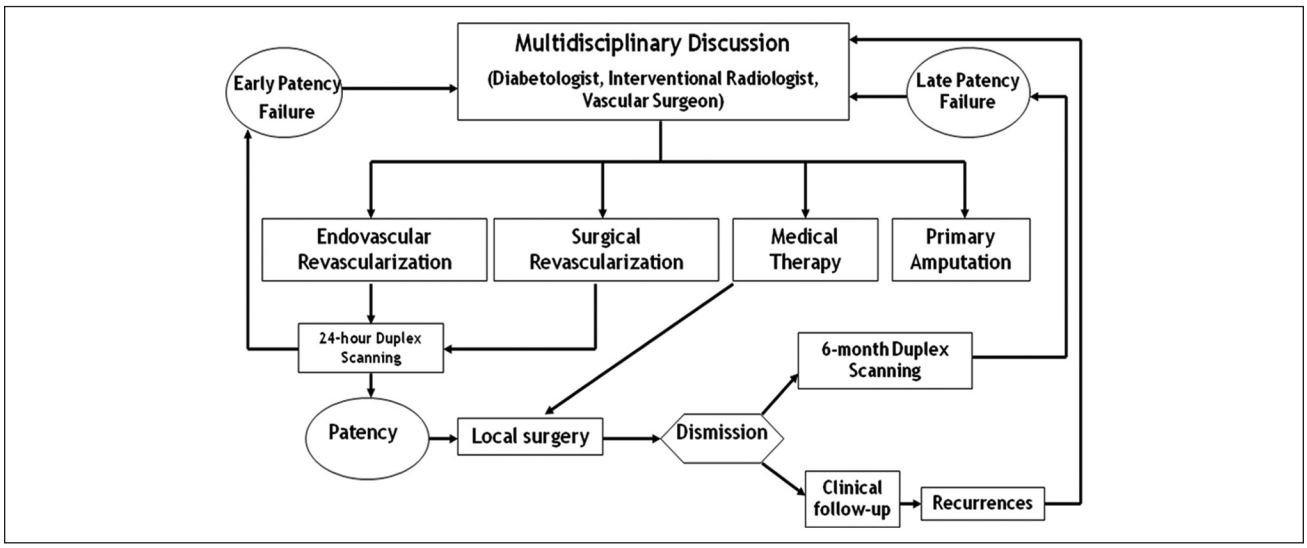

Figure 1. The scheme represents the algorithm followed to manage CLI diabetic patients in our third-level center, which has been followed in all the patients for this study

localization and distribution of the disease and the clinical evaluation of the surgeon.

Medical therapy consisted of the administration of empiric antibiotic therapy, iloprost according to the protocols adopted in our department and previously published; chronic antiplatelet treatment; low-molecular-weight eparin; and statins.[17]

Below (BKA) or above (AKA) the knee amputation was carried out by vascular surgeons after duplex scanning evaluation of the patency of the vessels to establish the level.

Patients, once dismissed, were followed-up on an outpatient basis and eventually rescheduled for a new admission in case of recurrences; a scheme of the protocol is provided in Figure 1.

Follow-up data were recovered by the DF clinic database (E-upodi@; Percorsi Multimediali, Roma, Italy). A period of 6 months after the discharge was considered as early follow-up, whereas late follow-up was determined by the mean duration of retrospective observation.

When not available from E-upodi@, data concerning patients' survival, actual condition of the lower limb, and general health status were inquired by means of a structured telephone interview.

The outcomes were defined as follows: death, major amputation, healing with minor amputation, healing without amputation, nonhealing.

Healing time, recurrence rates, number of reinterventions, and number of revascularizations were also considered, as part of a composite outcome descriptive of the complexity of the cases.

Data were analyzed with a statistical software (Statview; SAS institute, Cary, IL) on an iMac computer. Continuous variables were expressed as mean ± standard deviation and analyzed with Student's *t* test or with analysis of variance in case of nonparametrical distribution; categorical variables, expressed as rates, were analyzed with Fisher's exact test; correlation among the data was evaluated with simple regression and logistic regression: a P value less than .05 was considered as significant.

Results

In the study period, 304/1419 (21.42%) patients admitted in our department had a diagnosis at admission of CLI. Among these patients, 27 (8.88%) were excluded from the analysis because of wrong diagnosis of CLI; 13 (4.27%) because of the presence of advanced stage cancer, HIV infection, and other conditions that reduced life expectancy to less than 1 year; 10 (3.29%) because they were not diabetic; 6 (1.97%) were transferred to the critical care unit and dismissed or died without being treated; and 3 (0.98%) refused to be treated in our department and were dismissed despite the physicians' advice. Thus, 245 patients were included in the study: their demographic and clinical data at admission are reported in Table 1.

At admission, in 215 patients (87.7%) active lesions were present; their location was in the forefoot in 63.2%, in the midfoot in 9.1%, in the rearfoot in 14%, and in the leg in 10.6% of the cases. A total of 136 patients (55.5%) referred rest pain, in 57 (23.3%) claudicatio intermittens was present, while 59 (24.1%) patients experienced no pain,

Table 1. Characteristics of Patients Included in the Study

Feature	Mean ± SD	Range
Number (male/female)	245 (160/85)	—
Type 1/type 2 diabetes	24/221	—
Age (years)	68.3 ± 10.3	33-88
Duration of diabetes (years)	19.1 ± 12.1	1-57
HbA1c (%)	8.2 ± 1.8	6.4-15.5
Left ventricular ejection fraction (%)	47.9 ± 9.1	24.6-61.9
Creatinine (mg/dL)	1.3 ± 1.2	0.49-8.49
Hypertension (%)	83.0	—
Impaired renal function (%)	26.9	—
Macroalbuminuria (%)	21.8	—
Ischemic cardiomyopathy (%)	36.3	—
Vascular encefalopathy/TIA or stroke (%)	12.8/7.4	—
Nonproliferative/proliferative retinopathy (%)	21.7/42.7	—
Previous lower limb revascularization (%)	21.8	—
Previous ulceration or minor amputation (%)	49.1	—
Previous major amputation (%)	2.5	—

Abbreviation: TIA, transient ischemic attack.

despite the clinical diagnosis of CLI, confirmed by $TcPO_2$, which was 20.2 ± 6.4 mm Hg in the affected limb, compared with 31.2 ± 18.7 in the contralateral limb ($P < .001$).

After the initial evaluation, patients were treated with PTA in 189 cases (77%), medical therapy in 44 (18%), OSR in 11 (4.5%), and combined OSR/PTA in 2 (0.8%) cases.

The decision for going with a particular therapeutic option was taken because of local (84%) or systemic (12%) reasons or both (4%).

When systemic reasons where responsible for the decision, the presence of multiple comorbidities—HF + RF being the most frequent association—was the determiner in all but 1 case, in which the presence of a septic shock was the determinant.

Among local reasons, the number and localization of arterial lesions was the most frequent item that conditioned the decision in more than 80% of the cases; the others were related to the number and extension of foot lesions and eventually a previous major contralateral amputation.

The most frequent among local reasons for performing OSR instead of a PTA were a steno-obstruction of common femoral artery, which was considered an indication for a thrombus endo-atherectomy (TEA), or a long obstruction of superficial femoral artery with patent tibial arteries, which was considered an indication for a peripheral by-pass.

When both the aspects were considered equally relevant for the decision-making process, the association of old age with limited motility and number and extension of arterial lesions was the most frequent, followed by HD, sepsis, and local acute infection in the foot.

The complications of the interventional procedures were as follows: acute renal failure (ARF) in 8.2% of patients, all successfully treated with hydration and medical therapy; contrast-medium-induced allergic reaction in 5.3% of the patients; vascular access hematoma in 1.6% of the patients; and a dehiscence of surgical suture was observed in 0.8% of the cases. All the early complications were successfully managed with no sequelae. Patients who developed ARF had a higher serum creatinine at baseline compared with the others (1.9 ± 0.6 vs 1.3 ± 1.2 mg/dL, $P = .0326$).

At 6 months, 34.7% of the patients healed without minor amputations, 45.7% healed with minor amputations, 11.4% did not heal, 5.3% of patients underwent to LEA, while 0.8% died. Mean healing time was 97.4 ± 32.8 days.

The chronic follow-up duration was 19.5 ± 13.4 months (range = 6-46 months); in this period the cumulative incidence of deaths was 10.6%.

In this period, among the 189 patients treated with PTA, 19 (10%) repeated the procedure once, 1 (0.5%) twice, and 2 (1%) thrice, while among the 11 patients treated with OSR, 3 (27%) underwent a second intervention for extension of the by-pass.

Among the patients who underwent more than 1 revascularization, 2 (8%) died, 3 (12%) underwent an LEA, 18 (72%) healed with minor amputations, and 2 (8%) healed without any amputation.

The mean number of surgical intervention over the follow-up, apart from LEAs, did not change between the groups treated with revascularization, being 1.5 ± 0.4 in those treated with PTA, 1.6 ± 0.5 in those treated with OSR, and the medically treated patients showed a significant ($P < .05$) lower number of intervention (0.3 ± 0.8) compared with the others.

Ulcer recurrence occurred in 29 (11.8%) patients, 4 (1.6%) in PTA patients, 2 (0.8%) in OSR patients, and 23 (9.4%) in medical therapy group ($P < .05$).

Major amputations were performed in 9.3% of the patients in the 3 years of follow-up. In univariate analysis, variables significantly associated to major amputation were the following: age, duration of diabetes, HbA1c, fibrinogenemia, creatininemia, and $TcPO_2$. In logistic regression analysis, only TcP02 and creatininemia were shown to be reliable predictors for amputation (Table 2).

$TcPO_2$ in revascularized patients increased from 20.2 ± 16.4 mm Hg to 40.9 ± 15.3 mm Hg ($P < .001$), and the difference from baseline inversely correlated with healing time of the lesions ($Y = 32.11 - 1.698X$; $r^2 = .236$; $P = .0415$).

When patients were divided into 4 different groups according to the level of the revascularization (group A =

Table 2. Logistic Regression Among Potential Predictors of Major Amputation During Follow-Up

Item	Nonamputated	Amputated	OR (95th Percentile)	*P*
Age (years)	69.1 ± 10.4	65.1 ± 9.9	0.99 (0.94-1.05)	.8590
Duration of diabetes (years)	18.9 ± 11.9	24.9 ± 15.1	1.03 (0.98-1.08)	.1878
HbA1c (%)	7.9 ± 1.8	8.9 ± 1.4	1.19 (0.88-1.60)	.425
Fibrinogenemia (mg/dL)	547.2 ± 150.2	677.9 ± 158.0	1.01 (1.00-1.02)	.0682
Creatininemia (mg/dL)	1.2 ± 0.8	2.1 ± 2.2	1.65 (1.16-2.34)	.0051
$TcPO_2$ (mm Hg)	21.3 ± 16.4	8.8 ± 4.3	1.76 (1.54-2.55)	.0022

Table 3. Difference in the $TcPO_2$ (mm Hg) Before and After Revascularization Procedures According to the Site of Revascularization

Groups[a]	$TcPO_2$ Before Revascularization	$TcPO_2$ After Revascularization	*P*
Group A	17.1 ± 15.2	19.5 ± 14.8	.3990
Group B	23.8 ± 18.3	36.2 ± 11.6	.2716
Group C	20.8 ± 16.2	43.1 ± 17.1	.0001
Group D	19.9 ± 16.3	41.5 ± 13.9	.0001

[a]For groups characteristics see the text.

no revascularization, group B = revascularization in the femoropoliteal district, group C = revascularization in the tibioperoneal district, group D = revascularization in both femoropopliteal and tibioperoneal districts), a significant $TcPO_2$ increase was observed only in groups C and D (Table 3).

Major amputations were significantly more prevalent in patients treated with medical therapy, 40% of whom had rest pain, compared with those revascularized (13.8% vs 5.2%; χ^2 5.39, Fisher's exact test $P = .0426$), as well as deaths (16.4% vs 4.9%; χ^2 5.32, Fisher's exact test $P = .0192$).

In Figure 2, the differences of outcomes between patients revascularized and treated with medical therapy are reported.

Recurrences occurred in 11.8% of the patients, and in 8.6% of the cases a new revascularization was performed. No differences between females and males were found for any of the outcomes when results were analyzed separately.

Conclusions

Our study confirms that a team approach applied in a third-level center is successful in avoiding amputation in more than 85% of cases and containing deaths to 11.4% and recurrences to 11.8% in diabetic patients with CLI over a long-term follow-up.

Despite other studies emphasizing the positive role of a team approach in the management of such critically ill patients, this is the first time that the decision-making process has been analyzed and results linked to the different therapeutic options.

The possibility of effectively revascularizing the patients with CLI did change the prognosis of this severe condition.[18,19]

In fact, in our series basal $TcPO_2$ was a predictor of amputation and its increase, as a marker of an effective revascularization, inversely correlated with healing time, in line with previous findings.[16,20]

In our study, revascularization of the infrapopliteal arteries was the condition that guaranteed a significant increase in $TcPO_2$ at the level of the foot, which in association with the surgical management of the local lesions created the conditions for saving the limb.

In a study on 420 consecutive CLI patients managed with PTA, Faglia et al demonstrated that revascularization of at least 1 tibial artery down to the foot is required to prevent major amputation.[21] Accordingly, in a study on 367 diabetic patients with CLI, Pomposelli et al reported a 3-year limb salvage rate of 87% after distal by-pass.[18] Thus, an effective surgical or endovascular revascularization of the foot is required for limb salvage. However, 1 out of 5 patients is not suitable for revascularization and alternatives must be pursued to manage these patients.

In our series, the primary amputation rate is less than 1%. This favorable result could be achieved by enlarging indications to revascularization to one side and by providing effective medical treatment associated with management of comorbidities plus local surgical techniques to the other side, in patients excluded from vascular interventions.

In our experience, medical therapy was effective in avoiding amputations and in promoting healing in a considerable number of patients excluded from revascularization, as shown in Figure 2, although it was associated with a higher rate of recurrences.

Compared with previous studies, our data showed lower mortality (10.6%) and amputation (9.3%) rates: Norman et al, in a prospective study involving 531 diabetic subjects with peripheral arterial disease followed for 5 years, reported an

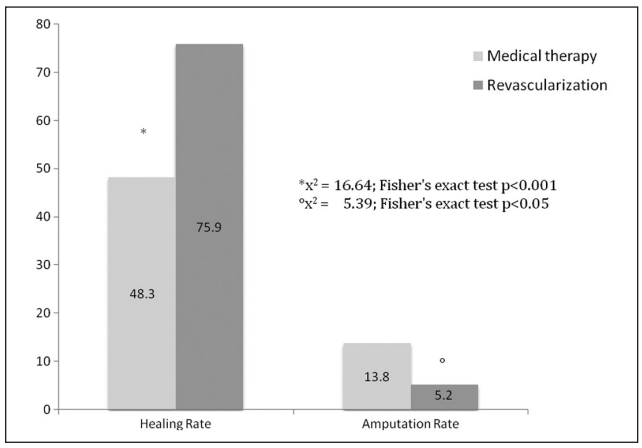

Figure 2. Differences in healing rate and amputation rate between patients treated with revascularization and those treated with medical therapy

increased risk of cardiac death of 67%,[22] while the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) reported a mortality rate of 20% and an amputation rate as high as 40%.[15] Also, interventional studies that evaluate the outcomes of peripheral revascularization showed similar figures. In a large cohort study, Faglia et al found a cumulative incidence of amputation higher than 15% and a mortality rate of more than 25% in a 3-year follow-up period.[23]

Similar results have been produced by other studies, with a variability that is related to the length of the observation period and to the population observed. In a cohort of 1000 mixed patients treated with PTA and followed-up for 2 years, DeRubertis et al reported an amputation rate of 20.7%[24]; whereas in a series of 456 patients with CLI followed-up for an average of 20 months, Uccioli et al found a prevalence of amputation and deaths of 14.9% and 16.2%, respectively.[25]

In a prospective study on 128 patients with critical ischemia evaluated by a hospital-based multidisciplinary team, El Sakka et al showed that 59.4% of the patients were revascularized (43.7% with PTA, 14.1% with OSR), while 40.6% of patients were treated with medical therapy and 1.5% of cases were primarily amputated; the reported mortality in the intervention group was 14%.[26]

The more favorable figures of our study could be the result of our multidisciplinary approach: sharing the same clinical protocol enables all the involved specialists to decide a common strategy for each patient, balancing risks and benefits, and producing better results with lower complications.

This is a concept that has been recently empowered in the scientific and clinical community dealing with DF, so that amputations are now considered a marker of the quality of foot care in diabetes, and the multidisciplinary approach has been recently recommended in a joint statement of the American Society for Vascular Surgery and the American Podiatric Medical Association.[27,28]

As a result of this multidisciplinary decision-making process, some considerations could be made. An endovascular-first option was chosen for the vast majority of CLI patients, mainly for local conditions, while for only a relatively small number of patients OSR was selected, confirming the suitability of PTA as first-line treatment modality in these patients.[29]

Another point is the relatively low mortality and amputation rates in the follow-up period, which probably relates to the medical management of the comorbidities, to the strict follow-up that these patients were submitted to, and to the possibility of prompt treatment in case of recurrences.

Moreover, a role for medical therapy in those patients with CLI not suitable for revascularization has been confirmed, since it was able to save the limbs and possibly improve the quality of life in a number of patients whose only other option was major amputation.

The possibility of managing these patients for multiple comorbidities, treating CLI, and managing foot lesions is a crucial factor to ensure a positive result in a vast number of cases.[30]

The limitations of this study, which is a retrospective analysis of the activity of a single center, do not allow any generalization of the results until further prospective multicenter studies eventually confirm the findings on a larger scale.

In conclusion, our study confirms the positive role of teamwork for the management of the complex cases of DF with CLI; and PTA should be considered the first option for effectively and safely revascularizing these patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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