Comparison between full and partial revascularization during endovascular management of multilevel lower limb arterial disease in diabetic patients: assessment of functional outcomes and midterm results

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Introduction
The multilevel arterial arteriosclerosis leads to a major loss of blood perfusion to the target tissues with resultant critical limb ischemia.
Aim
The aim of this article is to compare the results between total revascularization of all level arterial lesions versus revascularization of the proximal lesions regarding limb salvage rates, midterm primary patency rates, and secondary patency rates.
Patients and methods
A prospective study conducted on diabetic patients with symptomatic peripheral arterial disease affecting more than one level of lower limb arterial tree, from January 2013 till the end of December 2013, with critical limb ischemia and no previous attempts of revascularization. Follow-up was 1 year.
Results
A total of 101 diabetic patients were included. Their mean age was 64.4±14 years, and 62.4% were males. They were divided into two groups: group F had full revascularization for all diseased arterial levels and group P had revascularization for the proximal lesion only. Lesions were crossed intraluminal in 54 (53.5%) and subintimal in 47 (46.5%). Stents were used in 44 (43.6%). Primary patency rate was higher in group F than in group P (72.3 vs. 33.3%, P=0.002). The secondary patency rates were higher in group F compared with group P at 6 months (84 vs. 44%) and at 12 months (78 vs. 38%) (P=0.001). Total limb salvage rate was 80.2% and a major amputation rate was 19.8% over a 1-year follow-up period; limb salvage in group F was 88% and in group P was 44% (P=0.001).
Conclusion
In diabetic patients with multilevel arterial lesions affecting more than one arterial territory, total correction of all arterial lesions should be done with direct pulsatile flow to the foot as it is associated with better primary and secondary patency rates and higher limb salvage rates than correction of the proximal lesions.

Keywords:
angioplasty, critical limb ischemia, diabetics, multilevel arterial lesions, stenting

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Introduction

The most common reason of mortality and morbidity in patients with diabetes mellitus is diabetic vasculopathy, where macrovascular disease is responsible for high incidence of vascular diseases such as stroke, myocardial infarction, and peripheral arterial diseases (PAD) [1]. The multilevel arterial arteriosclerosis leads to a major loss of blood perfusion to the target tissues with frequent microthrombi that would obliterate distal vascular beds with resultant critical limb ischemia (CLI) [2]. Advances in endovascular techniques and tools have allowed the successful treatment of more complex occlusive diseases. This has led to a paradigm shift in the treatment of CLI where multiple series have reported successful treatment of CLI at the aortoiliac, femoral, popliteal, and tibial levels [3]. Many studies of patients with multilevel disease showed a significantly improved primary and secondary patency as well as limb salvage rates whenever multiple-level intervention is attempted as compared with single-level intervention for the same patient cohort [4]. Traditionally, endovascular management of multilevel arterial occlusive disease was perceived as a difficult procedure. Whenever such difficulties preclude treatment of all lesions, management usually reside to significant proximal lesions, thus improving the

head pressure for collateral circulation to more distal territories.

Aim

This is a prospective study to assess the clinical effectiveness and related midterm patency rates of endovascular management for atherosclerotic lesions affecting more than one level in lower limb arterial tree in diabetic patients comparing the results between total revascularization of all level arterial lesions versus revascularization of only significant proximal lesions. The following endpoints will be compared: the limb salvage rates, the midterm primary and secondary patency rates.

Patients and methods

This is a prospective study conducted during a 12-months period (January–December 2013) on diabetic patients with symptomatic PAD due to atherosclerotic arterial lesions, affecting more than one level of lower limb arterial tree, admitted to the Vascular Surgery Division, Kasr Al Ainy Hospital, Cairo University, and the Vascular Surgery Department, National Institute of Diabetes and Endocrinology, experiencing critical lower limb ischemia with no history of previous attempts of lower limb revascularization. The research was approved by the committee of the department of general surgery for evaluation of masters and doctorate theses in 2014. Nondiabetic patients, patients with mild or moderate claudication only, patients with single level of lower limb arterial lesions, those with previous history of lower limb revascularization, and those with severe renal impairment were excluded from the study. All patients had an arterial duplex performed for diagnosis and characterization of all the arterial lesions. Preoperative computed tomography angiography was standard practice in our study, performed for all patients before the intervention; all patients had a full vascular clinical assessment, including history, physical examination, risk factor profile, serum creatinine level test, ankle/brachial index (ABI), and peak systolic velocity measurements. Based on this assessment, appropriate medical management was commenced to all patients, along with risk factor modification.

Procedure details

Patients were admitted at the day of the procedure where a loading dose of clopidogrel (300 mg) was to be given the night of the procedure. Under local anesthetic (lidocaine 2%: 3–5 mg/kg), three sites of arterial access were used depending on the anatomy of the lesions and the operator's preference; ipsilateral antegrade femoral arterial access was performed in patients with middle one-third superficial femoral artery (SFA) lesion or more distal lesions, where contralateral femoral access with a cross-over sheath was performed in patients with either nonflush occlusion of common iliac artery (CIA), external iliac artery (EIA), common femoral artery, and proximal one-third SFA lesions. Brachial artery access technique was used in aortoiliac lesions. All patients received 5000 IU intra-arterial heparin immediately following sheath insertion, and a second dose of 5000 IU intra-arterial heparin was given if procedure time exceeds 2 h. Initial digital subtraction angiogram was performed to gather information regarding diseased segment's location(s), length and degree of stenosis or occlusion, and the extent of distal run-off.

Revascularization strategy

In aortoiliac lesions regardless of being either stenosis or occlusion, we adopt the primary stenting concept with balloon expandable stents for CIA and self-expanding stents for EIA. For SFA stenotic lesions, our policy involves liberal use of noncompliant plain balloons of appropriate lengths and diameters with slow increments (2 atm/30 s) till the nominal pressure is reached to minimize the incidence of subsequent dissection or rapid recoil; however, in total occlusion, the subsequent strategies differ according to the lesion crossing whether intraluminal or subintimal. Intraluminal passage would follow the prestated dilatation policy with secondary bail-out stenting in case of residual stenosis (? 30%) or flow-limiting dissection covering the whole lesion, whereas subintimal passage would call for selective stenting of either entry or exit points, if needed. For popliteal and infrapopliteal vessels, we change our platform to 0.018 or 0.014 with the use of their dedicated over-the-wire balloon catheters or rapid exchange ones. We encouraged the use of support catheters.

For ethical reasons, we attempted at total revascularization of all documented arterial lesions affecting the target limb; however, in certain conditions subjected to the operator's judgment, we were only able to treat the proximal lesions only leaving the more distal lesions without intervention. These conditions include extended time of procedure, use of large amount of contrast, patients with renal impairment, deterioration of the general condition of the patient during the procedure, or failure to cross-distal lesions.

Following percutaneous transluminal angioplasty (PTA), with or without stenting, final angiogram

was obtained, and procedure outcome was recorded. In case of arterial spasm, 0.1-mg nitroglycerine was given as an intra-arterial bolus. The arterial access sheath was removed when appropriate, and hemostasis achieved by manual compression. Most patients were discharged on the second day following the procedure after receiving instructions on risk factors to control and treatment including the following: enoxaparin subcutaneously every 12 h for 2 days, aspirin 81 mg/day for life, clopidogrel 75 mg/day for at least 3 months, and atorvastatin given routinely (40 mg for 2 weeks and then 20 mg for 6 months). Clinical outcome, including improvement in rest pain and ulcer healing/resolution, was documented before discharge and at subsequent outpatient visits, with repeat ABI and/or ankle peak systolic velocity, and arterial duplex was performed within 6 weeks.

Follow-up

Clinical improvement was documented before discharge and at subsequent outpatient visits. Wound closure and limb salvage are our primary endpoint. Clinical improvement was judged by palpable peripheral pulse, increase of claudication distance, disappearance of rest pain, wound healing, and limb salvage. Technical failure was defined as an inability to cross the proximal lesions at the time of the primary procedure or by the presence of greater than or equal to 50% restenosis within the first 30 days after the initial procedure. Clinical follow-up data were collected at each clinic visit. Surviving patients remained on this surveillance protocol at 3, 6, and 12 months, with follow-up duplex performed after 6 weeks and after 6 months. The clinical status of the patients and ABI index were evaluated at the same intervals, except in patients with huge ulceration in the leg or heavily calcified pedal arteries. The ultrasound examination measured the patency of the treated artery and any evidence of residual or new occlusions. Clinical outcomes, primary patency, secondary patency, and complications were reported according to the 'Recommended standards for reports' by Rutherford and Becker [5]. An increase in ABI of at least 0.10 was accepted as evidence of hemodynamic improvement, whereas a decrease of less than 0.10 or more was deemed to be a hemodynamic failure. Early mortality (<30 days) was reported. Limb salvage was defined as no amputation proximal to the metatarsus. Any above-the-ankle amputation was considered a failure of the revascularization procedure. All periprocedural and postprocedural complications were evaluated and documented. All statistical calculations were done using computer programs statistical package for the social science (SPSS, version 15; SPSS Inc., Chicago, Illinois, USA) for Microsoft Window.

Results

During the 12-month period of the study, 101 eligible diabetic patients were enrolled with mean age of 64.4±14 years; of which, 62.4% were male. Patient's presentations ranged from lifestyle-limiting claudication to major tissue loss (Rutherford clinical categories 3–6). As in inclusion criteria, all had multilevel atherosclerotic occlusive disease, and they were classified according to the most proximal significant lesions into four subgroups (Table 1):

(1) Group A: CIA.
(2) Group B: EIA or common femoral.
(3) Group C: SFA.
(4) Group D: popliteal artery.

The more distal the proximal lesion is, the worst the category of presentation.

Otherassociated comorbidities and risk factors (e.g. hypertension and ischemic heart disease, smoking, renal impairment, hyperlipidemia, stroke, or chest disease) were recorded for each group, together with the numbers of risk factors and comorbidities in each individual patient as shown in Table 2.

As our purpose of the study is to assess the effect of either total revascularization or partial revascularization on limb salvage, following completion of the intended procedures, our population was classified into two major groups: one group had full revascularization for all/most of significant lesions ending in at least one direct vessel uninterrupted continuous flow to the foot (group F), whereas the other had those unfortunate

Table 1 Presentations in different subgroups

Presentation	A [*n* (%)]	B [*n* (%)]	C [*n* (%)]	D [*n* (%)]	Total presentation [*n* (%)]
Intermittent claudication	0	0	3 (4)	0	3 (3.0)
Rest pain	3 (50.0)	1 (20.0)	14 (6.7)	1 (16.7)	19 (18.8)
Minor tissue loss	3 (50.0)	4 (80.0)	55 (65.0)	5 (83.3)	67 (66.3)
Major tissue loss	0	0	12 (14.3)	0	12(11.9)
Total subgroup	6	5	84	6	101

P=0.482.

Table 2 The numbers of risk factors and comorbidities among the subgroups

Subgroup	Number of comorbidities					Total
	1	2	3	4	5	
A	0	1	3	2	0	6
B	0	0	4	1	0	5
C	3	16	38	21	6	84
D	0	3	1	2	0	6
Total	3	20	46	26	6	101

P=0.6.

Table 3 Patients' distribution among groups

Subgroup	F [*n* (%)]	P [*n* (%)]	Total
A	3 (3.6)	3 (16.7)	6 (5.9)
B	3 (3.6)	2 (11.1)	5 (5.0)
C	71 (85.5)	13 (72.2)	84 (83.2)
D	6 (7.2)	0 (0.0)	6 (5.9)
Total	83 (100)	18 (100)	101 (100)

P=0.065.

Table 4 Initial technical success according to presentation

Presentation	Intermittent claudication (%)	Rest pain (%)	Minor tissue loss (%)	Major tissue loss (%)	Total (%)
Initial technical success	94.7	94.7	97.0	75.0	94.1

P=0.029.

Table 5 The primary patency rates for groups F and P

Primary patency	F (%)	P (%)	Total (%)	*P*-value
At 3 month	91.6	50.0	84.2	0.001
At 6 month	77.1	38.9	70.3	0.002
At 12 month	72.3	33.3	65.3	0.002

Table 6 Secondary patency rates for groups P and F

Groups	F (%)	P (%)	Total (%)	*P*-value
At 6 month	84.3	44.4	77.2	0.001
At 12 month	78.3	38.9	71.3	0.001

Table 7 Major amputation and limb salvage rates in both patient groups

	F [*n* (%)]	P [*n* (%)]	Total [*n* (%)]
Above-knee amputation	4 (4.8)	3 (16.7)	7 (6.9)
Below-knee amputation	6 (7.2)	7 (38.9)	13 (12.9)
Total amputations	10 (12)	10 (55.6)	20 (19.8)
Total limb salvage	73 (88)	8 (44.4)	81 (80.2)

patients in whom our strategy was not fulfilled with absent direct continuous uninterrupted flow to the foot (group P). The distribution of group F and group P among different subgroups (A, B, C, and D) is shown in Table 3.

Antegrade approach was used in 73 (72.2%) patients, divided into ipsilateral femoral access in 69 patients and brachial access in four patients (using long sheath), whereas contralateral access with cross-over sheath was used in 28 (27.7%) patients. The lesions were crossed intraluminal in 54 (53.5%) patients and subintimal in 47 (46.5%) patients. Stents were used in 44 (44/101, 43.6%) patients. The initial technical success was significantly better in patients presented with minor tissue loss (97.0%) (Table 4).

Vessel perforation occurred in three patients, one in anterior tibial artery (ATA) and two in posterior tibial artery (PTA), and all were managed by prolonged balloon inflation.

Primary patency rate at 12 months was significantly higher in group F than in group P (72.3 vs. 33.3%; *P* =0.002), as shown in Table 5.

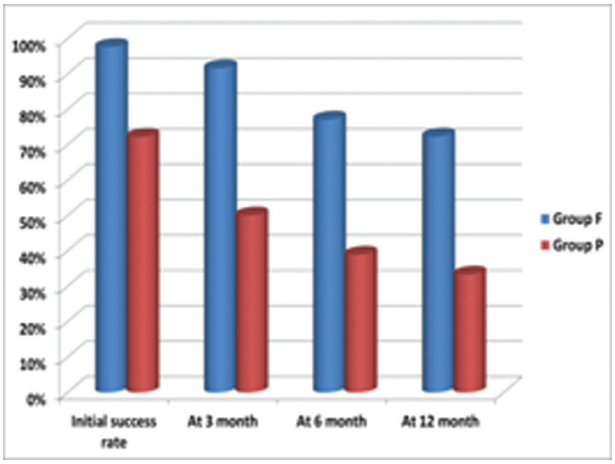
Reintervention was needed in eight patients owing to restenosis or total occlusion of the treated lesions presenting with either lost pulses, rest pain, or deterioration of the wound healing. The secondary patency rates were significantly higher in group F compared with group P at 6 months and at 12 months, as shown in Table 6.

We achieved a limb salvage rate of 80.2% (81 patients) and a major amputation rate of 19.8% (20 patients) over 1-year follow-up period. Above-knee amputation was done for seven (6.9%) patients and below-knee amputation for 13 (12.9%) patients in our study. Group F showed significantly higher limb salvage rate and significant lower amputation rate than group P (*P*=0.001). Furthermore, we had three not-procedure-related mortalities during the follow-up period (Table 7 and Figs 1 and 2).

Discussion

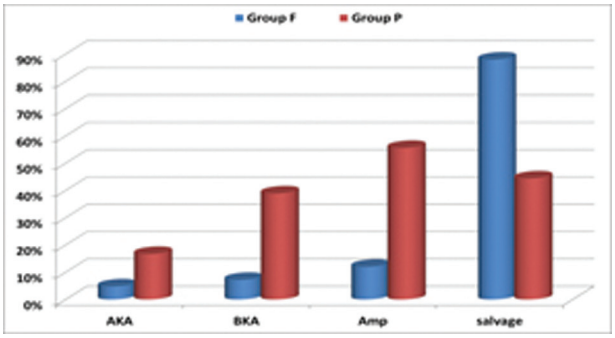
Diabetic vasculopathy (macrovascular disease) is the most common reason of mortality and morbidity in diabetes and is responsible for high incidence of vascular diseases such as stroke, myocardial infarction, and peripheral vascular diseases (PAD) [1]. Diabetics are up to 15 times more likely than nondiabetics to experience a major amputation. Diabetes is also associated with decreased primary patency following endovascular interventions [6]. Endovascular interventions for CLI continue to have variable reported results, adequate rates of limb salvage can be achieved in patients undergoing multilevel interventions for CLI, and improved patency is seen with multilevel compared with isolated tibial interventions [3]. In our study, 101 diabetic patients of different age and sex were scheduled for angioplasty

Figure 1



The primary patency rates for groups P and F.

Figure 2



Major amputation and limb salvage rates in both patient groups. AKA, above-knee amputation; Amp, amputations; BKA, before-knee amputation.

with multilevel arterial disease in lower limbs. All patients enrolled in our study were diabetics, and most of them had also other associated comorbidities and risk factors (e.g. hypertension, ischemic heart disease, smoking, renal impairment, stroke, or chest disease), which were presented in the study as numbers of comorbidities and risk factors for each patient. Among our 101 diabetic patients with critical lower limb ischemia, the technical success rate was 91.1%, and after 12 months of follow-up, primary patency rate, secondary patency rate, and limb salvage were 65.3, 71.3, and 80.2%, respectively. Our initial technical success was significantly better in patients with minor tissue loss (97.0%), patients with rest pain, and patients with intermittent claudication (94.7%) than in patients with major tissue loss (75%) (P=0.029).

Although there were no significant differences in primary patency rates between the different study subgroups (A, B, C, and D) at 12-month follow-up, primary patency was significantly higher in group F with full revascularization for all diseased arterial level than in group P, where the significant proximal lesions only were treated when we failed to deal with the distal level of occlusions. Such distal level of occlusion was the femoropopliteal segment in aortoiliac lesions or the tibial arteries in SFA lesion. Our secondary patency rate was 71.3%, and we noticed significantly higher secondary patency rates in group F compared with group P at 6 months (P=0.001) and at 12 months (P=0.001), but we did not notice significant differences of secondary patency rates between the different subgroups (A, B, C, and D). We also found that increasing numbers of risk factors and comorbidities had drawback on the primary patency rate at 3 month and 12 month and on limb salvage rates with increase in the amputation rate. Abularrage *et al.* [6] reviewed that diabetes mellitus is an independent predictor of decreased long-term primary patency after PTA/stent in 920 patients who underwent 1075 PTA/stent procedures, and long-term limb salvage remains inferior in diabetic patients compared with nondiabetic patients owing to a more severe clinical presentation and poor run-off. Miura *et al.* [7] in his study considered superficial femoral plus iliac lesions in addition to age, dialysis, left ventricular dysfunction, diabetes, hematoma prolonging hospitalization, and coronary artery disease as positive predictors of all-cause mortality.

Similar to our results, two studies of patients with multilevel lower limb arterial disease showed significantly improved secondary patency rates of multilevel intervention compared with single-level intervention. Sadek *et al.* [4] in a study for endovascular therapy of multilevel lower limb arterial lesions on 85 patients mentioned a limb salvage rate of 81%, similar to our limb salvage rate of 80.2%. Their group F patients showed significantly higher limb salvage rate and significant lower amputation rate than group P, but there were no significant differences in limb salvage rate or major amputations rate between the different subgroups (A, B, C, and D) [4]. Fernandez *et al.* [3] showed a limb salvage rate of 81% for isolated tibial disease and 95% for multilevel arterial lesions (P=0.05). Wound healing was achieved in 69% in isolated tibial lesions and in 87% in multilevel disease (P=0.05) [3].

Guo *et al.* [2] in a study including 53 patients with TASC II D femoropopliteal occlusive disease showed a technical success rate of 95% with mean follow-up period of 12.2±6.1 months (5–38 months). Primary

patency rate at 1 year was 63%, assisted primary patency rate at 1 year was 77%, and secondary patency rate at 1 year was 96%. These results were significantly better than our results because they included lesions in femoropopliteal segment only which was treated mainly by primary stenting whereas other levels of arterial lesion were not included [2].

We also noticed that patients who presented with minor tissue loss or rest pain showed significantly higher limb salvage rates whereas patients who presented with major tissue loss showed higher amputation rates. These findings were reported before in a study by Ghoneim *et al.* [8] for lower limb multilevel arterial diseases which showed that the presence of major tissue loss was associated with a significantly worse limb salvage rate with total limb salvage rate of 90.7% at 2-year follow-up.

In most of diabetic patients with multilevel arterial lesions, the tibial arteries most often are heavily calcified and plagued by long occlusive lesions, which add to the complexity of the procedure if the decision was taken to treat those below-the-knee tibial lesions after correction of the proximal aortoiliac or femoropopliteal disease with more radiation exposure and more contrast dye used. Graziani *et al.* [9] in their study reported that 66% of all below-the-knee lesions were occlusions in 417 diabetic patients with critical lower limb ischemic and foot ulcer, and 50% were occlusions >10 cm. Moreover, the vascular involvement is extremely diffuse and particularly severe in tibial arteries, with high prevalence of long occlusions [9]. If the original presentation was not in any form of tissue loss (i.e. incapacitating claudication or rest pain), it may be prudent to correct the proximal disease only if full correction of all lesions is technically challenging with close observation of clinical improvement. If no improvement was achieved in the early postintervention period, patients may be scheduled for secondary intervention to treat the distal disease at a second stage. So, based on our findings, we can outline that in diabetic patients with multiple levels of arterial diseases, all efforts should be exerted to achieve total correction of all lesions to secure good in-line pulsatile flow to the foot. Correction of the proximal lesions only cannot be considered satisfactory especially in patients presenting with tissue loss as it is usually associated with inferior patency rates and low overall limb salvage rates.

There are some limitations of the present study: first, this is a single-arm study without a control group. Therefore, the rates of technical success, patency rates, and limb salvage rates were not assessed for comparison with a single-level lesion or nondiabetic patients, and hybrid procedure was not included in the management as minimally invasive procedures in medically high-risk patients with complex anatomy. Second, study design was prospective which added a limitation affecting the number of patients and their distributions in the groups. Finally, we have relatively large number of patients who were lost to follow-up for more than 1 year. This may be attributed to socioeconomic factors and lack of proper insurance system. So, we consider these results as midterm results.

Conclusion

In diabetic patients with multiple level of arterial atherosclerotic lesions affecting more than one arterial territory, all efforts should be exerted to achieve total correction of all arterial lesions with direct pulsatile flow to the foot as it is associated with better primary and secondary patency rates and significantly higher limb salvage rates than correction of the proximal arterial lesions only.

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Conflicts of interest

There are no conflicts of interest.

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