Mid-term outcomes of endovascular interventions of critical lower-limb ischemia in patients with chronic renal failure

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Objective
Investigating the early results of percutaneous transluminal angioplasty of chronic lower-limb ischemia in patients with chronic renal failure.
Background
The concern that endovascular treatment of chronic lower-limb ischemia in patients with chronic renal failure is gaining popularity nowadays since the increase in morbidity and mortality rates in bypass surgery makes the procedure difficult for these patients.
Patients and methods
In total, 40 limbs in 40 consecutive patients (28 male, mean±SD age 59.65±8.54) were analyzed, 28 with lesion, either gangrene or ulcer, and 12 with rest pain. The follow-up of healing and foot vascularity was done at regular periods and up to 1 year as ABI was not a good indicator for follow-up because of the high false results due to severe calcification.
Results
After 12 months, the end results of the study are as the following: 10 (25%) cases were relieved from rest pain, another 12 (30%) cases had healed lesion, and three (7.5%) cases had major amputation, 11 (27.5%) cases had return of the same complaint as preoperative by the end of 12 months.
Conclusion
Despite improvement in endovascular techniques and their increasing utilization for lower-extremity revascularization, peripheral revascularization in chronic renal-failure patients has not led to high limb-salvage rate. Poor outcomes may be related to the severity of ischemia on presentation, the cumulative burden of the atherosclerotic disease, and the distal location of the disease.

Keywords:
chronic limb ischemia, chronic renal failure, endovascular therapy, limb salvage

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Introduction

Peripheral arterial disease is common in patients with chronic renal failure. Chronic limb ischemia, defined clinically as claudication pain, ischemic rest pain, nonhealing ulcers, or gangrene, represents an extreme manifestation of peripheral arterial disease [1,2].

The arterial system in chronic renal-failure patients undergoes structural remodeling, which may be quite similar to changes with aging, and is characterized by diffuse dilation, hypertrophy, and stiffening of the aorta and major arteries – although part of the arterial alterations in chronic renal-failure patients is associated with the aging process. Several features of arterial remodeling observed in chronic uremia are different, however, from those of the natural aging process. Remodeling is an active process aiming to maintain a constant tensile and/or shear stress. Arterial remodeling usually occurs in response to long-term changes in hemodynamic (physical) conditions, interaction with locally generated growth factors, vasoactive substances, and inflammatory mediators [3,4].

Acute variations in flow and shear stress modulate arterial diameter through the phenomenon of flow-dependent vasodilation. When increased during an augmentation in blood flow, shear stress induces an adaptive and functional enlargement of the vessel that acts as negative feedback to normalize the stress. This is accomplished through shear-stress release of nitric oxide (endothelium-dependent relaxing factor), hyperpolarizing factor, and release of prostacyclin. In end-stage renal-failure patients, a similar effect of chronically increased blood flow was observed in arteries of the arm bearing dialysis fistula [5].

Patients with chronic renal failure experience a higher rate of limb loss than patients with normal renal function. The rates of major lower-extremity amputations in the dialysis population have been estimated to be 4.3% after 1 year, and 13% among dialysis patients with diabetes [6].

Several factors may contribute to this poor outcome. Dialysis patients typically develop diffuse heavily calcified atherosclerotic lesions, frequently involving tibial arteries and small vessels of the pedal branches. A large percentage of dialysis patients suffer from diabetes, which in itself is a risk factor for atherosclerosis [7]. They commonly have increased susceptibility to lower-extremity life-threatening infections, which is an additional factor that may contribute to a poor outcome. In addition, dialysis patients who undergo reconstructive surgery for chronic limb ischemia experience higher perioperative mortality rates, reduced rates of graft patency, and poor limb-salvage rates compared with nondialysis patients [8,9].

Indeed, chronic renal failure has been shown to be an independent risk factor for major amputations following surgery, and the presence of renal insufficiency is an independent predictor for higher mortality in chronic limb ischemia. For patients undergoing revascularization because of these poor prognostic factors along with dialysis patients with forefoot and deep-heel defects or in extensive infection, primary amputation should be considered as some authors have advocated that revascularization should not be attempted for such patients [10].

The endovascular approach to peripheral arterial disease is gaining widespread use in the management of lower-extremity ischemia. These percutaneous interventions were found to reduce procedural morbidity and mortality. They can be performed under local anesthesia with minimal blood loss and fluid shifts, frequently in an elective setting and with reduced operative time compared with open surgery [11,12]. Intuitively, it would seem particularly attractive in high-risk populations such as dialysis patients, who are frequently prohibited from undergoing open surgical procedures.

Despite the above, it is somewhat surprising that the success rates of treating chronic limb ischemia in this challenging population remain obscure, and data regarding patency of treated vessels and limb-salvage rates are scarce [13].

Aim

The aim of the work was to assess the results of percutaneous transluminal angioplasty with or without stenting for chronic lower-limb ischemia in chronic renal-failure patients.

Patients and methods

A prospective study was carried on 40 patients admitted in Vascular Surgery Department of Alexandria University from July 2017 to February 2019. Patients who were complaining of chronic renal disease and suffering from chronic lower-limb ischemia were admitted to the Vascular Surgery Unit, Alexandria Main University Hospital. This research was performed at the Department of General Surgery, Alexandria University Hospitals. Ethical Committee approval and written, informed consent were obtained from all participants.

Inclusion criteria

(1) Patients known to be an end-stage renal disease on regular dialysis, and complaining of chronic lower-limb ischemia.

Exclusion criteria

(1) Patients with chronic lower-limb ischemia with normal renal function.
(2) Patients with long-segment occlusion and not amenable for endovascular intervention.

Methods

All patients were preoperatively assessed as regards to the present condition and symptoms related to critical lower-limb ischemia as well as associated comorbid conditions. They were clinically examined to assess their general condition, and the lower limb was locally examined. Dedicated duplex-ultrasound study was done for all patients. Cardiac and laboratory blood tests were also done before the intervention.

(1) Endovascular interventions were done through femoral percutaneous transluminal angioplasty.
(2) All patients prepared by loading a dose of Clopidogrel 600 mg a day before intervention.
(3) Local anesthesia or spinal anesthesia was used.
(4) All patients were given 5000 IU heparin intravenous before the start of the procedure and was not reversed by the end of the procedure.
(5) The duration of compression depended on the size of the sheath (sheath 6). Any prolonged duration of compression was recorded (arterial calcification does not allow for recoil of artery after puncture).
(6) After revascularization, debridement and amputation of the gangrenous tissues were done, except for dry gangrene, which was left for demarcation by dressing and left for delayed intervention.

Results

The study was conducted on 40 chronic ischemic limbs of 40 patients complaining of chronic kidney failure.

Patients' age at the time of intervention ranged between the ages 40 and 72 years, with mean age (±SD) 59.65 (±8.54). There were 28 (70%) male patients and 12 (30%) females (Table 1). About 45% of the patients were smokers, while 5% were ex-smokers. About 70% of the patients were diabetic, 80% were hypertensive, 30% were cardiac, one patient had a history of cerebrovascular stroke, and one patient had ascites and liver cirrhosis (Table 2). Twenty-eight (70%) patients were presented with foot lesion in the form of ischemic ulcers and/or gangrenous toe or toes. Meanwhile, 12 (30%) patients were presented by rest pain (Table 3).

All the cases were done by percutaneous transluminal angioplasty. Trials to dilate every vessel with adequate distal runoff were done.

Based on clinical and radiological data, some cases were done under local anesthesia, which is better for chronic renal-failure patients as multiple comorbidities. However, 28 cases were done under spinal anesthesia for further surgical intervention.

All the cases had infragenicular artery disease (tibialis disease) and trials to dilate one or more vessels were done. In addition to the tibialis disease, 20 (50%) cases had femropopliteal disease and only two (5%) cases had iliac-artery lesion.

Table 1 Demographic data

	Total (*N*=40)
Age (years)	
Minimum–maximum	40–72
Mean±SD	59.65±8.54
Sex [*n* (%)]	
Male	28 (70)
Female	17 (30)

Table 2 Comorbidities

	n (%)
Smoking	18 (45)
Diabetes mellitus	28 (70)
Hypertension	32 (80)
Cardiac	12 (30)
Ascites and liver cirrhosis	1 (2.5)

Table 3 Clinical presentation

	n (%)
Ischemic ulcer/gangrene	28 (70)
Rest pain	12 (30)

The inflation needed to be prolonged to more than 3 min because of balloons faced by severe resistance during dilatation with significant residual stenosis due to severe calcification.

Additional immediate interventions following the procedures were needed in 28 patients who were complaining of foot lesion (ischemic ulcers and/or gangrenous toe or toes) as the following:

(1) Ten cases needed immediate minor toe(s) amputation.
(2) Six cases needed metatarsal amputation where the amputated stump was led opened or slightly approximated with no tension.
(3) Twelve cases needed minor debridement or ulcer curettage.

Additional revision was done a few days after intervention, until the stabilization of line of demarcation:

(1) Two cases needed further metatarsal amputation.
(2) Two cases needed major amputation for BKA and one case needed AKA.

According to complication, 10 (25%) patients had ecchymosis and a small noncommunicating groin hematoma at the puncture site, which was confirmed by duplex ultrasound, and all these patients were conservatively managed successfully. Two (5%) patients suffered from communicating hematoma and pseudoaneurysm with ecchymosis and edema of the thigh, which was managed by Doppler probe compression and good compression for 24 h. Post-duplex ultrasound showed occlusion of neck of pseudoaneurysm and no other complication was seen as vessel perforation, distal embolization, and A–V fistula.

Follow-up

According to end results and follow-up of the cases, it is obvious that late presentation of cases led to bad outcomes. Nevertheless, the results of the cases with rest pain were better than those with lesion (gangrene or ulcer) (Tables 4–7).

Table 4 Follow-up of cases presented with rest pain (*N*=12)

	Rest pain [*n* (%)]		
	Decreased	Disappeared	Recurrence
1 week	2 (17)	10 (83)	0
1 month	0	12 (100)	0
6 months	0	10 (83)	2 (17)
1 year	0	10 (83)	2 (17)

Table 5 Follow-up of cases presented with ischemic lesions (*N*=28)

	Ischemic lesions (*N*=26) at 6 months [*n* (%)]				
	Curettage	Healed	Minor amputation	Major amputation	Death
1 week	12 (30)	0	14 (40)	1 (2.5)	0
1 month	2 (5)	8 (20)	2 (5)	2 (5)	0
6 months	0	3 (7.5)	–	0	2 (5)
1 year	0	1 (2.5)	–	0	–

Table 6 Distribution of the studied cases according to fate (*N*=40)

	n (%)
Fate	
Saved limbs	
Healed	12 (30.0)
Healing	2 (5.0)
Rest pain disappears	10 (25.0)
Total	24 (60.0)
Lost limbs	
Major amputation	3 (7.50)
Re-occlusion	11 (27.5)
Death	2 (5.0)
Total	16 (40.0)

Table 7 Relationship between success and clinical presentation (*N*=19)

Complaints	Success [*n* (%)]		χ^2	^{FE}P
	No	Yes		
Rest pain (*N*=12)	2 (5)	10 (25)	0.153	0.033
Ischemic lesions (*N*=28)	14 (35) 2 deaths)	14 (35)		

χ^2, *P*, χ^2 and *P* values for χ^2 test for comparing between the two groups. ^{FE}P: *P* value for Fisher exact for χ^2 test.

Discussion

Patients with chronic kidney disease (CKD) on regular dialysis who develop critical limb ischemia (CLI) are at significant risk of limb loss. The use of endovascular modalities in the treatment of CLI is gaining popularity because endovascular intervention is more suitable for patients with CKD compared with open surgery as those patients experience multiple morbidity and mortality rates with poor healing power when it comes to the latter [14].

The main problem in CKD patients is the severely calcific vessel, which mainly involves distal arteries, as most cases had infragenicular and pedal disease.

Poor outcome of endovascular management of cases of chronic lower-limb ischemia in CKD patients is increased by delayed presentation.

It is conceivable that timing the intervention for revascularization at an earlier stage, prior to the development of irreversible tissue loss, may yield a more favorable outcome. Another factor for the poor outcome is the presence of an open wound, rather than gangrene, which predisposes the patients (who are mostly diabetics) to severe limb-threatening infections, thus resulting in a higher amputation rate.

The technical improvements in dedicated endovascular devices as well as the experience obtained throughout the last few years with infrainguinal and infragenicular endovascular procedures will improve the outcome of these cases.

Silverberg *et al.* [3], Brosi *et al.* [14], and Graziani *et al.* [4] studied the intermediate and long-term outcome (with a mean period of follow-up range for 12 months) of endovascular treatment in patients with CKD. The presented study was done to assess the results (with a follow-up period up to 12 months) of endovascular treatment of chronic lower-limb ischemia in patients with CKD.

On one hand, similar to Brosi *et al.* [14], who reported their experience with percutaneous balloon angioplasty in 29 dialysis patients, the presented study included 40 end-stage renal-disease patients with chronic lower-limb ischemia. On the other hand, Graziani *et al.* [4] studied the long-term outcomes of treated 107 dialysis patients presenting 132 ischemic limbs.

The mean age of the present study was (±SD) 59.65 (±8.54). This was close to the mean age of Silverberg and colleagues, which was around (±SD) 69.65 (±8.54). The sex of the patients in the presented study was 28 (70%) males and 12 (30%) females. Compared with other studies, those of Silverberg *et al.* [3] were 29 (71%) males and 12 (29%) females.

While comparing the risk factors of patients, in the presented study, 70% of the patients were diabetic, 80% were hypertensive, and 45% smokers as major risk factors of peripheral ischemia in addition to the renal condition. Silverberg *et al.* [3] study had 82% of diabetic patients, 87% hypertensive, 14% current smokers, and 14% ex-smokers.

Regarding the patients' clinical presentation in the presented study, 28 (70%) patients were presented with ischemic lesions (Rutherford 5), whereas the remaining 12 (30%) patients were presented with rest pain (Rutherford 4). This is quite similar to Silverberg *et al.* [3], who included 41 patients with 50 limbs, of which 17 (34%) limbs were in Rutherford 4 and 33 (66%) limbs were in Rutherford 5.

Silverberg *et al.* [3] included 50 limbs of chronic ischemia that showed 17 (34%) iliac lesions, 43 (86%) cases with SFA lesions, and 50 (100%) cases with tibial disease. In the presented study, two (5%) cases showed iliac disease, 20 (50%) cases showed SFA disease, and 20 (100%) cases showed tibial diseases. Regarding the technical success in the presented study, it was 100% in iliac lesions, 100% in SFA lesions, and 65% in tibial lesions. Compared with other studies such as those of Silverbergs *et al.* [3], whose success was 100% for iliac lesions, 72% for SFA lesions, and 42% for tibial lesions, higher technical success of the presented study in tibial lesions may be due to multiple trials to pass lesions.

The limb-salvage rate in the presented study was 60% after 12 months of follow-up. Poor outcomes included distal tibial diseases, severe calcification, delayed presentation, presence of diabetes, low immunity, and poor healing power. Brosi *et al.* [14] reported after 12 months of follow-up that the limb salvage was achieved in 73% of their patients. Silverberg *et al.* [3] reported 65% after 12 months of follow-up with mean time of amputation about 6 months. The factors associated with poor outcome included the presence of diabetes and a higher number of treated tibial lesions. The authors concluded that amputations were most probably related to the severity of the pedal artery calcification with involvement of the pedal arch.

In the presented study, follow-up was for 12 months. During this period, three patients required major amputation, and four (10%) patients required reintervention by the end of the sixth month (one patient had recurrent gangrenous stump of little toe, while another patient had a return of rest pain and re-occlusion of tibial vessel proved by duplex study). Two (5%) deaths occurred after 6 months, one from liver failure and hepatic encephalopathy and the other from coronary ischemia.

According to Silverberg *et al.* [3], mean follow-up was 12 months. During this period, 19 (44%) patients required major amputations within an average time of 6 months. The factors associated with a higher rate of amputation included the presenting symptoms, nonhealing wounds, infection and gangrene, and the presence of diabetes. Six (14%) patients required reintervention during the first year. Six (14%) deaths happened, four patients died from sepsis and two from coronary ischemic events.

Abou-Zamzam *et al.* [15] studied the factors leading to major amputation and found that huge tissue loss was an independent predictor of treatment by primary amputation as compared with revascularization. Closely, all the patients suffered from extensive tibial disease, and it was conceivable that the timing of the intervention for revascularization at an earlier stage, prior to the development of irreversible tissue loss, may yield a more favorable outcome. In addition, wet gangrene and severe infection due to poor immunity and weak healing power in patients with chronic renal failure were seriously noted.

The survival rate of this study was higher compared with other reports. Vogel *et al.* [13] reported survival rates of 72% after 1 year. It is possible that earlier amputation with removal of the ischemic-infected limb might have prevented septic complications, resulting in an improved overall survival rate. In the presented study, the survival rate was 95%. Only two cases died after 6 months from the period of follow-up. The survival rate was high as some cases were done under local anesthesia to decrease the periprocedure morbidity and mortality rate.Early debridement of dead tissues to avoid sepsis and frequent dressing and good medical management of patients is a must postoperatively.

Following the procedures, close follow-up and revision were needed, as nine (35%) cases needed immediate intervention, whether it was a minor amputation or debridement to avoid septic complication.

In comparison with the results of bypass surgery in end-stage renal disease patients, Fallon *et al.* [16] said that among the 689 patients undergoing lower-extremity revascularization, 90% of revascularizations were performed for CLI and 8% for claudication. Overall survival at 1 and 2 years remained low at 60 and 43%, respectively. Again, 1-year and 2-year amputation-free survival rates were 40 and 17%, respectively. Survival and freedom from major adverse limb-event outcomes differed between revascularization techniques, although Torsello *et al.* [17] tried the use of drug-coated balloon for lesion dilatation with fair long-term outcomes. At 2 years, endovascular patency was higher than open bypass (76 vs. 26%) [14]. Kodama *et al.* [18] clarified that clinical outcomes following critical limb vascularization were toward angioplasty rather than bypass. So endovascular management of chronic lower-limb ischemia in patients with end-stage renal disease has better results than bypass surgery, but the result is still poorer than it is for patients with normal renal functions when it comes to the clinical outcomes and survival rates.

Conclusion

Despite improvement in endovascular techniques and their increasing utilization for lower-extremity

revascularization, peripheral revascularization in chronic renal-failure patients has not led to high limb-salvage rate. The poor outcome may be related to the severity of ischemia on presentation, the cumulative burden of the atherosclerotic disease, and the distal location of the disease.

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No conflict of interest.

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