

CALCIUM LOADING IMPACT ON ENDOVASCULAR MANAGEMENT OF INFRAGENICULAR BLOCK IN DIABETIC PATIENTS

By

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ABSTRACT

Background: Diabetes mellitus (DM) is one of the strongest predictors of peripheral arterial occlusive disease, and a significant risk factor for the progression of an asymptomatic disease or claudication into critical limb ischemia (CLI). (CLI) is the most advanced stage of peripheral arterial occlusive disease. The prognosis is poor, with amputation rates up to be 30%.

Objective: To assess the calcium burden of infragenicular native vessels in diabetic patients, to clarify its impact on primary and secondary patency rate (1ry and 2ry) and efficacy of endovascular management.

Patients and Method: Between 2018 and 2020, data from 30 consecutive diabetic patients with tibial arteries calcifications, at Al-Zahra'a University Hospital. All patients underwent lower extremity computed tomographic angiography (CTA) before the intervention. Based on CTA, tibial artery calcification (TAC) severity was categorized into three groups: minimal calcification (12 patients), intermediate calcification (10 patients), or extensive calcification (8 patients), with a total number of 42 limbs (12 patients were affected bilaterally). Immediate and late outcomes of the interventions were compared.

Results: There was a high correlation between calcification of tibial arteries and both DM and smoking. Claudication, rest pain, and major tissue loss presentation between all groups were higher in patients with extensive calcifications. Technical success rate was 88.1%, and primary patency rate was 83.3%. The 2-year patency rate for minimal calcification was 100%, 92.9% in the intermediate group, and 71.4% in the extensive group.

Conclusion: The outcomes of endovascular treatment (EVT) for patients with TAC were acceptable, with better technical success in minimal and intermediate calcification than extensive calcified lesions.

Keywords: Endovascular Treatment, Revascularisation, Tibial Artery Occlusion.

INTRODUCTION

Globally, over 170 million people have been diagnosed with DM, and by the year 2030, the prevalence is estimated to raise 2.5 fold (*Armstrong et al., 2013*). DM is

one of the strongest predictors of peripheral arterial occlusive disease and a significant risk factor for progression of the asymptomatic disease or claudication into CLI (*Thiruvoipati et al., 2015*).

Diabetic patients who develop CLI are more prone to ischemic events with an impaired functional status. Approximately, 80 % of diabetes-related lower limb amputations are preceded by a diabetic foot ulcer (*Hingorani et al., 2016*).

Treatment of CLI aims at wound healing, improvement in the quality of life, limb loss prevention, and prolonged survival. Current strategies propose open or endovascular revascularization of tibial arteries with runoff through the ankle, but not specifically targeted to the location of ischemia (*Bosanquet et al., 2016*).

Still, clear evidence of severe calcification is frequently observed in patients affected by metabolic disorders such as diabetes and chronic renal disease, and in general in the elderly population. Technical success and patency rates are reported to be lower in the case of highly calcified arteries (*Schillinger and Minar, 2012*).

Severe calcium completely alters morphology and compliance of the arterial wall reducing the effect of both angioplasty and stenting. Moreover, it increases the occurrence of flow-limiting dissections after percutaneous transluminal angioplasty (PTA) and acute vessel recoil, with the consequent increased use of stents. Also, in this condition, calcium persists in playing an unfavorable role by increasing the risk of stent sub expansion, malposition, and fractures as shown in the coronary environment (*Cioppa et al., 2012*).

The present work aimed to assess the calcium burden of infragenicular native vessels in diabetic patients, to clarify its

impact on 1ry and 2ry patency rate and efficacy of endovascular management.

PATIENTS AND METHODS

Between 2018 and 2020, data from 30 consecutive diabetic patients with the peripheral arterial occlusive disease (affecting only tibial arteries), at Al-Zahra'a University Hospital with 42 limbs with chronic tibial artery stenosis, and/or occlusion who were treated with endovascular angioplasty were reviewed. All patients underwent lower extremity CTA before the intervention.

Based on CTA, TAC severity was categorized into three groups: Minimal calcification was defined as spotty calcification of the target tibial artery in which the calcium mass was 10 mm or less and the total extent of calcification applied to <10% of the target vessel (12 patients). Extensive calcification was defined as linear calcification that extended longer than 50 mm or diffuse calcification that was distributed >50% of the total length (8 patients). Any TAC falling between these ranges was categorized as intermediate calcification (10 patients). If multiple tibial arteries were treated, we selected the artery with a lesser degree of calcification as the index target vessel, with a total number of 42 limbs (12 patients were affected bilaterally).

Patients with inflow block, i.e. multi-level arterial lesions, or the age of the patients < 30 years old and > 70 years old excluded.

Electronic medical records and angiography images were reviewed for demographic data, anatomic lesion,

procedural factors, complications, and other outcome variables.

All patients underwent preoperative duplex ultrasonography examinations with Ankle peak systolic velocity (APSV) measurement to determine the need for EVT. Additionally, all patients had radiological imaging CTA before therapeutic intervention.

Pre-intervention patients have received antiplatelet in the form of Aspirin (75-150mg/day) and Clopidogrel bisulfate (75 mg/day) were initiated at least 5 days before endovascular interventions. In those patients who did not complete their course of clopidogrel as instructed, clopidogrel loading dose (300 mg/day) was initiated on the same day. The procedure was performed in a fully equipped endovascular suite. The procedure was performed under local infiltration anesthesia.

Technical success was defined as the re-establishment of direct "in-line" flow to the foot through at least one tibial artery with no significant residual stenosis.

Primary patency was defined as Freedom from re-stenosis (Ultrasound patency) during the follow-up (persistent patency without any re-intervention).

Secondary patency was defined as a recurrent tibio-peroneal disease with a focal increase of at least 140% in the peak systolic velocity (PSV) was considered indicative of > 50% restenosis at that site, with a return of the symptoms were subjected to re-intervention.

Clinical follow-up data were collected and recorded at each clinic visit. Follow-up was conducted in Al-Zahra's vascular surgery outpatient clinic. Assessment of the patency rate at (1, 6, 12 and, 24 months after the procedure) was done by using duplex ultrasound. Patients who had a return of symptoms or worsening in ulceration, or a change APSV underwent further CTA imaging and endovascular re-intervention was done.

Statistical analyses: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, and standard deviation. The significance of the obtained results was judged at the 5% level. Comparisons between patients with minimal, intermediate, and extensive calcification were performed using the Chi-square or Fisher's exact tests.

RESULTS

The number of patients with minimal, intermediate, and extensive calcification was 12 (40%), 10 (33.3%), and 8 (26.7%) respectively. Demographic data were Min. – Max age of 48.0 – 68.0 which meant that TAC was the disease of the elderly. Sex distribution showed a male preference for this disease. According to co-

morbidities, all patients were diabetic, followed by hypertension (HTN) then dyslipidemia.

Smoking prevalence was 76.7%. There was a high correlation between calcification of tibial arteries and both DM and smoking (**Table 1**).

Table (1): Demographic data and co-morbidities distribution of the study group

Parameters \ Groups	Total patients (n = 30)	Minimal calcification	Intermediate calcification	Extensive Calcification
		(n = 12) (40%)	(n = 10) (33.3%),	(n = 8) (26.7%)
Sex				
Male	18 (60%)	7 (58.3%)	6 (60%)	5 (62.5%)
Female	12 (40%)	5 (41.7%)	4 (40%)	3 (37.5%)
Age (years)				
Min. – Max.	48 – 68	48 –66	50–68	54–68
Mean ± SD.	58.2± 6.58	54.83±5.57	59.4±6.76	61.75±5.99
Risk factors				
DM	30 (100%)	12 (100%)	10 (100%)	8 (100%)
Smoking	23 (76.7%)	8 (66.7%)	8 (80%)	7 (87.5%)
HTN	18 (60%)	5 (41.7%)	6 (60%)	7 (87.5%)
IHD	9 (30%)	2 (16.7%)	3 (30%)	4 (50%)
Dyslipidemia	16 (53.3%)	4 (33.3%)	6 (60%)	6 (75%)
CVD	12 (40%)	3 (25%)	5 (50%)	4 (50%)
Renal CR>1.1<1.5	8 (26.7%)	1 (8.3%)	2 (20%)	5 (62.5%)
COPD	4 (13.3%)	1 (8.3%)	1 (10%)	2 (25%)

A total of 42 limbs (30 patients) had been evaluated with anatomic variables, access site, and the time of the procedure. Most of the patients were treated for rest pain (66.7%), which was higher in the extensive calcification lesions than the 2 other groups. Technical success was 88.1% overall the patients, with lower

technical success in the extensive group (71.4%) in comparison to the intermediate and the minimal group (92.9%) and (100%) respectively. Technical failure was higher in the extensive group about (28.6%) due to failure to pass the calcified lesion (**Table 2**).

Table (2): Clinical presentation and completion angiography of the studied cases

Parameters \ Groups	Total limbs (n = 42)	Minimal calcification	Intermediate calcification	Extensive Calcification	P
		(n = 14 limb)	(n = 14 limb)	(n = 14 limb)	
Rest Pain	28 (66.7%)	7 (50%)	7 (50%)	14 (100%)	<0.001
Major tissue loss	14 (33.3%)	0 (0.0%)	3 (21.4%)	11 (78.6%)	<0.001
Minor tissue loss	15 (35.7%)	7 (50.0%)	5 (35.7%)	3 (21.4%)	0.288
Claudication category 2	15 (35.7%)	8 (57.1%)	7 (50.0%)	0 (0.0%)	<0.001
Claudication category 3	21 (50%)	0 (0.0%)	7 (50.0%)	14 (100%)	<0.001
Completion angiography					
Passed	37 (88.1%)	14 (100%)	13 (92.9%)	10 (71.4%)	0.023
Failed	5 (11.9%)	0 (0.0%)	1 (7.1%)	4 (28.6%)	

Follow-up of all cases in 1,6,12 and 24 months for patency, revealed statistical significance in the primary patency between all groups during the follow-up. The primary patency rate after 1 month was (83.3%) overall limbs. Patency at follow-up was documented by color duplex ultrasound with the result of <50%

diameter reduction, while 50% or more diameter reduction denoted restenosis and indicated for re-intervention of the treated artery. Re-intervention was done in the cases of restenosis with secondary patency about 92.9% in the intermediate group and 71.4% in the extensive group at 24 months (Table 3).

Table (3): Primary patency of all cases during follow-up

Follow up	Total limbs (n 42)	Calcification of Ca loading						P
		Minimal (n = 14 limb)		Intermediate (n = 14 limb)		Extensive (n = 14 limb)		
		No.	%	No.	%	No.	%	
First month								
Occluded	7 (16.7%)	0	0.0	1	7.1	6	42.9	<0.002
Patent	35 (83.3%)	14	100.0	13	92.9	8	57.1	
6 months								
Occluded	7 (16.7%)	0	0.0	1	7.1	6	42.9	<0.002
Patent	35 (83.3%)	14	100.0	13	92.9	8	57.1	
12 months								
Occluded	6 (14.3%)	0	0.0	2	14.3	4	28.6	0.036
Patent	36 (85.7%)	14	100.0	12	85.7	10	71.4	
24 months								
Occluded	5 (11.9%)	0	0.0	1	7.1	4	28.6	0.023
Patent	37 (88.1%)	14	100.0	13	92.9	10	71.4	

DISCUSSION

Our study was performed on 30 diabetic patients as diabetes is one of the strongest predictors for peripheral arterial disease with a technical success rate (88.1%), and primary patency rate (83.3%) overall patients.

In another study, infrapopliteal angioplasty was performed on patients with CLI. The median follow-up was 30 months. Diabetic patients were 75%. There were no significant differences between the diabetic group and non-diabetic group in technical success rate (Ryu et al., 2012). The reported technical success rates of endovascular intervention for below-the-knee lesions are variable,

ranging from 70% to 96% (Iida et al., 2012).

The primary goals of treatment for critical limb ischemia (CLI) are alleviation of ischemic rest pain, healing of arterial insufficiency ulcers, and improving quality of life. These goals are directed toward preventing limb loss and CLI-related mortality. Arterial revascularization serves as the foundation of a contemporary approach promoting amputation-free survival (Bunte and Shishehbor, 2013).

In our study, we found that patient’s presentation mostly for the alleviation of rest pain was 66.5%, and tissue loss with significant statistical presentation between

the three groups to be higher in extensive group.

Balloon angioplasty of the tibial arteries in patients with critical limb ischemia is considered as the main endovascular treatment modality for infrapopliteal disease, even with severe disease. There is no evidence that primary stenting improves patency or limb salvage compared to PTA alone (*Rana and Głowiczki, 2012*). In our study, we used balloon angioplasty without stenting of the treated arteries with technical success (88.1%) overall cases.

Although CTA is regarded as the most sensitive imaging modality for detecting calcification, it lacks sufficient resolution to determine whether the calcification is within the tunica intima, media, or both (*Lanzer et al., 2014*). In general, the presence of heavily calcified occlusions poses a great challenge to endovascular treatment (*Rocha-Singh et al., 2014*). Calcified lesions are generally difficult to cross with wires or balloons, and they prevent sufficient dilation. Furthermore, the lesions tend to be easily dissected or recoiled after balloon dilation, leading to restenosis.

In this study, extensive calcification in the tibial arteries was associated with lower technical success than minimal calcification or intermediate calcification.

Our results agreed with previous studies, which have demonstrated that arterial calcification increases the risk of amputation or mortality for patients with peripheral artery disease (*Huang et al., 2014*). However, few studies reported tibial artery calcification as a risk factor for the failure of endovascular intervention or amputation after

endovascular therapy. Endovascular treatment was successful in only 70% of the ESRD patients with CLI due to isolated infrapopliteal lesions, and calcified lesions were identified as an independent predictor of major amputation (*Nakano et al., 2015*).

In general, longer lesions, poor runoffs, infection, diabetes, and chronic kidney disease (CKD) are risk factors for amputation after infrapopliteal endovascular treatment (*Kawarada et al., 2012*).

This study has several limitations. It was in a single-center, small cohort study, which has the limitations of such studies. The three patients groups differed in baseline clinical and angiographic characteristics.

However, the severity of tibial artery calcification is reflective of general comorbidities, making it difficult to have patient groups with comparable baseline characteristics that differ only in the severity of calcification. End-stage renal patients with moderate to severe renal affection were not represented in this study because the use of contrast-enhanced CTA is limited in this population.

We recommended assessing the grade of calcifications at the level of the treated tibial lesion, CTA images may be used.

CONCLUSION

Infragenicular angioplasty can be performed safely with favorable results. Primary patency is related to disease extent. Secondary interventions may be necessary to maintain clinical success. These data indicated that PTA should be considered as initial therapy for

infragenicular occlusive disease in diabetic patients. A higher number of patients and a long duration of follow-up may be needed to further study the outcome of isolated tibial lesions in diabetic patients.

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تأثير وجود الكالسيوم على العلاج التداخلي لأمراض شرايين الساق لمرضى السكري

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خلفية البحث: داء السكري هو أحد أهم العوامل التي تؤدي إلى مرض إنسداد الشرايين الطرفية، ويعد عامل خطورة هام لتطور المرض ليتحول المريض من مرحلة عدم وجود أعراض أو مرحلة العرج إلى مرحلة القصور الحرج. والقصور الحرج بالدورة الدموية هو المرحلة الأكثر تقدمًا من مرض إنسداد الشرايين الطرفية مع معدلات بتر قد تصل إلى 30٪.

الهدف من البحث: تقييم تأثير وجود الكالسيوم على جدار الأوعية الدموية لشرايين تحت الركبة في مرضى السكري، ولتوضيح تأثير وجوده على معدلات الفتح الأولي والثانوي للشرايين، وفعالية التدخل الوعائي للقسطرة الطرفية.

المرضى وطرق البحث: بين عامي 2018 و 2020 تم تجميع بيانات 30 مريض سكري يعانون من تكدسات شرايين ما تحت الركبة من مستشفى الزهراء الجامعي. وقد خضع جميع المرضى لعمل أشعة مقطعية بالصبغة للطرفين السفليين قبل إجراء التدخل وبناء على نتيجة الأشعة المقطعية تم تصنيف تكدس شرايين الساق إلى ثلاث مجموعات: تكدس بسيط (12 مريضًا)، أو تكدس متوسط (10 مرضى)، أو تكدس شديد (8 مرضى)، بإجمالي 42 طرفًا (12 مريضًا يعانون من تكدس شرايين الساقين للطرفين السفليين). وقد تمت مقارنة النتائج الفورية والمتأخرة للتدخل الوعائي.

نتائج البحث: أظهرت هذه الدراسة أن هناك علاقة ارتباط قوية بين تكدس شرايين الساق وكلا من داء السكري والتدخين وكان العرج وألم الراحة

وغيرنا الأنسجة بين جميع المجموعات أعلى في المرضى الذين يعانون من تكلسات شديدة. وقد أظهرت النتائج معدل نجاح تقني (88.1%)، ومعدل فتح أولي (83.3%)، ومعدل الفتح في حالات التكلس البسيط 100%، وفي حالات التكلس المتوسطة 92.9%، وفي المجموعة ذات التكلس الشديد 71.4%.

الاستنتاج: نتائج التدخل الوعائي للمرضى الذين يعانون من تكلس بشرايين الساق مقبولة، مع وجود نجاح تقني أفضل في حالات التكلس البسيط والمتوسط مقارنة بحالات التكلس الشديد.

الكلمات الدالة: العلاج بالقسطرة التداخلية، إعادة سريان الدم بالأوعية الدموية، إنسداد شرايين الساق.