Eur J Vasc Endovasc Surg 33, 453–460 (2007)
doi:10.1016/j.ejvs.2006.11.022, available online at http://www.sciencedirect.com on ScienceDirect

Vascular Involvement in Diabetic Subjects with Ischemic Foot Ulcer: A New Morphologic Categorization of Disease Severity

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Objectives. *Arteriographic lesions of diabetic subjects with critical limb ischemia (CLI) and ischemic foot ulcer were reviewed retrospectively, to provide new criteria for stratification of these patients on the basis of their vascular involvement.*
Patients. *In 417 consecutive CLI diabetic subjects with ischemic foot ulcer undergoing lower limb angiography, lesions were defined as stenosis or occlusion, localization, and length (<5 cm, 5–10 cm, >10 cm). In a subgroup of 389 subjects, foot arteries also were evaluated. Patients then were categorized into 7 classes of progressive vascular involvement based on angiographic findings.*
Results. *Of the 2893 found lesions (55% occlusions) 1% were in the iliac arteries, whereas 74% were in below-the-knee (BTK) arteries. Sixty-six % of all BTK lesions were occlusions, and 50% were occlusions >10 cm* ($p < 0.001$ *vs proximal segments). Occlusions of all BTK were present in 28% of patients, although there was patency of at least one foot artery in 55% of patients. The morphologic Class 4 (two arteries occluded and multiple stenoses of tibial/peroneal and/or femoral/popliteal vessels) was the most common (36%). An inverse correlation between morphologic class and TcPO2 was observed* ($r = -0.187$, $p = 0.003$).
Conclusions. *In CLI diabetic subjects with ischemic foot ulcer, the vascular involvement is extremely diffuse and particularly severe in tibial arteries, with high prevalence of long occlusions. A new morphologic categorization of these patients is proposed.*

Keywords: Diabetes mellitus; Critical limb ischemia; Peripheral artery disease; Diabetic foot.

Lower limb peripheral arterial disease (PAD) is a common complication of diabetes mellitus.[1] As compared to normal subjects, PAD prevalence is significantly higher in diabetic patients[2] and is associated with more severe clinical manifestations and a higher risk of critical limb ischemia (CLI) and limb loss.[3] The majority of non-traumatic major amputations are performed in diabetic subjects.[4] PAD in patients with diabetes also is different in terms of histological features and anatomic distribution of obstructive lesions.[5,6]

Previous papers have described the variation in distribution of arterial lesions among lower limb arteries according to cardiovascular risk factor profile,[7–10] showing an association between diabetes and infrapopliteal vessel obstructions.[6–8] Few studies, however, specifically have addressed the distribution of lesions in diabetics[3,6,11,12] and most of those reports focus on small series consisting of heterogeneous groups of diabetic subjects with or without foot ulcer. To the best of our knowledge, only one paper[13] included a series of diabetic subjects exclusively selected for the presence of ischemic foot ulcer. This study[13] showed a predilection for distal artery involvement, but did not provide information about the length of lesions. Although the indications for revascularization in diabetics with CLI are well established,[14] a more informative morphologic picture to describe the typical arterial involvement could be useful. Furthermore, in our opinion, it would be

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important to have new criteria to stratify these patients according to the severity of their vascular involvement.

Methods

Population. The study population include 417 consecutive diabetic patients with CLI and ulcer and/or gangrene of the foot admitted in our Hospital for angiography of lower limb arteries between 2003 and 2004. In all patients the presence of diabetes mellitus was defined as the use of hypoglycemic drugs (either insulin and/or oral agents). All patients had critical limb ischemia (CLI) according to TASC criteria,[14] with non healing (>4 weeks of local dressing and conservative treatment) ulcer and/or gangrene of the foot. In particular, all were referred for angiography using the following diagnostic protocol: evaluation for the presence of pedal pulses and transcutaneous oxygen tension (TcPO2) values (posterior tibial and dorsalis pedis pulses were evaluated by palpation and Doppler continuous wave technique, TcPO2 was evaluated on the dorsum of the foot); in cases with reduced or absent foot pulses and TcPO2 <50 mmHg, duplex scanning was performed and when haemodynamically significant lesions were identified arteriography was carried out. All patients underwent digital subtraction angiography of the affected limb for planning the subsequent revascularization, which was endovascular treatment (first choice, same setting) or open surgery (if endovascular treatment was thought to be not feasible or if it was not accompanied by immediate technical success). Baseline angiographic findings have been retrospectively reviewed by expert readers (LG, AS). Approval of the Ethical Committee was not required for this retrospective study.

In all patients angiograms of the iliac, femoral, popliteal and crural arteries of the ulcerated side were obtained. In 389 cases angiography of foot arteries was also available, and the state of the dorsalis pedis and plantaris communis arteries was evaluated. In 28 cases the quality of foot artery angiographic picture was not good enough to allow a retrospective evaluation. The arch distal to dorsalis pedis was not evaluated. In case of a bilateral disease, only one leg was considered. Stenosis was defined by a reduction of lumen diameter between 50 and 99%. Occlusion was defined by a total obliteration of the lumen. The length of each encountered lesions was categorized into three groups: <5 cm, 5−10 cm, >10 cm. In case of a segment with multiple stenoses or short occlusions, the length refers to each individual lesion and not to the length of the entire affected segment. The location of the lesion could be iliac (common iliac artery, external iliac artery), femoral (common femoral artery, superficial femoral artery, profunda femoris), popliteal, anterior tibial, posterior tibial, peroneal. Tibioperoneal trunk was considered as part of the peroneal artery. Each lesion was then categorized according to location, type (stenosis or occlusion) and length. In the 389 cases with available foot angiograms, both dorsalis pedis and plantaris communis arteries were classified as significantly diseased (50−100% stenosis) or free from significant stenosis.

Morphological classification. All patients were categorized according to a new morphologic classification of disease severity based on 7 classes of increasing arterial involvement (Table 1). Class 2 is further divided in 2a (direct tibial flow) and 2b (direct peroneal flow). This classification is routinely used in our Catheterization Laboratory to define baseline disease severity and improvement of angiographic disease condition after endovascular treatment. Fig. 1 shows examples of different classes of arterial involvement. To validate this classification, a correlation was made between the angiographic score and transcutaneous oximetry before and after endovascular treatment in a consecutive series of other 249 patients with the same characteristics of patients included in the present study. TcPO2 was measured the day before the endovascular treatment and 3 weeks after the procedure[15] by an electrochemical transducer (TCM4, De Mori, Italy). The transducer was positioned at the dorsum

Table 1. Morphologic Classification of Below-The-Groin arterial lesions distribution, based on 7 Classes of progressive involvement severity

Class	Angiographic Finding	Patients, *n* (%)
1	Isolated, one vessel tibial or peroneal artery obstruction	3 (1%)
2a	Isolated femoral/popliteal artery or two below knee arteries obstructed but with patency of one of the two tibial arteries	12 (3%)
2b	Isolated femoral/popliteal artery or two below knee tibial arteries obstructed but with patency of the peroneal artery	23 (5%)
3	Isolated, one artery occluded and multiple stenosis of tibial/peroneal and/or femoral/popliteal arteries	58 (14%)
4	Two arteries occluded and multiple stenosis of tibial/peroneal and/or femoral/popliteal vessels	151 (36%)
5	Occlusion of all tibial and peroneal arteries (below knee cross-sectional occlusion)	47 (11%)
6	Three arteries occluded and multiple stenosis of tibial/peroneal and/or femoral/popliteal arteries	114 (27%)
7	Multiple femoro-popliteal obstructions with no visible below the knee arterial segments	3 (1%)

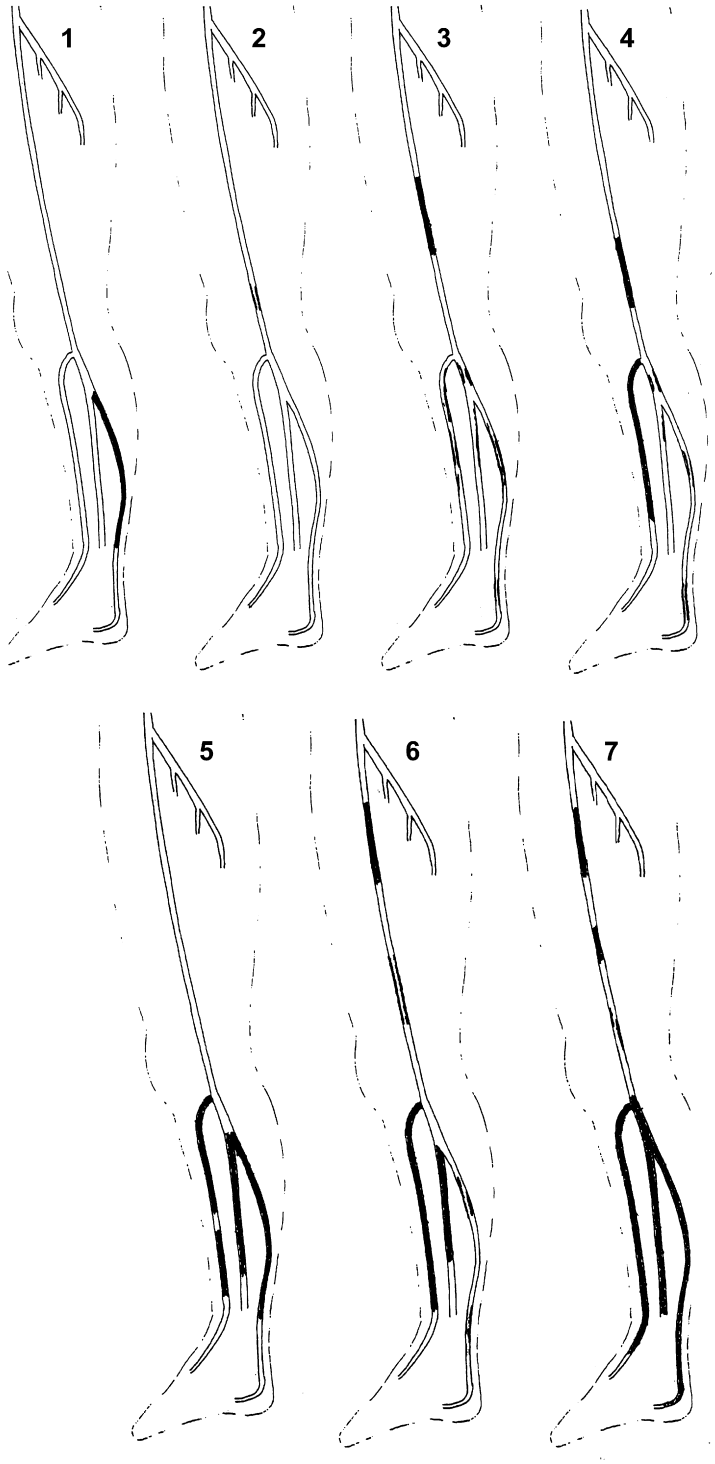

Fig. 1. Examples of below-the-groin arterial involvement corresponding to different Classes of the adopted morphologic classification.

of the foot in the first intermetatarsal space, after carefully cleaning of the measuring site. The electrode position was marked on the skin to allow identical positioning during the following measurements. Before each measurement, the electrode was calibrated automatically. To achieve a steady state, patients had to rest at least 20 minutes in the supine position before measurement was started. After an automated

hyperemic period of approximately 5 minutes at 45 °C, measurements were obtained with probe temperature of 44 °C. Patients with conditions influencing TcPO2 assessment were excluded (oedema, extensive skin defect of the foot, inability to rest supine for prolonged time).

Statistical analysis. Occlusions and stenoses were cross-tabulated. Each lesion was counted in the corresponding cell according to the localization and length. Chi-square tests were used to assess the statistical significance of the different kinds of lesion (stenosis or occlusion) and length (<5 cm, 5−10 cm, >10 cm) in each arterial segment. The lesion represented at each site is the most common in term of type (stenosis or occlusion) and length. Correlation between morphologic Class and TcPO2 has been analyzed by Spearman correlation test.

Results

Clinical characteristics of patients are reported in Table 2. A total number of 2893 vascular lesions were found in the consecutive series of 417 patients. Distribution of lesions according to location and length are reported in Fig. 2 (stenoses) and Fig. 3 (occlusions). The majority of lesions were found in infrapoplital arteries (2138, 74%), whereas only 1% of lesions was found in the iliac arteries.

As shown in Table 3, the prevalence of lesions longer than 10 cm, as well as occlusions and occlusions longer than 10 cm was significantly higher in distal vessels as compared to more proximal segments. In particular, occlusions longer than 10 cm represented 50% of all lesions in below-the-knee arteries, but only 11% in the femoral segment ($p < 0.001$). Interestingly, a higher prevalence of occlusions as compared to stenoses was found in both the anterior tibial and posterior tibial arteries but not in the peroneal artery (66%, 84%, 42%, respectively, $p < 0.001$).

Table 2. Demographics and clinical characteristics of study population

Age (years)	73 ± 12
Males, *n* (%)	252 (60%)
Diabetes therapy	
Insulin	270 (65%)
Oral agents	132 (32%)
Diet only	15 (4%)
Hypertension	327 (78%)
Smoking habit	
Smokers	52 (12%)
Former smokers	158 (38%)
Non smokers	207 (49%)
Coronary artery disease	287 (69%)

Table 1 reports distribution of patients according to the proposed morphologic classification, the most common categories were 4 (36%) and 6 (27%).

Occlusion of all crural vessels was observed in 118 (28%) patients. Patency of at least one pedal artery was present in 88% of patients with obstructions of all crural vessels, whereas patency of both dorsalis pedis and plantaris communis was observed in 55% of patients.

Correlation between morphologic Classes and TcPO2. As shown in Fig. 4, TcPO2 values were correlated with angiographic score both before and after PTA revascularization, ($r = -0.187$, $p = 0.003$ and $r = -0.194$, $p = 0.002$, respectively). After PTA, morphologic classes with direct tibial flow (Class 0, 1, 2a) had the highest TcPO2 >30 mmHg ($p = 0.018$).

Discussion

Our findings show that in diabetic subjects with CLI and ischemic foot ulcer obstructive lower limb lesions are extremely diffuse and preferentially located in crural arteries (74% of all lesions). Furthermore, we found that as compared to more proximal segments, in infrapopliteal vessels the lesions were mainly occlusions rather than stenoses, with a length in most cases exceeding 10 cm. This latter finding is particularly relevant for anterior and posterior tibial arteries, which give direct flow to the foot, and thus are thought to be clinically more relevant. Finally, we provide the morphologic classification we use routinely, which correlates with the degree of ischemia measured by TcPO2.

Patient selection in the present study was performed on the basis of TcPO2 and Duplex scan. Ankle pressure was not measured because of medial layer calcification, very common in diabetics[15]; toe pressure is less influenced by medial calcification but its measurement is technically more challenging.[16] Although Duplex Scan is less sensitive for crural arteries than for above-the-knee vessels,[17] the number of patients not offered angiography (low TcPO2 but no haemodynamically significant lesions on Duplex scan) is not relevant to this study.

Diabetic subjects with ischemic lesions of the foot are those with the highest risk of limb loss, the risk being reduced after successful revascularization.[14] However, vascular surgeons and endovascular specialists dealing with these patients have to be aware that they will encounter long occlusions of probably both femoral and infrapopliteal vessels. As the aim of the treatment should be to get direct flow to the foot,[18] knowledge of extension and characteristic of vascular

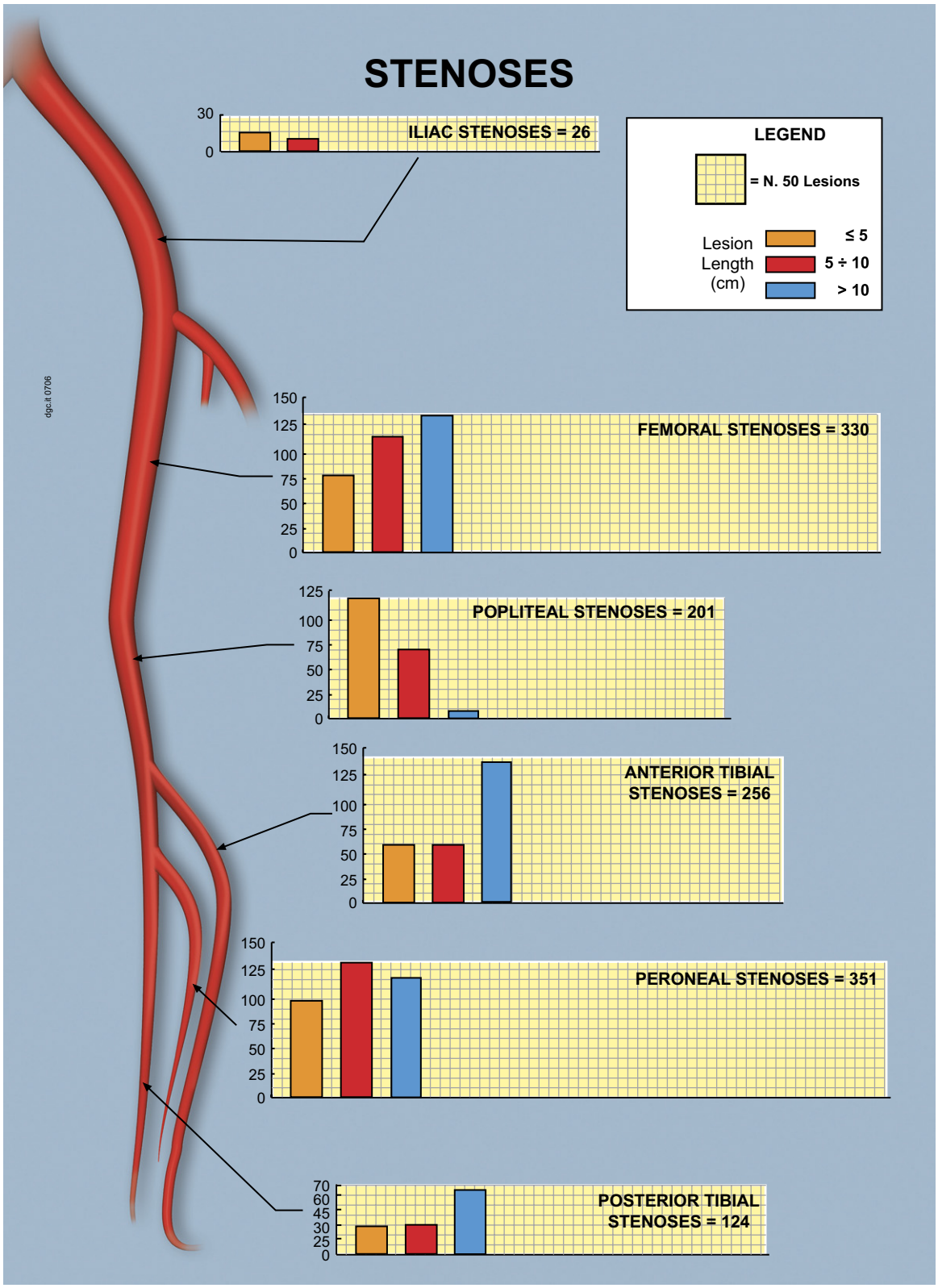

Fig. 2. Distribution according to the site and length of the 1288 significant stenoses found in the study population of 417 consecutive diabetic subjects with CLI and ischemic foot ulcer. The area of each graph corresponding to each vascular segment is proportional to the frequency of stenoses in that segment.

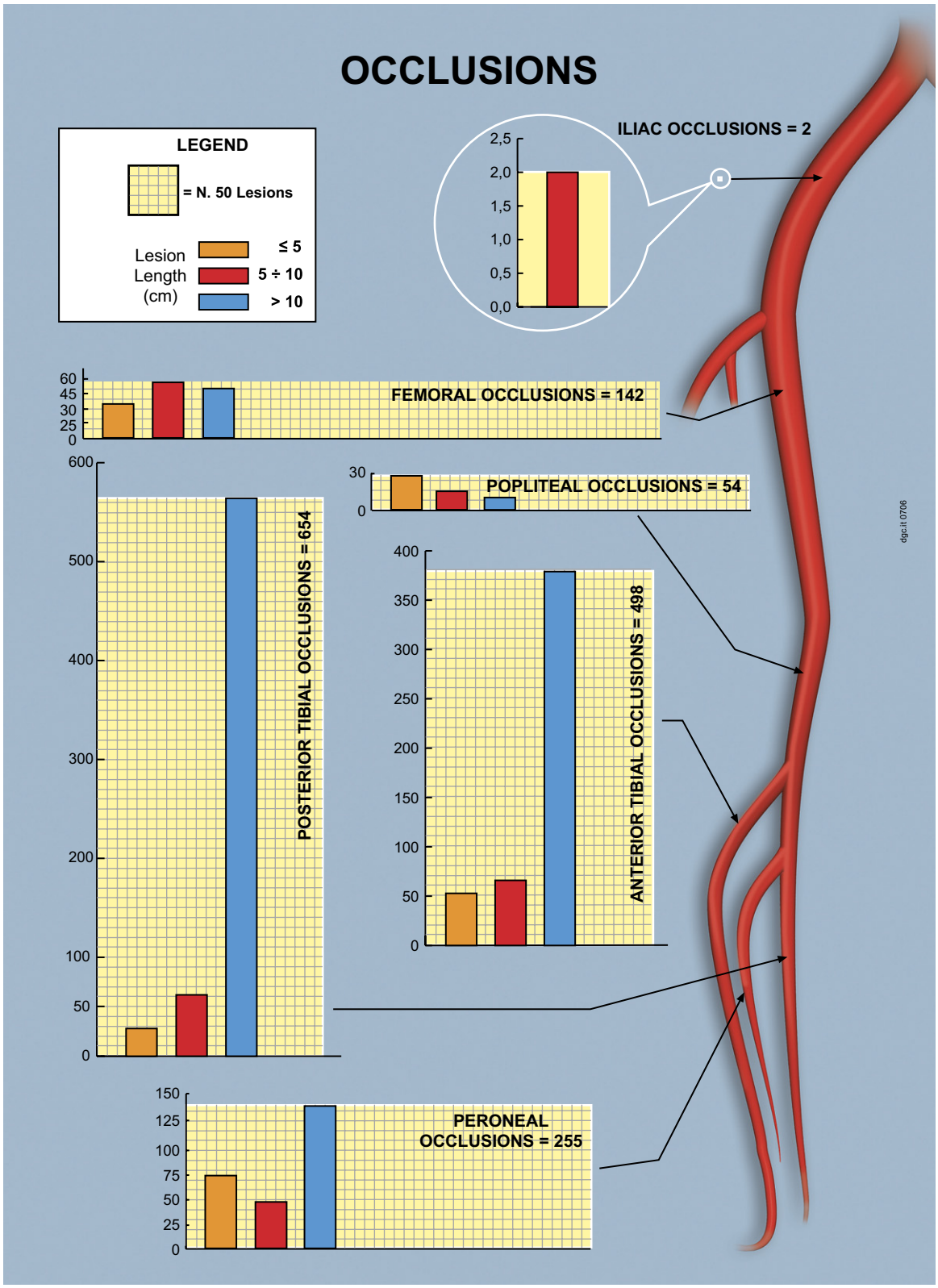

Fig. 3. Distribution according to site and length of the 1605 occlusions found in the study population of 417 consecutive diabetic subjects with CLI and ischemic foot ulcer. The area of each graph corresponding to each vascular segment is proportional to the frequency of occlusions in that segment.

Table 3. Rate of lesions > 10 cm, occlusions, and occlusions > 10 cm among vascular lesions found in different arterial segments in 417 consecutive patients with diabetes mellitus and ischemic ulcer and/or gangrene of the foot

	BTK	POP	FEM	ILIAC	*p* value
Lesions, *n*	2138	255	472	28	
>10 cm Lesions, *n* (%)	1410 (66%)	19 (7%)	187 (40%)	0 (0%)	<0.001*
Occlusions, *n* (%)	1407 (66%)	54 (21%)	142 (31%)	2 (7%)	<0.001*
>10 cm Occlusions, *n* (%)	1081 (50%)	11 (4%)	51 (11%)	0	<0.001*

BTK = all below the knee arteries; POP = popliteal artery; FEM = common femoral artery, profunda femoris and superficial femoral artery; ILIAC = common and external iliac arteries. * = BTK vs POP, FEM, ILIAC.

lesions is important. The most common morphologic classes were Class 4 (36%) and 6 (27%), whereas only 9% of patients were in the low disease severity categories (1, 2a, 2b). These data underlie the typical severe obstructive burden of CLI diabetic subjects.

The common multilevel disease of CLI diabetic subjects also means that, in case of endovascular treatment, different techniques and devices are used during the same procedure. Therefore, studies specifically addressing a single technique and/or device, such as stent[19] or drug eluting stent,[20] in diabetics with CLI could depend on the concomitant treatment of other vascular segments with different techniques. This has to be considered when judging the real impact of that technique/device on outcome.

The characteristics of vascular lesions in PAD and indications for their treatment are commonly categorized A-D according to TASC classification, which is based on degree of complexity, A being least complex and D most complex.[14] The indications for treatment were based on technical considerations 6 years ago, since when new techniques have developed. For instance, a lesion classified as type D by TASC currently can be treated in most cases by an endovascular rather than open surgical approach.[21] In current clinical practice these patients are first referred for an endovascular opinion.[22,23] In a consecutive series of 1191 diabetic patients with CLI referred for endovascular opinion, PTA was feasible in 84% and during a median follow-up of 23 months, the major amputation rate was only 1.7% (4% on intention-to-treat analysis). The clinical restenosis rate was 11.3%, while the cumulative 5 year primary patency was 88%.[23] These satisfactory results were obtained in a cohort of subjects similar to those analyzed in the present study, where most patients would have been in C or D according to TASC guidelines.[23]

Furthermore, our data, indicating that diffuse involvement is very common in diabetic patients with ischemic foot lesions, point out a second limitation of TASC classification. TASC criteria do not cope with this common anatomic situation of multilevel disease, because they consider separately each lesion, meaning that the TASC categories fail to describe either the severity of the disease or correct treatment. In addition, there is scope for a score that considers the entire morphologic complexity of the disease.

As an alternative to TASC criteria, we propose a morphologic classification based on seven classes of progressive vascular involvement. This classification offers the possibility of stratifying affected patients on the basis of the severity of their vascular involvement. The possible advantages could be the creation of a homogeneous group of patients, having the same involvement severity in which to study specific interventions. Our morphologic classification does not consider iliac

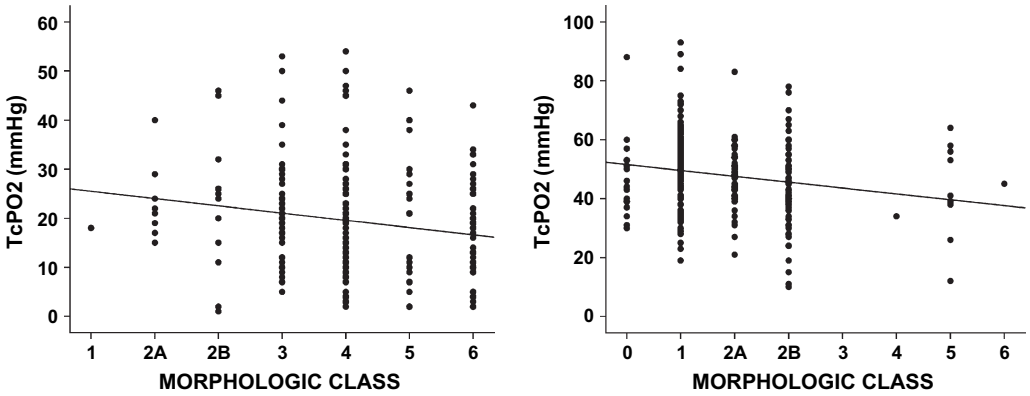

Fig. 4. Correlation between morphologic Classes and TcPO2 in 249 consecutive diabetic patients with ischemic foot ulcer before PTA (left panel, r = −0.187, $p = 0.003$) and after PTA (right panel, r = −0.194, $p = 0.002$).

arteries, which are, as shown by our results, only rarely involved in the diabetic patient with ulcers.

Our categorization is supported by the correlation with TcPO2 measurements, before and after revascularization, although the observed correlations were not strong. In particular for diabetic subjects, microcirculatory disorders are common and these may have an impact $TcPO_2$.[24] Nevertheless, in diabetic subjects $TcPO_2$ remains the most appropriate diagnostic tool, since ankle pressure measurement is strongly influenced by medial artery calcification[15] and toe pressure measurements are technically more challenging.[16]

Another finding of our study is that in case of occlusions of all crural vessels, in the majority of patients there is at least one patent pedal artery which could be used for distal anastomosis for a femoral- and popliteo-pedal graft. In 55% of patients we found that both dorsalis pedis and plantaris communis were patent. If only one main pedal artery is patent, the risk of graft failure is likely to increase.[25]

In conclusion, our data indicate that, in patients with diabetes mellitus and ischemic foot ulcer(s), the underlying vascular disease is widespread in the lower limb arteries and is particularly severe in vessels below the knee. The morphologic classification we adopt may provide a method to measure the overall severity of obstructive burden, creating the basis for a patient stratification, which is essential to guide further clinical decisions.

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Accepted 10 November 2006
Available online 29 December 2006