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Interventional Therapy in Diabetic Foot: Risk Factors, Clinical Events and Prognosis at One Year Follow-up (A Study of 103 Cases)

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Abstract: Diabetic foot is a common complication in diabetes mellitus course, able to increase the overall morbidity/mortality risk of such a disease. The aim was to investigate the outcomes, the incidence of clinical events, the number of recurrent ulcers in patients with diabetic foot during 1 year follow-up after angioplasty (PTA) revascularization. From January 2007 to August 2009, 103 diabetic patients with diabetic foot undergoing revascularization of a lower limb by PTA were recruited. At 1 year follow-up we assessed: "major" (death, stroke, Myocardial Infaction (MI) and "minor" (Deep Vein Thrombosis (DVT), renal failure, restenosis) events incidence; recurrent ulcers incidence; the predictive elements of all these events. At 1 year follow-up, "major"/"minor" events incidence was 15% (deaths:5, stroke:1, MI: 9%) and 34% (renal failure: 11, DVT: 9, restenosis: 14%), respectively. Obesity, high low density level-cholesterol levels and distal arterial lesions (at posterior tibial artery in particular) were statistically significantly associated with major events ($p<0.05$); only obesity resulted statistically associated with minors ($p = 0.043$). High levels of C-reactive protein had a statistically significant relationship with the recurrence of ulcers ($p = 0.006$) while distal arterial obstructions showed a trend toward significance. To improve diabetic foot mortality and morbidity rate, our study underlines the importance of a prompt diagnosis and appropriate revascularization treatment. Other studies are needed to ascertain these.

Key words: Diabetic foot, PTA, PAD, cardiovascular risk factors, mortality/morbidity

INTRODUCTION

According to the World Health Organization (WHO), the total number of diabetic subjects was 171 million in 2000 and is expected to rise to 366 million in 2030 due to population ageing, obesity, a sedentary lifestyle, as well as changes of diet (Setacci *et al*., 2009). There is a high prevalence of peripheral occlusive vascular disease in diabetic individuals (Andrade *et al*., 2004). In fact, the metabolic abnormalities caused by diabetes induce a vascular dysfunction that predisposes to atherosclerosis (Beckman *et al*., 2002). However, the true prevalence of peripheral occlusive vascular disease in diabetic subjects is difficult to determine, as most patients are asymptomatic, many do not report their symptoms, screening modalities have not been uniformly agreed upon and pain perception may be attenuated by the presence of peripheral neuropathy. All such characteristics define "diabetic foot", i.e. the foot of a diabetic patient that has the potential risk of pathologic consequences including infection, ulceration and/or destruction of deep tissue associated with neurologic abnormalities, various degrees of peripheral vascular disease and/or metabolic complications of diabetes in the lower limbs (Schaper *et al*., 2003; Apelqvist *et al*., 2008). Among patients diagnosed with diabetes mellitus, the prevalence of foot ulcers is 4-10%, while the annual population-based incidence is 1.0-4.1% and the lifetime incidence may be as high as 25% (Setacci *et al*., 2009). Lower extremity complications in diabetics are becoming an increasingly significant public health concern. These ulcers frequently become infected, cause great morbidity and are the usual first step to lower extremity amputation, even in the absence of critical limb ischemia (Singh *et al*., 2005; Wu *et al*., 2007). Amputation, the ultimate endpoint of diabetic foot disease, is associated with significant morbidity and mortality rates, besides having immense social, psychological and financial consequences

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(Khanolkar *et al*., 2008). Foot ulcer associated to peripheral occlusive vascular disease requires revascularization, although the outcome in these subjects is less successful than in non-diabetic patients (Setacci *et al*., 2009). The number of Percutaneous Angioplasty (PTA) procedures performed for revascularization of an ischemic limb has increased over the last few years, with the offer of minimally invasive therapeutic alternatives to surgical procedures, which result in significant morbidity and mortality (Al-Omran *et al*., 2003). In present study we evaluated the clinical course, the outcome, the incidence of some major and "minor" vascular events, the recurrence of lower limb arterial ulcers and the risk factors associated to these complications in patients with diabetic foot in the first year after PTA revascularization.

MATERIALS AND METHODS

The study was conducted by recruiting, over the period from January 2007 to August 2009, 103 consecutive patients, all suffering from diabetes (type 2) for at least 10 years, with diabetic foot, namely ulcers, gangrene or amputations of the distal ends of the legs, who underwent revascularization by angioplasty (with balloon or stent). At enrolment patients had an Ankle/brachial Index (ABI) <0.6 and Echo Colour Doppler diagnosis of at least one hemodynamically significant stenosis or occlusion of the vascular bed of a lower limb. All patients were informed of the purpose and the nature of the study and gave informed consent to take part. The study was performed in accordance with the guidelines proposed in the Declaration of Helsinki and approved by the Ethic Committee.

Study population: All 103 patients enrolled (68% men, mean age 68+10 years) had suffered from diabetes (type 2) for at least 10 years, treated with oral antidiabetic drugs (74%) and/or with insulin (36%). All patients had lower limb ischemia-diabetic foot-with ulceration (92%), gangrene (1%) and amputations (8%) of the lower limbs. A smoking habit was present in 30% of patients, with a daily consumption of 23±9 cigarettes, 71% were hypertensive, 69% dyslipidemic and 70% overweight, with a Body Mass Index (BMI) of 27±5 kg m^{-2}. Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP), performed during hospitalization for angioplasty, were 39±30 mm h^{-1} and 16±29 mg L^{-1}, respectively. The Glomerular Filtration Rate (GFR) was 65±25 mL min^{-1} with a blood creatinine value of 1.29±1.3 mg dL^{-1}. Patients demographic, pharmacological and relevant clinical findings are summarized in Table 1.

Table 1: Patients demographic, clinical and treatments data

Parameters	Value (n = 103)	Parameters (%)	Percent (n = 103)
Age (years)	68±10	Medicaments	
Male (%)	78	Calcium-channel blockers	23
Systolic blood pressure (mmHg)	137±19	Beta-blockers	36
Diastolic blood pressure (mmHg)	81±13	Statins	66
Diabetic familiarity (%)	41	ACE inhibitors	35
Cardiovascular familiarity (%)	35	Sartani	33
Cerebrovascular familiarity (%)	21	Diuretics	37
Vascular familiarity (%)	38	Nitrates	21
Smoke (%)	30	Others drugs	54
Number of cigarettes (%)	23±9	Insulin	34
Hypertension (%)	71	Human insulin	28
Body mass index (kg m^{-2})	27±5	Insulin aspart	17
Obesity (%)	70	Oral hypoglycemic agents	74
Dyslipidemia (%)	69	Pioglitazone 15/30 mg	7
Total cholesterol (mg dL^{-1})	181±53	Metformin Hydrochloride 500/850/1000	42
HDL cholesterol (mg dL^{-1})	45±12	Glibenclamidemetformin 2.5/5+400 mg	16
LDL cholesterol (mg dL^{-1})	106±43	Glimepiride	8
Triglycerides (mg dL^{-1})	143±84	Gliclazide	4
Blood glucose (mg dL^{-1})	147±65	Pioglitazone+metformin	8
Creatinine (mg dL^{-1})	1.29±1.03	Repaglinide 0,5-1-2	11
GFR (mL min^{-1})	65±25	Acarbose 100/50	1
CRP (mg L^{-1})	16±29	Rosiglitazone+metformin	3
ESR (mm h^{-1})	39±30	PTA	53
Ulcers (%)	91	POBA	38
Gangrene (%)	1	Stent	65
Amputation (%)	8		
Vascular lesions (%)			
Femoral	65		
Popliteal	21		
Tibial ant	22		
Tibial post	21		
Interosseous	12		

Values are Mean±SD, PTA: Percutaneous transluminal angioplasty, POBA: Plain old balloon angioplasty, Tibial ant.: Tibial anterior; Tibial post.: Tibialis posterior, GFR: Glomerular filtration rate, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: Creactive protein, ESR: Erythrocyte sedimentation rate, ACE: Angiotensin-converting enzyme

PTA technique: All patients underwent quantitative angiography and subsequent angioplasty with the same protocol: after local anesthesia with Xylocaine 2%, vascular angiography was performed with a percutaneous femoral artery approach using the Judkins technique with a 6 french pig-tail catheter. PTA was performed using the monorail or over-the-wire system with an antegrade or retrograde approach, as needed, after intravenous administration of Unfractionated Heparin (UFH) 5000 UI. The diameter of the balloon used for angioplasty was calculated by Philips angiographic software using the calibre of the vessel to be treated as reference. All patients underwent single or multiple balloon inflation, depending on the operator's needs, while stents were applied only in presence of large spiral dissection of vessels. The inflation pressure, number and size of stents placed were determined by individual needs during the procedure. In particular, angioplasty was performed with the use of stents in 65% of cases and only balloon dilation in the remaining 35%. Each patient received, on average, 4 insufflations at a pressure of 12 ATM and with an inflation time of 231 sec.

Site and occlusion grade of vascular lesions treated with PTA: Treated lesions were distributed along the entire vascular tree of the lower leg from the femoral artery, through the popliteal artery to the tibio-peroneal trifurcations including the anterior tibial artery, posterior tibial artery and interosseous artery. Specifically, vascular lesions are located in Table 1.

Stenosis ranged from a minimum of 75-100% with complete occlusion of the vessel. The success rate of the procedure was 100%, with a residual stenosis of less than 20%. After PTA, 24 patients were discharged with a single antiplatelet drug: acetyl salicylic acid, clopidogrel or ticlopidine; 79 with two drugs, while low molecular weight heparin was prescribed to 21 patients over a period of one month.

Follow-up: All patients were subsequently monitored by phone follow-up after about 12 months from the revascularization treatment, to assess the major end-points: death, strokes and MI and "minor" end-points: deep vein thrombosis, renal failure, clinic vascular restenosis and recurrence of ulcers. We also searched for risk factors of these events.

Statistical analysis: Continuous variables were expressed as Mean±SD deviation and frequencies as percentage of patients. Between-group comparisons were made by using Student's t test for independent samples or non-parametric Mann-Whitney U test. Frequencies were compared using the chi-squared or Fisher's exact test when appropriate. P-values of $p<0.05$ were considered statistically significant. The data were analysed using the statistical software packages Statistica version 6.1 (StatSoft Inc., Tulsa, Oklahoma).

RESULTS

At 1 year follow-up the incidence of major events: death, stroke and MI was 15% and of "minor" events: vascular restenosis, renal failure and deep vein thrombosis was 34%. With regard to major events (15%), deaths accounted for 5% (including 2 patients who died of cancer), strokes for 1% and MI for 9% (Table 2). As regards "minor" events, 11% of patients developed renal failure, 9% a deep vein thrombosis and 14% a restenosis (including 5 subjects who underwent PTA with a balloon only) (Table 2). Smokers had a higher risk of major events, although this was not statistically significant ($p = 0.14$). Another interesting datum emerged, namely that subjects taking insulin therapy and subjects using oral antidiabetic drugs did not differ statistically about the incidence of major events ($p = 0.77$). The presence or absence of obesity was significant ($p = 0.035$), so obese subjects with ulcers have an increased risk of major events. Dyslipidemia (total cholesterol >200 mg mL^{-1}) ($p = 0.77$) was not related to major events; nevertheless, increased Low Density Level (LDL) (>130 mg d^{-1}) ($p = 0.017$) resulted positively correlated with major events. Analysing our population blood tests, there was not a significant correlation with increased values of ESR and CRP ($p = 0.31$ and 0.23, respectively), indicating that these markers were not potential predictors of major events for the population sample considered. Regarding the vascular lesion site, we observed that patients with more distal lesions, especially of the posterior tibial artery, exhibited a statistically significant ($p = 0.017$) higher incidence of

Table 2: Incidence of major (death, stroke and myocardial infarction) and minor (vascular restenosis, renal failure and deep vein thrombosis) events at 1 year follow-up

Parameters (%)	Incidence at 1 year follow-up
Major events TOT	15
Death	5
Stroke	1
Myocardial infarction	9
Minor events TOT	34
Vascular restenosis	14
Renal failure	11
Deep vein thrombosis	9

Table 3: Correlation among smoke, insulin therapy, obesity, dyslipidemia, CRP, ESR values, vascular lesion site and major events

Variable	Major events (n = 15)	No major events (n = 88)	p-values
Smoke (%)	47	27	0.14
Insulin therapy (%)	27	35	0.77
Obesity (%)	93	66	0.035
Dyslipidemia (%)	73	68	0.77
Col TOT (mg dL^{-1})	205±63	177±50	0.07
Col HDL (mg dL^{-1})	46±12	45±12	0.71
Col LDL (mg dL^{-1})	132±39	102±43	0.017
ESR (mg L^{-1})	41±25	39±31	0.31
CRP (mm h^{-1})	18±23	16±30	0.23
Vascular lesion (%)			
Fem.	73	64	0.57
Popl.	20	22	1
Ant. Tib.	7	25	0.18
Post. Tib.	47	17	0.017
Interos.	7	13	1

p<0.05, Col TOT: Total cholesterol, Col HDL: High density lipoprotein cholesterol, LDL Col: Low density lipoprotein cholesterol, CRP: Creactive protein, ESR: Erythrocyte sedimentation rate, Fem: Femoral artery, Popl: Popliteal artery, Ant Tib: Anterior tibial artery, Post Tib: Posterior tibial artery, Inter: Interosseous artery

Table 4: Correlation among smoke, obesity, triglyceridemia and minor events

Variable	Minor events (n = 31)	No minor events (n = 72)	p-values
Smoke (%)	35	28	0.043
Obesity (%)	84	64	0.043
Triglycerides (mg dL^{-1})	157±97	136±78	0.025

p<0.05

Table 5: Correlation among insulin therapy, obesity, CRP, ESR values, vascular lesion site and ulcer relapse

Variable	Ulcer relapse n = 22	No ulcer relapse n = 81	p-value
Insulin therapy (%)	45	31	0.21
Obesity (%)	77	68	0.45
CRP (mm h^{-1})	33±46	11±20	0.006
ESR (mg L^{-1})	45±33	38±30	0.32
Vascular lesion (%)			
Fem.	41	72	0.011
Popl.	27	20	0.56
Ant. Tib.	36	19	0.09
Post. Tib.	14	24	0.39
Interos.	23	9	0.13

p<0.05, CRP: Creactive protein, ESR: Erythrocyte sedimentation rate, Fem: Femoral artery, Popl: Popliteal artery, Ant Tib: Anterior tibial artery, Post Tib: Posterior tibial artery, Inter: Interosseous artery

major events (Table 3). As regards "minor" events (Table 4), smokers again showed a higher incidence of events, though this did not reach statistical significance (p = 0.43).

Hypertriglyceridemia (triglycerides >150 mg dL^{-1}) was also positively correlated with the incidence of "minor" events even if this did not reach statistical significance (p = 0.25), as well as obesity (p = 0.043), which represent thus a risk factor of minor events.

No important data emerged about blood tests, the type of therapy and the stenosis site. Finally, evaluating the incidence of recurrent ulcers (Table 5), that occurred in 21% of patients, we observed that subjects under insulin therapy were not at higher risk than those who did not use insulin (p = 0.21). Furthermore, obese subjects seemed not to have a tendency to ulcer relapse (p = 0.45). Instead, we found a strong association with blood chemistry marker levels, in particular with CRP levels, which were elevated (p = 0.006) in patients with recurrent ulcer. The last interesting finding was about the site of the vascular disease. We observed, in fact, that patients with a proximal stenosis (femoral artery, p = 0.11) had a lower tendency to develop a new ulcer than patients with distal lesions (anterior tibial in particular, p = 0.09).

DISCUSSION

In diabetic patients with lower limb ischemia the risk of cardiovascular disease increases significantly, as amply reported in literature (Faglia *et al*., 2009). In particular, the 5-year mortality rate in patients with ulcer is between 43% and 55%, increasing to 74% in patients subjected to amputation of the distal extremities. These figures far exceed those related to mortality for many types of cancers including prostate, colon and Hodgkin's lymphoma (Robbins *et al*., 2008). Assessing a series of studies (Faglia *et al*., 2009; Robbins *et al*., 2008) comparing the 1-year mortality rate of patients with diabetic foot, we observed that this varied from 15-40%, increasing to 50% at 3 years and up to 60% at 5 years. In particular, the overall annual rate of major cardiovascular events, MI, ischemic stroke and cardiovascular death, was 20-30%. At 5, 10 and 15 years the morbidity and mortality rates for all causes are 30%, 50% and 70%, respectively (Faglia *et al*., 2009). Ischemic heart disease is the most frequent cause of death in patients with diabetic foot (40-60%), while cerebrovascular disease accounts for 20-30% of cases. Other vascular events, especially rupture of an aortic aneurysm, cause about 10% of deaths. Thus, 20-30% of patients do not die of cardiovascular causes. Analyzing clinical trials that evaluated patients who could not undergo artery reconstruction and those in which the attempt had failed, 40% of patients lost the limb at 6 months and 20% died. However, these data were referred to patients with diabetic foot who had not undergone any revascularization treatment (Norgren *et al*., 2007). Literature data on the mortality incidence are rather limited. In a relatively recent study, Faglia *et al*. (2006) documented the clinical course and outcome of patients with diabetic foot at 5 years after revascularization: 173 of 566 patients died (30.7%). However, the non-revascularized control group consisted of only 27 subjects versus 566 revascularized subjects. Jamsen *et al*. (2002) reported a survival incidence of 41% at 2 years, 26% at 5 and 14% at 10 years, in 100 diabetic patients with lower limb ischemia. Bailey *et al*. (2003)

reported data from 134 patients with diabetic foot followed up for 9 months. They found a mortality incidence of 12%, which was higher in patients with ulcers or gangrene. Finally, Bertele *et al*. (1999) found a mortality of 19% at one year's follow-up in a cohort of 1560 patients with ischemic diabetic foot. Against this literature background, results of our observational study show that patients suffering from diabetes for at least 10 years, with lower limbs ulcers, revascularized using a PTA technique, had a total mortality of only 5% with a negligible incidence of stroke (1%) and MI (9%). This result may be related to lower limb revascularization with angioplasty, which can clearly improve the prognosis of these subjects. Therefore, our study highlights firstly the relative importance of an early diagnosis of diabetic foot because of the high mortality that literature data (Norgren *et al*., 2007) showed for non-treated cases. Secondly, a prompt reperfusion treatment, either endovascular or surgical, could ameliorate the quality of life of diabetic foot patients. The lacking of a control group could be considered as a limitation of the present study, although we preferred not to consider a control group formed by diabetic foot patients not undergoing to revascularization therapy in relation to the life-threating risk that literature data pointed out in such comparisons.

Regarding predictive factors of events and new ulcers, analytical and experimental studies have identified several independent risk factors such as smoking, dyslipidemia and obesity (Norgren *et al*., 2007). None of these, however, proved to be a sure marker of events. In our study, confirming this, we identified obesity and LDL cholesterol as likely indicators of an unfavourable evolution in these patients. Finally distal vascular lesions, typical of diabetes involving mainly small-sized arteries (Dinh *et al*., 2009), were associated with an increased risk of developing new ulcers. This finding is no surprise, since vascular restenosis, which does not always reflect a clinical relapse, is more frequent in small vessels compared with vessels of a larger calibre (West *et al*., 2004).

CONCLUSIONS

Our analysis, far from being a comprehensive research about the matter and although with its limitations, highlights the fact that diabetic foot disease is an important social problem because of the high incidence in the population and the risk of major and minor complications. A rapid diagnosis and prompt revascularization treatment, if needed, are essential to improve the quality of life and prolong survival.

Unfortunately, no certain markers of risk for diabetic foot disease have yet been identified. Insulin therapy, smoking, obesity, dyslipidemia may be taken into consideration but further studies are needed to confirm this.

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