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Severe peripheral arterial disease is associated with diabetic foot ulcer, and its treatment with percutaneous transluminal angioplasty leads to improved healing of ulcers

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Abstract

Background: **Peripheral Arterial Disease (PAD) is a condition characterized by atherosclerotic occlusion of arteries of the lower extremities. In patients with type 2 diabetes, PAD is a risk factor for the development of Diabetic Foot Ulcers (DFU). Computed Tomography Angiography (CTA) can be used for the evaluation of PAD. PAD can be treated with Percutaneous Transluminal Angioplasty (PTA) or pharmacological treatments.**

Objective: **We aimed at testing the association between PAD and DFU in a cohort of type 2 diabetic patients followed at the Shandong Provincial Hospital. Moreover, we aimed at evaluating the role of CTA for the diagnosis of PAD and for the prediction of DFU. Furthermore, we aimed at assessing the DFU outcome of the PTA treatment.**

Patients, Methods, and Results: **A total of 523 type 2 diabetics were evaluated for PAD. The overall prevalence of PAD was 59.5%. Among patients with PAD, 95 had DFU, and 22 of them (23.2%) received an amputation after one year. A group of 62 patients with DFU and PAD was further investigated. A subgroup of these 62 patients was treated with PTA (PTA group) while the other subgroup was treated with pharmacological treatment (control group). In the PTA group, 18 (82%) of the patients showed a remarkable improvement of symptoms. Compared to controls, PTA-treated patients healed their DFU faster, with a difference of 20±5 days. Lastly, the amputation and recurrence rates of DFUs after one year were 6.0% and 8.0% in the PTA group, respectively, compared to 16.0% and 17.6% in the control group.**

Conclusions: **We conclude that the angiographic analysis could help in the diagnosis of PAD and prediction of DFU, as severe PAD is positively correlated to DFU. Moreover, the PTA treatment of PAD could significantly shorten the time of DFU healing and decrease the rate of ulcer recurrence.**

Introduction

Complications of foot ulcers are the leading cause of hospitalization and amputation in type 2 diabetic patients[1]. Diabetic patients are more prone to undergo an amputation than the non-diabetic patients by 12-46 folds[2]. Amputation affects profoundly the quality of life and is associated with increased mortality. The main risk factors for the development of diabetic foot ulcers (DFU) are peripheral arterial disease (PAD) and peripheral neuropathy[3]. It was found that PAD is present in up to 50% of the patients with DFU and is an independent risk factor for amputation[4]. However, the prevalence of PAD and the relationship between PAD and DFU remained uncertain.

PAD is an obstructive atherosclerotic disease resulting in a reduction of distal arterial blood flow and perfusion pressure[5]. Previous studies had shown that a high angiographic score could be a potential indicator of PAD and may be an independent risk factor for major amputation in diabetic subjects[6]. The angiographic score could be defined as the sum of points assigned by the stenoses in the iliac trunk, superficial femoral artery, profound femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery and peroneal artery[6]. On the basis of reduction of vessel lumen diameter, the score could be determined from Grade 0 to 4 (see the details in the "Patients, Methods, and Results" section). The identification of PAD in diabetic patients, however, is difficult because symptoms and signs are frequently masked by coexisting distal symmetric polyneuropathy[7]. To this regard, patients with DFU are often recommended to receive noninvasive imaging procedure to assess PAD severity[8]. Although digital subtraction angiography (DSA) remains the gold standard imaging method for evaluation of PAD in patients, its invasiveness and time-consuming procedure limited its clinical application, and better monitoring procedures for PAD should be further explored[9]. Regarding the treatment options, a minimally invasive procedure termed Percutaneous Transluminal Angioplasty (PTA) has attracted significant interest for the revascularization of PAD to restore tissue oxygenation in ischemic tissues, and this procedure could be superior to traditional surgical bypass[10]. It was shown recently that revascularization by PTA is greatly efficacious in diabetic patients with critical limb ischemia[11]. Until now, however, no randomized controlled clinical trial has been reported to directly compare conservative medical treatment to revascularization with PTA in patients with diabetic foot disease.

The current study aimed to determine the prevalence of Peripheral Arterial Disease (PAD) in a population of Type 2 diabetic patients with or without DFU and to evaluate the role of CT angiography (CTA) in predicting prognosis of DFU with severe PAD. Further analysis of the association of DFU and PAD treated with PTA, and traditional pharmacological therapy was also evaluated.

Patients, Methods, and Results

All protocols were approved by the Ethical Committee of Shandong Provincial Hospital, China. The statistical analysis was performed using the SPSS Statistics software (SPSS Inc., Chicago, IL, USA), and the sequential variable data were presented as means±standard deviation (SD). The Student's *t*-test was used to evaluate differences in continuous variables between groups. The X^2-test was used to compare differences in the distribution of categorical variables. The comparison among all groups' frequency was checked by chi-square test. Multivariate logistic regression analysis was used to analyze the risk factors. A *p*-value lower than 0.05 was considered to be statistically significant.

A total of 523 patients with type 2 diabetes were included in this study. Patient data were collected in the Provincial Hospital affiliated to Shandong University from December 2008 to December 2010. We analyzed the prevalence of PAD in diabetic patients with (diabetes duration: 13.1±4.0 years) or without (diabetes duration: 9.2±4.5 years) diabetic foot disease. Basic information of these 523 diabetic patients is presented in Table 1. In brief, (A) 281 men and 242 women were enrolled; (B) Age of participants ranged from 33 to 85 years old (mean=55.4±9.8 years); (C) DM duration ranged from 0 to 33 years (mean=6.98±3.14 years); (D) 311 patients (59.5%) had PAD and (E) 95 patients (18.2%) were afflicted by diabetic foot disease. Among the patients with diabetic foot disease, 55 had severe PAD, 18 patients had moderate PAD, and 22 patients did not present PAD.

To evaluate and diagnose PAD, vascular diameters were measured and monitored with a Doppler ultrasound (DUS) analysis. A 4-11 MHz Doppler probe was placed while patients were in supine position. The vascular diameters of femoral artery, profunda femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery and the peroneal artery were analyzed to determine PAD. The following grading system was used to define DUS outcome: Grade 0, normal vessel; Grade I, <50% luminal narrowing, without obvious hemorheological disturbances; Grade II, 51%-74% luminal narrowing, hemodynamically insignificant; Grade III, 75%-99% luminal narrowing, hemodynamically significant and Grade IV-total occlusion. Based on the grading, all patients were categorized into three groups: group **A** – no evident peripheral artery disease (including grade 0); group **B** – moderate peripheral artery disease, (including grade I and grade II) and group **C** – severe peripheral artery disease (including grade III and grade IV).

Table 1. Demographic and clinical characteristics of the patients (N=523).

Group	DFU	NON-DFU
N	95	428
Without or moderate PAD	40	352
Severe PAD	55*	76
Age (years)	61.1±12.1**	58.1±10.0
Diabetes duration (years)	13.1±4.0**	9.2±4.5
Hyper-SBP (Y/N)	50/45*	80/348
Hyper-DBP (Y/N)	9/86	46/352
BMI (kg/m^2)	23.4±1.7	23.7±2.1
Smoking habit (Y/N)	44/55*	40/388
GHBA1 (%)	8.2±1.1**	7.1±1.2
DPN (Y/N)	61/34*	92/336
FBG (mmol/L)	8.9±2.1**	8.2±1.5
PPG (mmol/L)	9.7±2.1	10.0±2.6
HDL (mmol/L)	1.09±2.28**	1.23±0.23
LDL (mmol/L)	5.33±1.18**	3.53±0.94
DR (Y/N)	10/85	50/365
DN (Y/N)	30/65*	51/377

*$p<0.01$, vs. NON-DFU group value; **$p<0.05$, *vs*. NON-DFU group value.
Abbreviations: DFU, diabetic foot ulcers; PAD, peripheral arterial disease; GHBA1C, glycated hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; DPN: diabetic peripheral neuropathy; FBG, fasting blood glucose; PPG, postprandial glucose; HDL, high density lipoproteins; LDL, low density lipoproteins; DR, diabetic retinopathy; DN, diabetic nephropathy.

Subjects were also grouped based on the presence or absence of diabetic foot ulcers. In the 95 DFU patients (46 female and 49 male), the age ranged between 40-85-year-old (mean=61.1±12.1 year-old) and the duration of DM was 6-29 years (mean=13.1±4.0 years). The differences of demographic and clinical characteristics between the two groups are shown in Table 1.

Among patients with DFU, 55 patients (57.9%) presented severe PAD, 18 patients (10%) displayed moderate PAD, and 22 patients (10.4%) showed no sign of PAD. Statistical analysis showed no significant difference in the prevalence of diabetic foot between the latter two groups ($X^2=0.015$, $p=0.902$). Moreover, the multivariate logistic regression analysis revealed that severe PAD was associated with an increased prevalence of DFU (Odds Ratio, OR=5.00). Duration of diabetes (OR=0.89), smoking (OR=2.61), hypertension (OR=7.92), increased levels of serum HbA_1C (OR=4.24) and LDL (OR=0.21) were all associated with increased risk of DFU (Table 1).

The second part of this study was aimed at evaluating the efficiency of angiographic examination of peripheral arterial occlusive disease and diagnosis for amputation in patients with diabetic foot ulcer (DFU). To this end, the patients with DFU (n=95) were divided into two groups based on the necessity of amputation with one-year follow-up. DFU was diagnosed according to the Wagner classification. The clinical data of DFU patients with and without amputation are presented in Table 2. After one-year follow-up, 22 patients (23.2%) were treated with amputation. An angiographic analysis, dual source slice Computed Tomography analysis (CTA), was also applied to perform contrast enhanced computed tomography angiography on DFU patients. Eight major arteries were analyzed by CTA: common iliac artery, external iliac artery, superficial femoral artery, popliteal artery, anterior tibial artery, peroneal artery, posterior tibial artery and dorsal artery of the foot. For stenosis of the arteries above popliteal artery (including popliteal artery), the scoring system is defined as follows: reduction of vessel diameter by 50%-75% scores 1; stenosis >75% scores 2; total occlusion scores 3. For anterior tibial artery, posterior tibial artery, peroneal artery and dorsal pedis artery, stenosis >50% scores 1 and total occlusion scores 2. Also, if multiple stenoses are detected at the same vessel, the score was determined by the most advanced lesion. Based on this scoring system, the PAD score of the DFU patients with or without amputation is shown in

Table 2. Comparison between the clinic data of DFU patients with or without amputation.

Group	N	PAD score	Age (y)	Diabetic course (y)	Smoking (n, Y/N)	High systolic pressure (n, Y/N)	High diastolic pressure (n, Y/N)	BMI (kg/m²)	Concurrent infection (n, Y/N)	Prior amputation (n, Y/N)
With amputation	22	12.5±4.7*	62.1±10.1	13.2±4.0	10/12	12/10	2/20	23.6±1.9	18/4	9/13**
Without amputation	73	4.9±2.9	60.6±10.4	12.8±4.5	34/39	38/35	7/68	23.1±2.1	30/43	3/70

Continued

Group	GHBA1C %	DPN (n, Y/N)	Fasting blood-glucose c/mmol•L^{-1}	Postprandial plasma glucose c/mmol•L^{-1}	Urinary albumin quantification (n, Y/N)	HDL c/mmol •L^{-1}	LDL c/mmol •L^{-1}	DR (n, Y/N	DN (n, Y/N)
With amputation	8.1±1.0*	20/2**	8.8±2.0	9.4±2.0	4/18	1.04±0.29	5.23±1.08	3/19	7/15
Without amputation	8.5±1.2	41/32	9.1±1.8	10.0±2.1	8/65	1.10±0.24	5.53±1.04	7/67	23/50

Abbreviations: GHBA1C, glycated hemoglobin A1c; DPN, diabetic peripheral neuropathy; HDL, high density lipoproteins; LDL, low density lipoproteins; DR, diabetic retinopathy; DN, diabetic nephropathy.
*The comparison of "*t*-test" and without amputation group: PAD score increases, with statistical difference (p<0.01). **The comparison of "x^2-test" and without amputation group: the increase of diabetic peripheral neuropathy (DNP), concurrent infection and prior amputation have statistical significance (p<0.01).

Table 3. In amputation group, 81.8% DFU patients (N=22) had PAD score of 6 and up, and only 1 patients scored 0 at PAD examination. In comparison, 28 DFU patients with score 0 did not undergo amputation, indicating that CTA analysis could be a useful clinical tool for prediction of amputation. Also, further analysis suggested that PAD score (OR=1.2, p=0.012), concurrent infection (OR=4.2, p=0.027) and prior amputation (OR=5.8, p=0.017) are the independent risk factors for amputation in DFU patients during one-year follow-up (Table 2).

The last part of the current investigation aimed to evaluate the effectiveness of PTA as a revascularization procedure in DFU patients with critical limb ischemia. A group of 62 DFU patients with severe PAD (recorded for clinic visit from June 2009 to May 2011) were enrolled into the study. According to the experimental paradigm, 22 DFU patients were treated with PTA and the other 40 patients were treated with conventional pharmacological treatment. The time elapsed between complete ulcer healing, the recurrence rate and amputation percentage were followed for a year. The results showed no significant difference in basic clinical index between two groups (Table 4). All critical stenosis mainly occurred in the infrapopliteal artery while the average angiographic score was 7 in both groups. In the group of the 22 patients treated with PTA, 18 subjects (82%) showed remarkable improvements in clinical symptoms.

Table 3. Score of Peripheral arterial occlusive disease (PAD) for the diabetic foot ulcer (DFU) patients with or without amputation. The score was obtained via Computed Tomography Analysis (CTA).

Group	N	Score 0	1-5	6-10	11-15	16-20
With amputation	22	1	3	9	7	2
Without amputation	73	28	22	15	8	0
Total	95	29	25	24	15	2

The recovery time for complete ulcer healing in DFU patients with lower limb ischemia resulted shorter in the PTA group than in control group by 20±5 days ($p<0.05$). After one year, the amputation rate was 6% in the PTA group and 16% in the control group, respectively ($p<0.05$) while the recurrence rate of DFU was 8% in PTA group and 17.6% in the control group, respectively ($p<0.01$).

Discussion

The globally increased prevalence of diabetes has resulted in an inevitable rise in diabetes-related micro and macrovascular complications. Every year more than 1 million people undergo a lower limb amputation as a consequence of diabetes, and more than 85% of all amputations are preceded by DFU. Previous studies have shown that PAD is closely related to the development of DFU[12,13] and is present in 50% of DFU patients[14-16]. Indeed, PAD is shown to be an important predictor of the outcome of foot ulcer in diabetic patients[5]. Recent studies showed that PAD is an independent risk factor for subsequent ulceration and amputation in diabetic patients. PAD lesions are more distal, more diffusely distributed and progress more aggressively in diabetic patients compared to non-diabetic patients[13]. The DFU patients with PAD healed more slowly and appeared more likely to require amputation compared to patients without PAD. Thus, it is essential to provide a PAD index for diabetic patients; symptoms of arterial insufficiency and physical examination contribute poorly to the diagnosis of PAD and noninvasive screening tools are mandatory[17]. Our study suggests that the occurrence of DFU correlated only with severe PAD but not moderate PAD. During healing, injured and elevated inflammation leads metabolic demands sequentially resulting in higher arterial perfusion pressure[18]. This may explain why only severe PAD with significant hemorheological disturbances is associated with the occurrence of DFU. It thus could be concluded that hemodynamics might play a central role in determining the outcome of PAD. Other risk factors including smoking, hypertension, glycosylated hemoglobin and LDL should be corrected accordingly.

The large prospective multicenter EURODIALE study has demonstrated a significantly reduced healing rate in DFU with concomitant PAD compared to those without PAD after one-year follow-up[18]. Once a diagnosis of PAD is established, it becomes important to assess the severity of the perfusion deficit and impact of PAD on ulcer healing. DUS is a non-invasive and inexpensive modality with high sensitivity in detecting high-grade stenosis, but its operator-dependence and restriction for vessels below knee indeed limited its clinical application. Digital subtraction angiography remains the gold standard imaging modality for evaluation the distribution of PAD and allows simultaneous endovascular intervention. However, its invasiveness, time-consuming procedure and potential risk to induce nephropathy hampered its use.

In the recent years, slice spiral CT angiography (CTA) has been increasingly utilized for detection of peripheral arterial occlusive disease[19]. CTA is a low-invasive, fast imaging modality with high sensitivity and good spatial resolution, but it is limited by image interference from heavily calcified vessels. In the current study, we performed CTA in 95 DFU patients and followed them up for one year. The result showed that almost all DFU patients who required an amputation within one year exhibited severe PAD, indicating that CTA based detection for PAD could be a reliable indicator for amputation in patients with DFU. All of 12 DFU patients with prior amputation suffered from severe PAD (PAD score=11.2±2.1) while the risk of re-amputation is remarkably elevated for DFU patient with prior amputation (data not shown). By using multivariate logistic regression analysis, it was further demonstrated that PAD score is an independent risk factor for subsequent amputation[20]. Our findings also demonstrated that concurrent infection is another risk factor for amputation within one year for patients with DFU, which is consistent with the data from the EURODIALE cohort.

Revascularization including surgical bypass and endovascular intervention is the treatment of choice for patients with critical limb ischemia, as it optimizes blood flow and restores compromised perfusion. However, not all diabetic patients with PAD and ulceration of the foot require revascularization. Various factors influence wound healing in DFU patients. Patients with mild PAD and adequate perfusion measurements (ABI >0.6, TcPO2 >50 mmHg) should be initially managed with optimal wound care. In patients with large ulcers and in those with a combination of PAD and local/systemic infection, the expected outcome of conservative treatment is poor, and earlier revas-

Table 4. The clinic data of PTA group and non-PTA group.

Group	N	Age (years)	Diabetes duration (years)	Smoking (n, Y/N)	Hypertension (n, Y/N)	BMI (kg/m^2)	Concurrent infection (n, Y/N)
PTA	18	63.2±7.1	11.5±3.8	7/11	13/5	23.1±1.6	12/6
non-PTA	44	61.8±9.4	12.1±4.3	18/26	30/14	23.4±2.1	29/15

Continued

Group	GHBA1C %	LDL c/mmol•L^{-1}	FBG c/mmol•L^{-1}	DPN (n, Y/N)	DR (n, Y/N)	DN (n, Y/N)
PTA	7.9±1.0	5.53±1.12	9.5±2.1	16/2	8/10	7/11
non-PTA	8.1±1.2	5.23±1.08	9.1±1.5	38/6	19/25	20/24

Continued

Group	Ulcer recovery time (days)	Amputation rate %	DFU recurrence rate %
PTA	13.9±1.0	6	8
non-PTA	20±5.0	16	17.6

Abbreviations: PTA, percutaneous transluminal angioplasty; BMI, body mass index; GHBA1C, glycated hemoglobin A1c; LDL, low density lipoprotein; DPN, diabetic peripheral neuropathy; FBG, fasting blood glucose; DR, diabetic retinopathy; DN, diabetic nephropathy.

cularization would be required. Revascularization in diabetic patients can be technically difficult due to the distal distribution of disease, impaired formation of collateral vessels and vessel calcification. However, endovascular interventions are highly efficacious in patients with short-segment infrapopliteal stenosis[21]. To our best knowledge, there are no randomized controlled clinical trials to compare directly conservative treatment with a revascularization procedure in patients with PAD associated DFU to date[4]. Furthermore, the role of endovascular therapy in treating DFU patients with PAD remained unclear while the results are highly conflicting[22].

In this study, we carried out the evaluation of the PTA revascularization procedure in treating DFU patients with infrapopliteal arterial diseases. The results showed that PTA could accelerate the healing process in patients with DFU and decrease the recurrence of ulcers, as well as reduce needs for amputations within one year. Previous findings using data library pooled by IWGDF from 19 studies, the patients with DFU and PAD showed a median salvage rate of 85% after 1 year[21]. Other studies suggested that patients who underwent successful revascularization recovered better than those who received major amputation with mortality rising to 50% within 3 years[23,24]. No randomized controlled trial has compared surgical bypass and endovascular interventions in DFU patients, although these techniques appear to offer equivalent outcomes where revascularization is successful. From the point of view of treatment for patients with DFU, the revascularization procedures should be part of a comprehensive care plan including aggressive treatment of infection, wound debridement, biomechanical off-loading, blood glucose control and treatment of co-morbidities. Early referral, non-invasive vascular testing, imaging, and intervention are crucial to improve ulcer healing and to prevent amputation for DFU patients[1].

Conclusions

Diabetic Foot Ulcer (DFU) predominantly develops under conditions of severe Peripheral Arterial Disease (PAD) in diabetic patients. Moreover, DFU patients with severe PAD, concurrent infection and history of amputation also have increased risks of (re)amputation within one year. Our study suggests that early evaluation of clinically confirmed PAD through the use of Computed Tomography Angiography (CTA) may be an effective method to identify severe PAD that requires more comprehensive care by a multidisciplinary team.

Treatment could reduce the risk of DFU and amputation. Moreover, under conditions of DFU associated with severe PAD, revascularization with percutaneous transluminal angioplasty (PTA) could promote the healing efficiency of ulcers, decrease the ulcer recurrence and the needs for amputations within one year. These findings highlight the fact that PAD diagnosis and treatment could be extremely valuable for the prevention and treatment of DFU, and for the prevention of amputations in Type 2 diabetic patients. There is an urgent need for large-scale prospective randomized controlled trials to better define the role of PTA treatment in DFU patients with severe PAD.

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Conflict of Interests:

The authors do not have and have not had any actual or potential conflict of interest within three years of beginning the work submitted.

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