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Original research

Impact of heart failure and dialysis in the prognosis of diabetic patients with ischemic foot ulcers

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ABSTRACT

Aim: To establish the role of heart failure (HF) and dialysis (D) in the prognosis of diabetic patients with critical limb ischemia and foot ulcers (FUs).

Methods: Consecutive diabetic patients with ischemic FUs who referred to our Diabetic Foot Centre were prospectively included. All patients underwent a preset limb salvage protocol including peripheral revascularization. According to the presence of HF and D, they were divided in four groups: group 1 without HF and without D defined as ischemic foot (IF); group 2 with HF and without D defined as heart ischemic foot (H-IF); group 3 without HF and with D defined as renal ischemic foot (R-IF); group 4 with HF and with dialysis defined as heart-renal foot (HR-IF). Survival with limb salvage, survival with major amputation and death were reported after 1 year of follow-up.

Results: 136 patient have been included: 66 with IF, 26 with H-IF, 24 with R-IF and 20 with HR-IF. The mean age was 68,9 ± 9,7 years, the diabetes duration 20,7 ± 11,6 years, the mean HbA1c 62,7 ± 22,3 mmol/mol. 103/136 (75,7%) survived with limb salvage, 10/136 (7,4%) survived with major amputation, 23/136 (16,9%) died. The outcomes for group IF patients, H-IF, R-IF and HR-IF were respectively: survival with limb salvage (92,4%, 61,5%, 79,2% and 35%), survival with major amputation (6,1%, 7,7%, 8,3% and 10%), death (1,5%, 30,8%, 12,5% and 55%) $\chi = 0.0001$. Heart failure was an independent predictor of death.

Discussion: The presence of heart failure and dialysis in diabetic patients with ischemic foot ulcers was associated to high risk of amputation and mortality.

Introduction

Diabetic foot patients are often very fragile patients due to the presence of several co-morbidities and foot ulceration may be only a part of a very complex clinical condition. In fact, diabetes chronic complications can affect other organs, such as kidney and heart. Impairment of renal and heart function, by their own, may deeply influence not only the general health but also the outcomes of diabetic foot ulcers (DFUs). Among patients with DFUs, those with peripheral arterial disease (PAD) show usually worse outcomes than neuropathic patients [1]. Nevertheless, PAD is a marker of cardiovascular disorders and increases the risk of ischemic heart disease, fatal myocardial infarction, stroke [2]. Furthermore, patients with ischemic DFUs show different stages of chronic kidney disease and the rate of diabetic patients on dialysis treatment with PAD is increasing.

In our experience, ischemic diabetic foot patients with heart failure and dialysis are very difficult to treat. In fact, the presence of these co-morbidities often influences the limb salvage procedures reducing the chance of success. However, the role of co-morbidities in the prognosis of patients with ischemic DFUs is usually underestimated.

Otherwise, we retain that a deeply analysis of co-morbidities is required to define a potential prognosis of patients affected by ischemic DFUs and to help clinicians in the best approach.

The aim of this study is to evaluate the impact of heart failure and dialysis on the outcomes of patients with diabetes and ischemic foot ulcers treated by a preset limb salvage procedure.

Methods

Patients with diabetes, critical limb ischemia (CLI) and ischemic foot ulcer belonging to stage C (ischemia) or D (ischemia plus infection) of Texas Wound Classification [3] who referred consecutively at our

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Diabetic Foot Centre were prospectively included.

All patients were hospitalized and treated by a preset limb salvage protocol: ulcer debridement, antibiotic therapy in case of infection, offloading of affected foot and lower limb revascularization. After discharge, they had continuous follow up until ulcer healing or death. All revascularization procedures were performed by endovascular technique (percutaneous transluminal angioplasty, PTA). Angioplasty was indicated in case of significant arterial stenosis (> 50%) or complete obstruction [4]. All patients were treated by both aspirin (100 mg/die) and clopidogrel (75 mg/die) before the procedure and for at least one month after. Afterwards, clopidogrel was discontinued. In case of intolerance to aspirin or clopidogrel, ticlopidine was administered. Statin therapy was administered in all patients after lower limb revascularization.

Revascularization failure was considered in case of technical recanalization failure of the vessel affected without direct arterial flow to the foot and/or absence of distal run-off also in case of technical revascularization success.

Severity of foot infection was considered according to Infectious Disease Society of America classification. Severe infection identifies an extended cellulitis (> 2 cm) and a deep tissue infection with a condition of systemic involvement associated with clinical signs of systemic toxicity (fever, vomiting, confusion, metabolic instability, shock) [5].

Surgical debridement was routinely performed at each examination and repeated during the follow-up according to the ulcer status. In case of extended infection (abscess, compartment syndrome, extended gangrene, open fistulas) an emergency debridement was performed to limit the progression of infection and completed after the revascularization when an adequate perfusion was ensured.

Broad spectrum antibiotic therapy was administered in case of infected ulcer and adapted to microbiological results and severity of infection if required.

Adequate offloading were prescribed during the acute phase according to the ulcer localization and the amount of tissue lost to preserve the wound area and allow the patient's activity.

Patients general health was optimized: heart disease, renal function, glycemic levels, electrolyte balance, malnutrition, anemia and pain were closely checked and treated. A standard electrocardiogram was routinely performed and in case of clinical or instrumental abnormalities, further examination have been performed (echocardiogram, myocardial perfusion scintigraphy, 24 h Holter electrocardiogram monitoring). In case of significant coronary heart disease, coronary revascularization was performed before lower limb revascularization. Carotid arteries were studied by Doppler ultrasound exam and in selected cases by computed tomography (CT). Carotid artery disease was considered present in case of occlusion or stenosis > 50% or in case of previous carotid revascularization (by open surgery o by endovascular approach). In case of stenosis > 70% or ulcerated plaque, angioplasty of carotid vessels or thromboendarterectomy was performed before lower limbs angioplasty. PAD was evaluated by transcutaneous oxygen pressure (TcPO2), Doppler ultrasound and in selected cases by magnetic resonance or CT to detect arterial stenosis and/or obstruction as required by interventional radiologists or vascular surgeons. Hypertension was considered in case of blood pressure values > 140/90 mmHg or therapy with anti-hypertensive drugs [6]; dyslipidemia was considered in case of low density protein > 70 mg/dl or statin therapy [6].

Heart failure (HF) was considered in case of typical symptoms and signs of HF reduced left ventricular ejection fraction (LVEF) (< 40%) or normal or only mildly reduced LVEF and elevated levels of brain natriuretic peptides (BNP > 35 pg/ml and/or NT-proBNP > 125 pg/ml) with not dilated left ventricle (LV) associated to relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction [7]. Dialysis was considered in case of chronic renal replacement therapy.

According to the presence of HF and dialysis, patients were divided in four groups: group 1 without HF and without D, defined as ischemic foot (IF); group 2 with HF and without dialysis, defined as heart ischemic foot (H-IF); group 3 without HF and with dialysis, defined as renal ischemic foot (R-IF); group 4 with HF and with dialysis, defined as heart-renal ischemic foot (HR-IF).

After 12 months of follow-up, we evaluated the followed outcomes: survival with limb salvage, survival with major amputation and death. Limb salvage was defined as healed ulcer or unhealed ulcer with preserved ability to walk no requiring new revascularization or major amputation. Major amputation was defined any amputation above the ankle. All potential predictors of major amputation and death where evaluated.

Statistical analysis was performed by SAS (JMP12; SAS Institute, Cary, NC) for personal computer. Data were expressed as means ± SEM. Comparison between groups were reported by a X^2 test (frequency data) or ANOVA (continuous data). Univariate logistic analysis was performed for all potential predictors variables according to the detected outcome. All predictors identified by univariate analysis were evaluated simultaneously in a multivariable regression. $P < 0.05$ was considered as statistically significant.

Results

Data from a total of 136 Caucasian diabetic patients were analyzed. Sixty-six patients (48,5%) were included in Group A (IF group); twenty-six patients (19,1%) were included in Group B (H-IF group); twenty-four patients (17,6%) were included in Group C (R-IF group) and twenty patients (14,7%) were included in Group D (HR-IF group).

Baseline characteristics of whole population and groups 1,2,3,4 are separately reported in table 1.

The majority of patients were aged (mean age > 65 years), male (72,8%) and had type 2 diabetes (90,4%) with a disease duration of ≈20 years.

Outcomes

After one year of follow-up 103/136 (75,7%) patients survived with limb salvage, 10/136 (7,4%) survived with major amputation, 23/136 (16,9%) patients died.

Survival with limb salvage

The rate of survival with limb salvage for group 1 (IF) in comparison to group 2 (H-IF), group 3 (R-IF) and group 4 (HR-IF) was respectively 92,4% vs 61,5%, 79,2%, 35% ($\chi < 0.0001$) Fig. 1.

Survival with major amputation

The rate of survival with major amputation for group 1 (IF) in comparison to group 2 (H-IF), group 3 (R-IF) and group 4 (HR-IF) was respectively 6,1% vs 7,7%, 8,3%, 10% ($\chi = 0.002$) Fig. 2.

10/136 patients were amputee. The mean time to amputation was 3,5 ± 3,2 months. At the multivariate analysis of all predictors found at univariate analysis, severe infection [HR 2.5 (CI 95% 1.6–3.8) $p = 0.001$], ulcer dimension (> 5 cm^2) [HR 4.7 (CI 95% 2.2–11.3) $p = 0.02$], PTA failure [HR 4.8 (CI 95% 1.9–6.7) $p = 0.02$], inability to walk without help [HR 9.3 (CI 95% 2.4–10.2) $p = 0.002$] were independent predictors of major amputation.

Mortality

The rate of death for group 1 (IF) in comparison to group 2 (H-IF), group 3 (R-IF) and group 4 (HR-IF) was respectively 1,5% vs 30,8%, 12,5%,55% ($\chi < 0.0001$) Fig. 3.

7/23 patients died for septic shock, 11/23 patients for acute heart failure, 2/23 for sudden death, 2/23 for cancer. The mean time to death

Table 1
Baseline characteristic of whole populations and subgroups.

Variables	Whole population (136 patients)	Group 1 (66 patients)	Group 2 (26 patients)	Group 3 (24 patients)	Group 4 (20 patients)	X
Age (years)	68,9 ± 9,7	68,4 ± 10,5	71,9 ± 7,9	67,4 ± 9,7	68,5 ± 8,6	0.3
Sex (male)	72,8%	69,7%	65,4%	79,2%	85%	0.3
Type 2 Diabetes	90,4%	92,4%	76,9%	100%	90%	0.02
Diabetes duration (years)	20,7 ± 11,6	19,6 ± 10,5	23,4 ± 14,5	20,7 ± 10,5	20,8 ± 12,3	0.6
HbA1c* (mmol/mol)	62,7 ± 22,3	59,1 ± 25,1	65,8 ± 24,3	66,9 ± 14,4	63,7 ± 18,5	0.4
HbA1c* (%)	7,88 ± 2,1	7,55 ± 2,28	8,16 ± 2,12	8,26 ± 1,31	7,97 ± 1,68	0.4
Anemia	77,2%	60,6%	100%	79,2%	100%	< 0.0001
Dyslipidemia	68,3%	69,5%	78,2%	66,7%	52,9%	0.4
Ischemic heart disease	64,1%	43,7%	87,5%	75%	89,5%	< 0.0001
Cerebrovascular disease	16,9%	11,1%	16,7%	20,8%	31,6%	0.2
Hypertension	87,7%	93,7%	95,8%	83,3%	63,1%	0.01
Carotid artery disease	34,5%	31,8%	42,3%	25%	45%	0.4
Smoke	13,2%	23,8%	4%	0%	5,2%	0.001
Hospital complications	24,2%	12,1%	34,6%	16,7%	60%	0.0002
Inability to walk	30,8%	12,1%	42,3%	33,3%	75%	< 0.0001
Ulcers size (> 5 cm^2)	66,4%	53%	79,1%	70,8%	90%	0.004
Infection	68,6%	57,6%	83,3%	79,1%	75%	0.04
Severe infection	16,9%	3%	19,2%	20,8%	55%	< 0.0001
Vessels affected (number)	4,3 ± 1,5	3,8 ± 1,3	4,3 ± 1,5	4,4 ± 1,6	5,4 ± 1,5	0.003
PTA† failure	22,4%	9,7%	20,8%	20,8%	68,4%	< 0.0001
PTA† complications	11,2%	17,2%	15,4%	0%	0%	0.004
1 month TcPO2 (mmHg)	44 ± 12,8	47,5 ± 12	43,7 ± 12,1	41,3 ± 12,8	36,5 ± 13	0.004

* HbA1c: glycated haemoglobin.
† PTA: peripheral transluminal angioplasty.

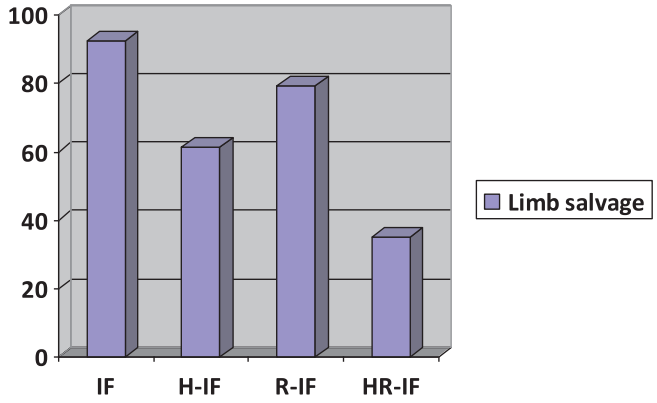

Fig. 1. Survival with limb salvage. $\chi = 0.0001$. IF: ischemic foot; H-IF: Heart ischemic foot; R-IF: renal ischemic foot; HR-IF: hear-renal ischemic foot.

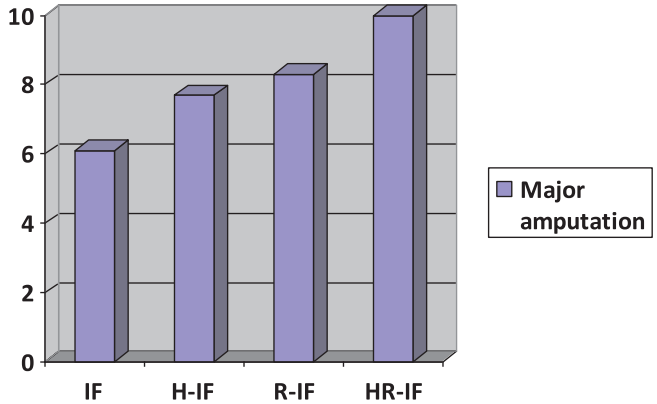

Fig. 2. Survival with major amputaion. $\chi = 0.002$. IF: ischemic foot; H-IF: Heart ischemic foot; R-IF: renal ischemic foot; HR-IF: hear-renal ischemic foot.

was 5,3 ± 3 months.

At the multivariate analysis of all predictors found at univariate analysis, heart failure [HR 3.6 (CI 95% 1.8–6.6) p = 0.0001] and severe infection [HR 2.6 (CI 95% 1.8–4.7) p = 0.003] were independent predictors of death.

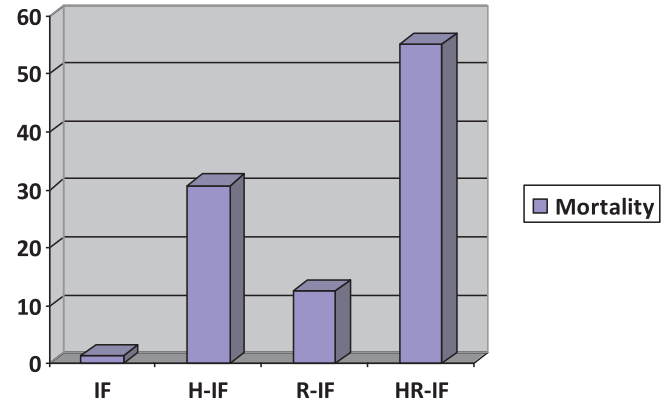

Fig. 3. Mortality. $\chi = 0.0001$. IF: ischemic foot; H-IF: Heart ischemic foot; R-IF: renal ischemic foot; HR-IF: hear-renal ischemic foot.

Conclusions

Diabetic foot patients with PAD show usually worse outcomes than neuropathic patients [1] and according to this data, we focused our study on the role of co-morbidities only in patients with PAD. In fact, PAD is usually considered as independent risk factor for non-healing, major amputation and death while the rate of healing of neuropathic ulcers is close to 100% when removed peaks pressure. [4,8]

Our cohort of patients was composed of diabetic patients with ischemic foot ulcers; half of subjects showed an impairment of heart or renal function. This means that, nowadays, diabetic foot patient with ischemic ulcer is a very complicated and fragile subject and foot ulcers should be considered only an aspect of a complex clinical framework.

However, our data show that ischemic foot without severe heart and renal complications is associated to good results in terms of limb salvage and survival (approximately 95% of limb salvage after one year of follow-up).

Instead, renal ischemic foot is characterized by worse outcomes than not complicated ischemic foot in terms of amputation and mortality. Dialysis is a well recognized factor for foot ulceration, non-

healing and amputation in diabetic subjects [1,9–11]. In a large *meta*-analysis on diabetic-dialyzed patients with ischemic DFUs, Hincliffe reported one-year limb salvage approximately of 70% among the survivors who underwent revascularization and a global mortality approximately of 38% [12]. In a recent paper, our group confirmed that dialyzed subjects have a higher risk of major amputation and death if compared to not dialyzed patients [13]. We reported in fact 65% of limb salvage, 21% of mortality and 14% of major amputation after endovascular revascularization during a mean follow-up of 15 months. Our results are similar to that reported by literature in terms of limb salvage [13], even if our data referred to consecutive subjects while the patients included in similar studies are usually considered for lower limbs revascularization after a careful selection.

This study confirms that dialyzed patients in comparison to patients without renal and heart impairment have higher risk of amputation (8,3 vs 6,1%) and death (12,5 vs 1,5%); however, it must be highlighted that dialyzed patients without heart failure compared to dialyzed patients with heart failure show lower rate of major amputation (8,3% vs 10%) and death (12,5% vs 55%). This group of dialyzed patients have also better outcomes than those reported in our previous above-mentioned study in which we did not discriminate between heart failure and not heart failure dialyzed subjects: major amputation 8,3% (current study) vs 14,8% (previous study) and death 12,5% (current study) vs 21,1% (previous study) [13]. This deeper analysis highlights that probably heart failure plays a key role also in the outcomes of dialyzed patients. However, dialysis and dialysis related complications are able by itself to influence the prognosis, probably due to the severity of PAD, the risk of revascularization failure and the high risk of infection.

The outcomes of heart ischemic foot are fairly similar to renal ischemic foot. Cardiac dysfunction appears to be common in DFUs patient, even in those without known heart disease [14]. It's reported that heart diseases increases the risk of non-healing of ischemic DFUs [15] and coronary artery disease (CAD) was the leading cause of death [16]; furthermore, impaired ejection fraction was independently associated with death in diabetic patients [15].

To our knowledge, only one paper evaluated specifically the role of heart failure in hospitalized patients with DFUs. Lei Xu et al. documented that HF reduces the healing rate and increases the rate of ulcer recurrences, amputation and death [17]. The rate of amputation (minor and major) has been high (28,6%) while the mortality was 11,1%, lower than that reported in out cohort of patients (30,8%), even if we have followed the patients for a longer period (12 vs 3 months) and all subjects involved were exclusively ischemic subjects, therefore affected by several comorbidities [17].

Our mortality resulted also higher than that reported in diabetic patients with HF but without foot ulcers (30,8% vs 9,4%) [18].

Therefore, our study reinforce the concept that HF has a negative impact in the prognosis of DFUs patients, being the leading cause of death as reported in other studies; however, our mortality resulted higher than that reported in general diabetic patients with HF and this data highlights the potential role of ulceration per se for increasing the risk of death. It may be due to hospitalization related factors and mainly to the high risk of infection (79% patients with HF had infected ulcers and 21% severe infection) and infection related complication as septic shock and/or acute HF.

Heart-renal ischemic foot is the most severe pattern of ischemic foot with highest risk of major amputation and mortality. HR-IF patients show a more severe pattern of PAD (more vessels affected, high risk of revascularization failure), higher risk of severe foot infection, higher rate of hospital complications and worse outcomes in comparison to other groups (we report a mortality of approximately 50%).Probably, an active ulcer increases the fragility of these patients and may influence dramatically their prognosis both in terms of limb salvage and life expectancy.

Furthermore, heart-renal ischemic foot patients reported more heart complications and severe infection than other groups and heart failure and severe infection resulted independently related to mortality.

According to the impact of co-morbidities that we found in our analysis, we retain that ischemic diabetic foot patients may be divided in three classes of risk: ischemic foot patients without renal and heart impairment at low risk, renal and heart ischemic foot patients at moderate-high risk, heart-renal ischemic foot patients at highest risk.

In conclusion we retain that an adequate knowledge of co-morbidities may help clinicians in the evaluation of prognosis of diabetic patients with ischemic foot ulcers and to establish the best approach. The fragility related to heart failure and dialysis requires a clinical global approach with a close monitoring of potential heart complications and foot infection.

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Authors contribution: M.M. and L.U. designed the study; M.M. researched data, conducted statistical analysis and wrote the manuscript; L.U. reviewed the manuscript; V.I. contributed to the discussion and reviewed the manuscript; L.G. and R.G. researched data and provided input; V.C. and R.G. contributed to the discussion. M.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

[1] Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51:747–55.
[2] Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg 2007;33:S1–75.
[3] Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998;21:855–9.
[4] Aiello A, Anichini R, Brocco E, et al. Treatment of peripheral arterial disease in diabetes: a consensus of the Italian Societies of Diabetes (SID, AMD), Radiology (SIRM) and Vascular Endovascular Surgery (SICVE). Italian Society of Diabetes; Italian Society of Radiology; Italian Society of Vascular Endovascular Surgery. Nutr Metab Cardiovasc Dis 2014;24(4):355–69.
[5] Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Infectious Diseases Society of America. Clin Infect Dis 2012;54(12):e132–73.
[6] American Diabetes Association. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. Clin Diabetes 2017;35(1):5–26.
[7] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129–200.
[8] Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50(1):18–25.
[9] Ndip A, Lavery LA, Boulton AJ. Diabetic foot disease in people with advance nephropathy and those on renal dialysis. Curr Diab Rep 2010;10:283–90.
[10] Jaar BG, Astor BC, Berns JS, Powe NR. Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. Kidney Int 2004;65:613–20.
[11] Albers M, Romiti M, Braganca Pereira CA, Fonseca RL, da Silva Junior M. A meta-analysis of infra-inguinal arterial reconstruction in patients with end stage renal disease. Eur J Vasc Endovasc Surg 2001;22:294–300.
[12] Hinchliffe RJ, Andros G, Apelqvist J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev 2012;28:179–217.
[13] Meloni M, Giurato L, Izzo V, et al. Long term outcomes of diabetic haemodialysis patients with critical limb ischemia and foot ulcers. Diabetes Res Clin Pract 2016;116:117–22.
[14] Löndahl M, Katzman P, Fredholm O, Nilsson A, Apelqvist J. Is chronic diabetic foot ulcer an indicator of cardiac disease? J Wound Care 2008;17:12–6.
[15] Gershater MA, Löndahl M, Nyberg P, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. Diabetologia 2009;52:398–407.

[16] Faglia E, Clerici G, Clerissi J, et al. Long-term prognosis of diabetic patients with critical limb ischemia. Diabetes Care 2009;32:822–7.
[17] Xu L, Qian H, Gu J, Shi J, Gu X, Tang Z. Heart failure in hospitalized patients with diabetic foot ulcers: Clinical characteristics and their relationship with prognosis. J diabetes 2013;5:429–38.
[18] Dauriz M, Targher G, Laroche C, et al. ESC-HFA Heart Failure Long-Term Registry. Association Between Diabetes and 1-Year Adverse Clinical Outcomes in a Multinational Cohort of Ambulatory Patients With Chronic Heart Failure: Results From the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care 2017 May;40(5):671–8.