Study On Clinical Features and Pathogenetic Factors Associated with Diabetic Foot Gangrene

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1. Abstract

Objective to explore the differences in clinical features, lesion location, and pathomechanism between different types of diabetic foot gangrene and provide evidence-based evidence for the choice of clinical treatment options. Methods A cross-sectional survey study was conducted to collect 266 patients with incipient diabetic foot who were hospitalized in the vasculopathy Department of Shanghai Integrated Traditional Chinese and Western medicine hospital, Shanghai University of Chinese medicine (Shanghai, China), between January 2018 and December 2018, and were divided into wet gangrene group (139 patients) and dry gangrene group (127 patients). The symptomatic signs, infection and inflammation indicators, neuropathy and pain scores, and lower limb vascular examination were collected, and all data were entered into spss21.0 for statistical analysis. Results Patients in the wet gangrene group were heavier than those in the dry gangrene group in terms of body temperature, calf skin temperature on the affected side and rate of abnormality in peripheral diameter, rate of gastrocnemius tenderness, WBC, neut, CRP, ESR, PCT, IL-6, TCSs score, and had a moderate positive correlation with WBC, neut, CRP, IL-6, ABI, TCSs score levels; Patients in the dry gangrene group were heavier than those in the wet gangrene group in BMI, WHR, NRS pain score, ABI, popliteal artery flow rate, and all had significant differences (P < 0.05). Conclusion Wet gangrene has a significant positive correlation with infection, inflammation, neuropathy, and local debridement should not be delayed at an early time; Dry gangrene has a significant positive correlation with vasculopathy, obesity, pain, and local debridement should not be used early.

Diabetic foot (DF) is a serious complication of diabetes, and has become one of the important reasons for the high disability rate, high cost and high mortality rate of diabetic patients [1]. In 1999, WHO defined diabetic foot as: lower extremity infection, ulceration and/or destruction of deep tissues in diabetic patients due to neuropathy and various degrees of peripheral vascular disease [2]. Diabetic foot gangrene is often divided into three categories: wet gangrene, dry gangrene and mixed gangrene in clinical practice. In clinical treatment, the treatment of different types of gangrene is mainly debridement, or vascular intervention, and debridement Timing selection, the current classification still lacks clinical guiding significance, and cannot effectively judge the prognosis, which plagues the choice of treatment methods and timing in clinical treatment.

This study intends to explore clinical rules and provide evidence-based basis for clinical treatment through the study of clinical features, lesion sites and pathological mechanisms of different types of diabetic foot gangrene. Therefore, it is clear whether to choose the debridement surgery program or the vascular intervention program, and to determine the order of use of the two programs.

2. Information and Methods

2.1. General information adopts cross-sectional survey research method. From January 2018 to December 2018, consecutive patients with diabetic foot gangrene admitted to the Department of Vascular Diseases, Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, affiliated to Shanghai University of Traditional Chinese Medicine, were selected as the research subjects, and patients who were repeatedly hospitalized were excluded. The project research has been approved by the Ethics Committee of Shanghai Hospital of Integrated Traditional Chinese and Western Medicine affiliated to Shanghai Traditional Chinese Medicine (Ethics Number: 2017-018-1). A total of 266 patients were included in this study, including 139 cases (70.21±10.75) in the wet gangrene group, 98 males and 41 females; 127 cases (68.95±10.93) in the dry gangrene group, 85 males and 42 females. There was no statistical difference in gender and age between the two groups (P>0.05).

2.2 Diagnostic criteria for the diagnosis of diabetes, refer to the relevant standards in the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2013 Edition)" by the Diabetes Society of the Chinese Medical Association [3], and for the diagnosis of diabetic foot, refer to the "IDF diabetes Relevant standards in Foot Clinical Practice Recommendations [4].

2.3 Inclusion criteria ①meet the diagnostic criteria for diabetic foot; ②appear diabetic foot for the first time; ③meet the diagnostic criteria for wet gangrene and dry gangrene of diabetic foot; ④obtain the consent of the patient himself and sign the informed consent form.

2.4 Exclusion criteria ①with digestive tract, respiratory tract, urinary tract infection, etc., or with taking anti-infective drugs, hormone drugs and other diseases or drugs that affect inflammatory indicators such as white blood cells and C-reactive protein; ②with severe heart, brain, etc. 1. Kidney dysfunction or failure; 3. Incomplete clinical data, which affects the judgment of the results; 4. Patients or their family members disagree.

2.5 Observation indicators (1) Symptoms and signs: body mass index (BMI), waist-to-hip ratio (WHR), body temperature, skin temperature and circumference of the affected and healthy limbs, gastrocnemius tenderness test, etc.; (2) Infection and inflammation indicators: white blood cells (WBC), neutrophil ratio (NEUT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), interleukin-6 (IL-6), etc.; (3) nerve Lesions and pain scores: Toronto Clinical Scoring System (TCSS), Numerical Pain Scale (NRS), etc.; (4) Lower extremity vascular examination: ankle-brachial index (ABI), popliteal artery velocity, etc.

2.6 Statistical methods Statistical and analysis were performed on the entered results by IBM SPSS21.0 software. The measurement data are uniformly represented by (($\overline{x} \pm s$)). Firstly, the normality and homogeneity of variance tests are carried out on the data, and the Student-t test is used for the data satisfying the normal distribution, and the Satterthwaite approximate t test is used for the data satisfying the normal distribution but uneven variance. , and the rank sum test was used for the data that did not meet the normal distribution; the count data were represented by the composition ratio, and the x^2 test was used as the method; the rank sum test was used for the rank data; the Spearman rank correlation analysis was used to study the relationship between the indicators. The test level α=0.05, P<0.05 is statistically significant.

3. Results

3.1. Comparison of symptoms and signs between the two groups of patients (Table 1-4): Compared with the wet gangrene group（W-group）, the dry gangrene group（D-group） had higher BMI and WHR, while the wet gangrene group had higher body temperature, abnormal skin temperature of the affected calf, The abnormal rate of calf circumference and the rate of gastrocnemius muscle tenderness on the affected side were significantly higher than those in the dry gangrene group (P<0.01), and the difference was statistically significant.

3.2. Comparison of infection and inflammation indicators between the two groups: (Table 5) shows that WBC, NEUT, CRP, ESR, PCT, and IL-6 in the wet gangrene group were significantly higher than those in the dry gangrene group (P<0.01), and the difference was statistically significant learning meaning.

3.3. Comparison of neuropathy and pain scores between the two groups (Table 6-7) shows that there are statistically significant differences in the comparison of TCSS scores and NRS pain scores between the two groups (P<0.01). The abnormal TCSS scores of patients in the dry gangrene group were mainly concentrated in 6-8 points, accounting for 28.3% of the total number, and the abnormal NRS scores were mainly concentrated in 4-6 points, accounting for 68.5% of the total number of patients. Mainly concentrated in 9~11 points, accounting for 42.4% of the total number, NRS abnormalities mainly concentrated in 1~3 points, 4~6 points, accounting for 28.8% and 34.5% of the total number, respectively, the incidence of DPN in the wet gangrene group The patients in the dry gangrene group were more obvious, and the pain degree was lower than that of the patients in the dry gangrene group.

3.4. Comparison of vascular lesions in the lower extremities of the two groups (Table 8) shows that the ABI and popliteal artery velocity of the patients in the wet gangrene group were significantly higher than those in the dry gangrene group (P<0.01), and the difference was statistically significant. Among the patients in the wet gangrene group The mean values of ABI and popliteal artery flow velocity were 1.00 and 56.63 respectively, and the mean values of ABI and popliteal artery flow velocity in dry gangrene group were 0.53 and 41.69, respectively.

3.5. Spearman correlation analysis between different types of diabetic foot gangrene and various clinical features (Table 9) shows

that through Spearman correlation analysis, the wet gangrene group is moderately positively correlated with WBC, NEUT, CRP, IL-6, ABI, and TCSS scores There was a low positive correlation with body temperature, abnormal rate of affected calf (skin temperature, circumference, and gastrocnemius tenderness), PCT, ESR, and popliteal artery blood flow velocity, and a negative correlation with BMI, WHR, and NRS score (P <0.01), the difference was statistically significant.

Table 1: Comparison of BMI, WHR, and body temperature between the two groups ($\bar{\mathrm{X}} \pm \mathrm{s}$).

Group	Number	Age	BMI	WHR	Temperature
D-group	127	70.21±10.75	24.63±2.37	0.988±0.058	36.8±0.306
W-group	139	68.95±10.93	23.04±2.74	0.948±0.060	37.4±0.736
Statistical Results		P=0.344	P＜0.01	P＜0.01	P＜0.01

Table 2: Comparison of skin temperature difference between two groups of patients.

Skin Temperature of Affected Leg（Comparison with healthy side)					
Group	Number	Normal	Skin temperature difference≤1℃	1℃＜Skin temperature difference≤2℃	Skin temperature difference＞2℃
D-group	127	94	21	10	2
W-group	139	40	52	42	5
Statistical Results			Z=-7.22; P＜0.01		

Table 3: Comparison of circumference difference between two groups of patients.

Circumferential Diameter of Affected Leg (Comparison with healthy side)					
Group	Number	Same（≤1cm)	1cm≤circumference≤2cm	2cm＜circumference≤4cm	Circumference＞4cm
D-group	127	95	28	4	0
W-group	139	50	57	31	1
Statistical Results			Z=-6.70; P＜0.01		

Table 4: Comparison of gastrocnemius tenderness in the affected calf between the two groups.

Tenderness of Affected Gastrocnemius					
Group	Number	Nothing	Pressing it again will cause pain	Light pressing causes pain	It hurts not to press
D-group	127	84	30	11	2
W-group	139	47	59	24	9
Statistical Results			Z=-5.20; P＜0.01		

Table 5: Comparison of general information and clinical biochemistry of patients in the two groups ($\bar{\mathrm{x}} \pm \mathrm{s}$).

Group	Number	WBC	NEUT	CRP	ESR	PCT	IL-6
		6.61±1.93	62.88±8.8	11.8±20.77	35.92±31.64	0.0614±0.2	13.78±20.82
D-group	127	10.67±4.62	74.97±10.57	91.73±79.6	64.88±37.17	0.2374±0.483	59.05±59.29
Statistical Results		P＜0.01	P＜0.01	P＜0.01	P＜0.01	P＜0.01	P＜0.01

Table 6: Comparison of TCSS scores between the two groups of patients.

			TCSS Scoring system		
Group	Number	0~5分	6~8分	9~11分	12~19分
D-group	127	76	36	12	3
W-group	139	18	32	59	30
Statistical Results		Z=-9.312; P＜0.01			

Table 7: Comparison of NRS pain scores between the two groups.

NRS Pain Rating					
Group	Number	0分	1~3分	4~6分	7~10分
D-group	127	8	10	87	22
W-group	139	41	40	48	10
Statistical Results		Z=-6.956; P＜0.01			

Table 8: Comparison of ABI and popliteal artery blood flow velocity between the two groups of patients ($\bar{x} \pm s$).

Group	Number	ABI	Popliteal Artery Velocity
		0.53±0.215	41.69±25.42
D-group	127	1.00±0.206	56.63±19.87
Statistical Results		P＜0.01	P＜0.01

Table 9: Correlation between different types of diabetic foot gangrene and various clinical features.

Different Types of Gangrene		
Clinical Features	R value	P value
Age	-0.054	0.38
BMI	-0.361	＜0.01
WHR	-0.359	＜0.01
Temperature	0.454	＜0.01
Calf skin temperature difference	0.444	＜0.01
Calf circumference difference	0.412	＜0.01
Calf gastrocnemius tenderness	0.32	＜0.01
WBC	0.526	＜0.01
NEUT	0.528	＜0.01
CRP	0.644	＜0.01
ESR	0.39	＜0.01
PCT	0.489	＜0.01
IL-6	0.562	＜0.01
TCSS score	0.594	＜0.01
NRS score	-0.456	＜0.01
ABI	0.759	＜0.01
Popliteal artery blood flow velocity	0.407	＜0.01

4. Discussion

The occurrence and development of diabetes are closely related to BMI and WHR [5], and WHR mainly reflects the distribution of fat in the waist and hips. Some studies have found that abdominal obesity is more harmful than general obesity [6]. This study found that the BMI and WHR of patients in the dry gangrene group were significantly higher than those in the wet gangrene group, and the difference was statistically significant. The proportion of obese and overweight patients in the gangrene group is also higher, which fully demonstrates that obesity has a certain impact on the lower extremity arteries of diabetic patients.

WBC, NEUT, CRP, ESR, PCT, IL-6, etc. are all important indicators of infection and inflammation in the body, and they are also the most widely used clinical markers of infection and inflammation. WBC is an important cell for the body to resist external infections and produce immunity. CRP appears earlier than WBC and NEUT. It is an acute phase protein synthesized by liver cells when the body is stimulated by inflammation. It is generally considered to be a very sensitive inflammation and tissue damage. Marker [7], also involved in the whole process of inflammatory response [8]; IL-6 can stimulate and improve the proliferation and differentiation of cells involved in immune response, including stimulating CRP PCT is an early inflammatory marker of bacterial infection, and it is widely used in the diagnosis and treatment of infectious diseases [9], it is useful for the monitoring of diabetic foot infection and the prediction of amputation/toe risk important value [10]. ESR is a test index that reflects the aggregation of erythrocytes, and ESR will increase rapidly under various pathological conditions such as inflammation, tissue damage, and necrosis. The reasons for the increase of ESR are complex and often non-specific, but there will be a significant increase in the active phase of inflammation and

injury [11], so it can be used as a marker for judging the activity and prognosis of diabetic foot gangrene lesions an important indicator. This study found that WBC, NEUT, CRP, ESR, PCT, and IL-6 in the wet gangrene group were significantly higher than those in the dry gangrene group. The abnormal rate and gastrocnemius tenderness rate were also significantly higher than those in the dry gangrene group (P<0.01), indicating that the infection and inflammatory response in the wet gangrene group were more severe than those in the dry gangrene group, and the abnormal rate of the affected calf circumference and gastrocnemius muscle tenderness were significantly higher The dry gangrene group also showed that the wet gangrene group had a wide range of infection and necrosis, suggesting that the diabetic foot wet gangrene type is a type of diabetic foot mainly infected. WBC, NEUT, CRP, ESR, PCT, IL-6, The abnormal rate of body temperature and ipsilateral calf (skin temperature, circumference, gastrocnemius tenderness) can effectively distinguish wet gangrene type from dry gangrene type. Because the infection is more serious in the wet gangrene group, the condition should be judged timely and correctly, and effective anti-infection treatment should be given. Assess the severity of diabetic foot infection.

The American Diabetes Association (ADA) recommends that diabetic patients should be screened for DPN at least once a year [12], and among the many DPN screening methods, the TCSS clinical scoring system combines independent individual screening It can also improve the shortcomings of neuro electrophysiology, so it has irreplaceable advantages in the screening and diagnosis of DPN, and can be used for preliminary assessment of the severity of DPN. NRS Pain Scale is a pain assessment scale that is widely used clinically. It is suitable for elderly patients [13] and has a high accuracy for pain assessment. In this trial, 172 patients (64.7%) had DPN with TCSS score. At the same time, the positive rate and severity of DPN in the TCSS score of the patients in the wet gangrene group were significantly higher than those in the dry gangrene group. Among them, the positive rate and degree of pain in the dry gangrene group were significantly heavier than those in the wet gangrene group, which also fully demonstrated that the diabetic peripheral nerve damage in the wet gangrene group was significantly heavier than that in the dry gangrene group, especially for pain Sensation of sensation and temperature is weaker than that of the dry gangrene group, and the response to external stimuli is more sluggish, and skin lesions and ulcers are more likely to occur due to various inducements. At the same time, due to neuron damage, the neurotrophic supply of DPN patients becomes poor. Atrophy of the limbs, gradual prominence and deformity of the bones of the foot, and more prone to friction and ulceration, which in turn leads to the occurrence and development of diabetic foot [14].

ABI is often used to assess the severity of lower extremity arterial ischemia, which is simple, inexpensive, effective, and specific, and is often used in the screening of lower extremity arterial lesions. The results of this study showed that the mean value of ABI in the wet gangrene group reached 1.0, which belonged to the normal range, while the mean value of ABI in the dry gangrene group was 0.53, which belonged to moderate stenosis. ABI and popliteal artery velocity were also significantly higher than those in the dry gangrene group (P<0.01), and the difference was statistically significant. It can be seen that ABI can be used as an effective index to distinguish wet gangrene group from dry gangrene group, and vascular occlusion ischemia is a very important reason why dry gangrene group is different from wet gangrene group.

In this study, Spearman correlation analysis was performed on different types of diabetic foot gangrene and various clinical features, and found that there were significant correlations between different clinical features of diabetic foot gangrene and pathogenic factors (infection, vascular disease, neuropathy, etc.). It can be considered that wet gangrene has a significant positive correlation with infection, inflammation, and neuropathy, and dry gangrene has a significant positive correlation with vascular disease, obesity, and pain.

The late famous doctor Xi Jiuyi summed up decades of experience in clinical diagnosis and treatment of diabetic foot, and first proposed the concept of "diabetic foot tendinosis and necrosis (gangrenes)" in the 1980s [15], concluded that all these patients had tendon and fascia degeneration and necrosis. In the dry gangrene group, because the main cause is vascular ischemia, hyperglycemia, inflammation and other changes did not significantly affect the nerves, tendons, fascia and other tissues of the foot, so the necrosis characteristics were also different from those in the wet gangrene group. There are big differences in severe infections, mainly dry gangrene with local blackening, relatively light infection, and the body's immune cells and immune factors are also difficult to reach the local area to produce corresponding inflammation due to poor blood supply reaction. In this study, the symptoms, signs, clinical tests, imaging and other indicators of diabetic foot gangrene were collected through a large sample to clarify the pathological mechanism of different pathogenic factors and guide the selection of different debridement methods and surgical timing.

To sum up, the treatment of wet gangrene wounds: in principle, local debridement should be done sooner rather than later. Incision and drainage, removal of putrid tendons and other necrotic tissues are possible to remove degenerated and necrotic tendons and other necrotic tissues, and adequate drainage should be maintained. At the same time, infection control should be strengthened, and systemic circulation and microcirculation should be improved to prevent infection and wound spread. Treatment of dry gangrene wounds: in principle, local debridement should be delayed rather than early, and vascular interventional therapy can be done if necessary. Keep the dry gangrene stable, pay attention to local disinfection, keep the wound surface and per wound dry, and after the

necrotic boundary is clear, the local collateral circulation is basically established, and then the necrotic tissue removal operation is performed. Remove necrotic tissue, open the wound, and the bone section should be slightly shorter than the soft tissue section. If the blood supply is improved, necrotic tissue resection and suture can also be performed, and an incision proximal to the boundary can be used, and toe resection and suture or hemi foot resection and suture can be performed.

5. Acknowledgment

6. Competing Interests

The authors have declared that no competing interests exist.

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