Differences in initial versus recurrent diabetic foot ulcers at a specialized tertiary diabetic foot care center in China

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Abstract

Objective: To investigate the characteristics of diabetic foot ulcer (DFU) recurrence.

Methods: A total of 573 patients with DFUs were recruited and divided into an initial group (395 patients) and a recurrence group (178 patients). The factors related to recurrence were analyzed using multivariate regression.

Results: The recurrence group had longer diabetes duration (odds ratio [OR] 192; 95% confidence interval 120, 252 vs. 156; 96, 240); lower glycated hemoglobin levels (OR 8.1; 95% CI 6.8, 9.6 vs. 9.1; 7.4, 10.5), and higher rates than the initial group of amputation (37.5% vs. 2.0%), history of vascular intervention (21.3% vs. 3.9%), retinopathy (77.7% vs. 64.7%), callus (44.4% vs. 20.8%), foot deformity (51.2% vs. 24.6%), and outdoor sports shoe wearing (34.0% vs. 21.2%). Multiple factor logistic regression analysis showed that diabetes duration (OR 1.004), callus (OR 2.769), vascular intervention (OR 2.824) and amputation (OR 22.256) were independent risk factors for DFU recurrence.

Conclusion: Diabetes duration, callus, history of vascular intervention, and amputation were independent risk factors for recurrent DFUs in a cohort of Chinese patients with active DFU. The prevention and treatment of DFUs, especially callus treatment, foot care, and blood glucose control, should be improved in China.

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Introduction
Diabetic foot ulcers (DFUs) are one of the most serious complications of diabetes. DFUs are associated with high disability and mortality rates and are the main reason for nontraumatic amputation in patients with diabetes.\(^1\)\(^-\)\(^3\) The annual incidence of initial DFUs is 8.1% in patients with diabetes over 50 years old in China,\(^4\) which is higher than the global rate of 6.3% among individuals with diabetes reported by Armstrong et al. in 2017.\(^5\) Owing to the varying degrees of DFU healing that occur during different periods, the recurrence rates of diabetic foot differ in the published literature, ranging from 17% to 40% at 12 months.\(^5\)\(^,\)\(^6\) In a cohort study, 31.6% of Chinese patients with diabetic foot reportedly experienced recurrence at 12 months after ulcer healing. However, national data on DFUs in China are lacking.\(^4\)

For patients with recurrent ulcers, follow-up and treatment at a specialized tertiary diabetic foot care center are the most important elements of management. Integrated foot care\(^7\) and effective pathophysiological treatment targeting DFUs are the main tasks for clinicians. The International Working Group on the Diabetic Foot (IWGDF) considers integrated foot care and foot surgery as the main preventive interventions.\(^8\)

In China, specialized diabetic foot centers are newly developing, and foot treatment is gradually becoming standardized.\(^9\) It is important to understand the clinical characteristics and changes in patients with diabetic foot, especially those with recurrent ulcers, after several years of standardized treatment so as to improve the level of DFU diagnosis and treatment. Therefore, we designed a cross-sectional study to clarify the clinical characteristics of recurrent DFUs at our center. We specifically included data regarding foot care and self-management in the center and compared these with traditional risk factors of DFUs, to evaluate risk factors of ulcer recurrence and optimize clinical diagnosis and treatment.

Methods
Patients with DFUs were continuously enrolled at our specialized tertiary diabetic foot care center in the PLA Strategic Support Force Medical Center (The 306th Hospital of the PLA) in China between March 2014 and October 2018. The study protocol and informed consent were in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the 306th Hospital of the PLA. All enrolled patients signed a written informed consent form. Daily management and services for DFUs at the center included: 1) foot screening and follow-up visits (including foot clinical manifestations and medical history inquiry, foot inspection, plantar pressure detection, foot neuropathy screening, and ankle–brachial index (ABI) evaluation); 2) debridement and offloading intervention and daily medical care and dressing change for foot ulcers; 3) hypoglycemic therapy, antihypertensive therapy, anti-inflammatory treatment, and other
comprehensive internal medicine and complication evaluations; and 4) the departments involved should be consulted to determine whether referral is needed, according to the referral criteria. The criteria for referral were as follows: 1) patients with ischemic foot ulcer should be transferred to vascular surgery for vascular intervention; 2) patients with diabetic foot and uncontrollable resting pain should be transferred to vascular surgery for vascular intervention; 3) patients with a large ulcerated area of the foot, which cannot be treated with routine dressing change and debridement, should be transferred to the wound care center; 4) patients with major amputation should be transferred to the orthopedics department for amputation.

Inclusion and exclusion criteria

The inclusion criterion was patients with DFU in our specialized tertiary diabetic foot care center. The diagnosis of DFU was in line with the definition of diabetic foot of the IWGDF. We excluded patients with nondiabetic foot conditions. A recurrent ulcer was defined as any secondary ulcer, regardless of its location. Patients with recurrent ulcers were classified as the recurrence group and those with a first foot ulcer were classified as the initial group.

Data collection

The clinical characteristics of interest included sex, age, disease duration, smoking history, vascular intervention, amputation, diet control, and shoe and sock use. The diagnosis of chronic complications of diabetes referred to guidelines for the prevention and treatment of type 2 diabetes in China (2017 version), the type 2 diabetes guidelines formulated by the American Diabetes Association (ADA, 2019 Edition) and the diabetic foot guidelines developed by the IWGDF (2019 update). Laboratory examination included the indicators blood glucose and hemoglobin A1c (HbA1c). The presence of neuropathy was determined according to the following: 1) diabetes mellitus; 2) neuropathy at or after diagnosis of diabetes mellitus; 3) clinical symptoms and signs consistent with those of diabetic neuropathy (DPN); 4) in patients with clinical symptoms (e.g., pain, numbness, or abnormal sensation), any indicators of nerve abnormality (ankle reflex, acupuncture pain, vibration, pressure, temperature); in patients without clinical symptoms, abnormal results in any two of the above five examinations, indicating a clinical diagnosis of DPN; 5) other nerve system diseases were excluded; and 6) in unconfirmed results of the above examinations, a differential diagnosis is needed. Neuroelectromyography can be performed. The indicators for a diagnosis of diabetes mellitus with lower extremity arterial disease (LEAD) were as follows: 1) a diagnosis of diabetes mellitus; 2) clinical manifestations of arterial stenosis or occlusion of a lower extremity (resting pain and intermittent claudication); 3) with resting ABI ≤ 0.9, LEAD should be diagnosed regardless of patient’s lower limb discomfort; 4) patients with lower limb discomfort during exercise and a resting ABI > 0.9 should be diagnosed with LEAD if the ABI decreases by 15% to 20% after a treadmill test or imaging indicating vascular stenosis; 5) Doppler ultrasound, computed tomography angiography, magnetic resonance angiography, and digital subtraction angiography (DSA) showing stenosis or occlusion of a lower extremity artery; and 6) severe limb ischemia diagnosed with resting ABI < 0.4, ankle artery pressure < 50 mmHg, or toe artery pressure < 30 mmHg. We described callus and foot deformity as characteristics of at-risk feet. Foot skin abnormalities were defined as thinning of the skin, intradermal and subcutaneous
bleeding, blisters, and chapped skin usually not reaching the dermis. The degree of foot ulcer was defined according to the Meggitt–Wagner classification.

**Statistical analysis**

We used IBM SPSS 24.0 software for the statistical analyses (IBM Corp., Armonk, NY, USA). Classification variables are expressed as percentage (%), and the χ² test was performed. Continuous variables with normal distributions are presented as mean ± standard deviation (x ± s), and comparisons between groups were performed with the t-test. Nonnormally distributed variables are represented as quartiles, and the nonparametric test was adopted. Ten risk factors were significant in single factor analysis (P < 0.05 was considered statistically significant) including diabetes duration, HbA1c, retinopathy, callus, foot skin abnormality, foot deformity, a history of vascular intervention, amputation, Wagner DFU classification, and use of outdoor sports shoes. These factors were tested in multivariable analysis. With use of a backward elimination variable-selection procedure, only covariables that were significant (P < 0.05) were retained in the final model.

**Results**

In total, 573 patients with DFU were included. Of these, 64.6% in the initial group were men, with median age 61 years; 72.5% were men in the recurrence group, with median age 60 years; 31.1% had recurrent ulcers. When comparing the clinical data between the two groups, there were no significant differences according to sex or age. The recurrence group had a longer diabetes duration and lower HbA1c level than the initial group (P < 0.05). Regarding the incidence of complications, the recurrence group had a significantly higher rate of diabetic retinopathy than the initial group (77.7% vs. 64.7%), but there were no significant difference in the percentages of neurological or renal complications between the two groups. A higher proportion of patients in the recurrence group than in the initial group underwent amputation (37.5% vs. 2.0%, P < 0.05) and vascular intervention (21.3% vs. 3.9%, P < 0.05). Regarding foot ulcer characteristics and grading, the recurrence group had significantly higher percentages of foot deformity (51.2% vs. 24.6%, P < 0.05), callus (44.4% vs. 20.8%, P < 0.05) and foot skin abnormality (80.0% vs. 70.9%, P < 0.05) than the initial group. There were no differences in the percentages of ABI abnormalities, pulse wave shape abnormalities, or clinical manifestations including resting pain and intermittent claudication between the groups. Our research also indicated that the percentage of Wagner 2 and 3 grades in the recurrence group were significantly higher than the percentages in the initial group (Table 1).

Regarding patient self-management, there were no significant differences in diet control, smoking, or indoor sock use between the two groups. The percentage of outdoor sport shoe use in the recurrence group was higher than that in the initial group, and the difference was statistically significant (P < 0.05) (Table 2).

The results of multiple factor logistic regression analyses are shown in Table 3. Diabetes duration (odds ratio [OR = 1.004, P = 0.002), history of vascular intervention (OR = 2.824, P < 0.001), amputation (OR = 22.256, P < 0.001), and callus (OR = 2.769, P < 0.001) were independent risk factors for DFU recurrence.

**Discussion**

High rates of ulcer recurrence have been confirmed to be associated with the degree of limb pathophysiology, which mainly
| Factors                        | Initial group | Recurrence group | $\chi^2/Z$ | P     |
|-------------------------------|---------------|------------------|-----------|-------|
| N                             | 395 (68.9%)   | 178 (31.1%)      | 3.478     | 0.062 |
| Sex                           |               |                  |           |       |
| Male                          | 255 (64.6%)   | 129 (72.5%)      |           |       |
| Female                        | 140 (35.4%)   | 49 (27.5%)       |           |       |
| Age (years)                   | 61 (53, 70)   | 60 (55, 70)      | -0.477    | 0.633 |
| Diabetes duration (months)    | 156 (96, 240) | 192 (120, 252)   | -3.578    | < 0.001 |
| HbA1c (%)                     | 9.1 (7.4, 10.5)| 8.1 (6.8, 9.6)  | -3.836    | < 0.001 |
| Retinopathy                   |               |                  |           |       |
| Yes                           | 205 (64.7%)   | 115 (77.7%)      | 7.798     | 0.005 |
| No                            | 112 (35.3%)   | 33 (22.3%)       |           |       |
| Neuropathy                    |               |                  |           |       |
| Yes                           | 275 (75.8%)   | 135 (81.8%)      | 2.401     | 0.121 |
| No                            | 112 (35.3%)   | 33 (22.3%)       |           |       |
| Diabetic nephropathy          |               |                  |           |       |
| Yes                           | 203 (53.7%)   | 104 (61.9%)      | 3.178     | 0.075 |
| No                            | 175 (46.3%)   | 64 (38.1%)       |           |       |
| Callus                        |               |                  |           |       |
| Yes                           | 73 (20.8%)    | 68 (44.4%)       | 22.570    | < 0.001 |
| No                            | 278 (79.2%)   | 85 (55.6%)       |           |       |
| Intermittent claudication     |               |                  |           |       |
| Yes                           | 64 (19.0%)    | 19 (12.8%)       | 2.745     | 0.098 |
| No                            | 273 (81.0%)   | 129 (87.2%)      |           |       |
| Resting pain                  |               |                  |           |       |
| Yes                           | 48 (14.3%)    | 14 (9.4%)        | 2.214     | 0.137 |
| No                            | 288 (85.7%)   | 135 (90.6%)      |           |       |
| Foot skin abnormality         |               |                  |           |       |
| Yes                           | 266 (70.9%)   | 136 (80.0%)      | 4.968     | 0.026 |
| No                            | 109 (29.1%)   | 34 (20.0%)       |           |       |
| Foot deformity                |               |                  |           |       |
| Yes                           | 73 (24.6%)    | 63 (51.2%)       | 28.193    | < 0.001 |
| No                            | 224 (75.4%)   | 60 (48.8%)       |           |       |
| Abnormal ABI in the affected  | 1.04 (0.78, 1.13)| 1.01 (0.72, 1.15) | -0.458 | 0.647 |
| dorsalis pedis artery         |               |                  |           |       |
| Abnormal ABI in the affected  | 1.06 (0.78, 1.17)| 1.06 (0.73, 1.19) | -0.444 | 0.657 |
| posterior tibial artery       |               |                  |           |       |
| Abnormal ABI in the contralat-| 1.013 | 0.314 |
| eral dorsalis pedis artery    |               |                  |           |       |
| Yes                           | 121 (36.8%)   | 60 (41.7%)       |           |       |
| No                            | 208 (63.2%)   | 84 (58.3%)       |           |       |
| Abnormal ABI in the contralat-| 0.669 | 0.413 |
| eral posterior tibial artery  |               |                  |           |       |
| Yes                           | 139 (41.9%)   | 67 (45.1%)       |           |       |
| No                            | 193 (58.1%)   | 79 (54.1%)       |           |       |
| Abnormal waveform of the dor- |               |                  |           |       |
| salis pedis artery            |               |                  |           |       |
| One-way                       | 197 (64.0%)   | 101 (74.8%)      |           |       |

(continued)
comprises ischemia, infection, DPN, and abnormal biomechanical loading of the foot. Therefore, we selected indexes of the above four aspects to analyze the risk factors for foot ulcer recurrence. Four risk factors that were identified: duration of diabetes, history of vascular intervention, amputation, and callus.

We found that amputation was the strongest predictor of DFU recurrence, which is consistent with previous studies. Although amputation can remove local infection foci to avoid severe bacteremia and multiple organ damage and maintain high-level limb function, amputation is associated with changes in biomechanics, such as plantar pressure and gait, thus increasing the risk of ulcer recurrence. Paola et al. showed that using shoes with a rocker-type sole and custom-molded insoles together with intensive ambulatory check-ups can reduce ulceration recurrence and re-amputation rates. Although the guidelines for DFU in China also mention plantar decompression, the clinical use of personalized shoes and insoles is relatively rare in China.

Peripheral arterial disease is the primary cause of DFUs and a risk factor for ulcer recurrence. Vascular intervention can ameliorate the blood supply to lower extremity blood vessels and supply ischemic tissue oxygen to a certain extent. Vascular intervention is currently the main treatment for refractory ulcers and chronic ischemic disease of the lower extremities. Our study showed that patients in the recurrence group received vascular interventions five times more often than those in the initial group (see Table 3). This means that the proportion of patients with chronic lower extremity ischemic disease was higher in

| Factors | Initial group | Recurrence group | $\chi^2/Z$ | P |
|---------|---------------|------------------|-----------|---|
| Two-way | 68 (22.1%)    | 23 (17.1%)       |           |   |
| Three directions | 43 (13.9%) | 11 (8.1%)       |           |   |
| Abnormal waveform of the posterior tibial artery on the affected side | | | 4.003 | 0.235 |
| One-way | 187 (60.5%)  | 87 (64.0%)       |           |   |
| Two-way | 76 (24.6%)   | 38 (27.9%)       |           |   |
| Three directions | 46 (14.9%) | 11 (8.1%)       |           |   |
| History of vascular intervention | | | 43.786 | < 0.001 |
| Yes | 15 (3.9%) | 38 (21.3%) |           |   |
| No | 372 (96.1%) | 140 (78.7%) |           |   |
| Amputation | | | 134.786 | < 0.001 |
| Yes | 8 (2.0%) | 66 (37.5%) |           |   |
| No | 384 (98.0%) | 110 (62.5%) |           |   |
| Wagner grade | | | 13.859 | 0.017 |
| 0–1 | 31 (8.1%) | 12 (7.0%) |           |   |
| 2 | 98 (25.9%) | 54 (31.4%) |           |   |
| 3 | 154 (40.6%) | 85 (49.4%) |           |   |
| 4 | 95 (25.1%) | 21 (12.2%) |           |   |
| 5 | 1 (0.3%) | 0 (0.0%) |           |   |

Data are presented as n (%) or median (P25, P75). HbA1c: glycated hemoglobin; ABI: ankle–brachial index.
the recurrence group than in the initial group. Most patients received timely surgical treatment. Therefore, vascular intervention has more than an etiological role in the development of an ulcer; it might be better to speak in terms of indicators for potential recurrent ulceration rather than risk factors.

Callus is a response to high mechanical stress on some areas of the foot. Subcutaneous hemorrhage within the callus and continuing to walk on a foot with protective sensory loss are important factors that can induce an ulcer. Lesions can be managed with the use of properly fitting shoes and padding or with surgery to correct abnormal mechanical stresses. The 2019 IWGDF guidelines emphasize that the removal of calluses, including calluses under a wound and calluses at non-wound sites can effectively reduce foot pressure, increase local blood supply, and promote wound healing. Callus was a clear risk factor for recurrent ulcers in our study, indicating that the treatment of neuropathy and plantar decompression in patients with recurrent ulcer remains insufficient. In fact, screening for calluses has been included in the guidelines for diabetic foot in China. However, few podiatry clinics and podiatry nurses and other specialized professionals exist in the country. Patients usually visit local nonmedical personal care facilities to seek toenail and callus care and treatment, which greatly increases the probability of ulcer occurrence and recurrence.

Table 2. Self-management in the two groups.

| Factors                        | Initial group, n (%) | Recurrence group n (%) | $\chi^2$ | P   |
|--------------------------------|----------------------|------------------------|---------|-----|
| Total number (%)               | 395 (68.9%)          | 178 (31.1%)            | 0.591   | 0.442 |
| Diet                           |                      |                        |         |     |
| Not controlled                 | 286 (73.3%)          | 125 (70.2%)            |         |     |
| Controlled                     | 104 (26.7%)          | 53 (29.8%)             |         |     |
| Smoking                        |                      |                        | 1.943   | 0.378 |
| No smoking                     | 214 (56.0%)          | 89 (54.3%)             |         |     |
| Smoking                        | 107 (28.0%)          | 41 (25.0%)             |         |     |
| Quit smoking                   | 61 (16.0%)           | 34 (20.7%)             |         |     |
| Wears socks every day          |                      |                        | 4.001   | 0.135 |
| Always                         | 265 (83.1%)          | 106 (75.2%)            |         |     |
| Only in summer                 | 37 (11.6%)           | 25 (17.7%)             |         |     |
| Often                          | 17 (5.3%)            | 10 (7.1%)              |         |     |
| Wears socks indoors            |                      |                        | 0.213   | 0.889 |
| Always                         | 163 (51.1%)          | 73 (52.5%)             |         |     |
| Only in summer                 | 68 (21.3%)           | 27 (19.4%)             |         |     |
| Often                          | 88 (27.6%)           | 39 (28.1%)             |         |     |
| Wears outdoor sports shoes     |                      |                        | 8.599   | 0.003 |
| Seldom                         | 252 (78.8%)          | 95 (66.0%)             |         |     |
| Regularly                      | 68 (21.2%)           | 49 (34.0%)             |         |     |
| Wears outdoor leather shoes   |                      |                        | 0.498   | 0.524 |
| Seldom                         | 258 (80.6%)          | 112 (77.8%)            |         |     |
| Regularly                      | 62 (19.4%)           | 32 (22.2%)             |         |     |
| Shoes                          |                      |                        | 0.223   | 0.637 |
| Suitable                       | 185 (58.2%)          | 77 (55.8%)             |         |     |
| Unsuitable                     | 133 (41.8%)          | 61 (44.2%)             |         |     |
To prevent diabetic foot, foot care is as important as foot treatment. For patients with diabetes who have initial or recurrent foot ulcers, nursing staff should cooperate with doctors in foot inspection, supervise patients with respect to follow up, and educate patients with diabetic foot, including persuading patients to quit smoking, formulating a diabetic diet, and recommending that patients wear protective, comfortable shoes and socks. Our results showed that patients in the recurrence group were more likely to wear outdoor sports shoes than those in the initial group, and the difference was statistically significant. However, there was no significant difference in smoking cessation, reasonable diet control, and sock-wearing habits between the two groups, suggesting that the effectiveness of foot care education in the center needs to be enhanced.

Hypoglycemic therapy can significantly reduce the risk of diabetic microvascular complications. HbA1c should be lower than 7% in patients with DFUs. Neither the value of HbA1c in the recurrence group nor that in the initial group were up to this standard, suggesting that blood glucose control in patients with DFUs should be improved. Moreover, the level of glycosylation in the recurrent group was lower than that in the initial group, which may be a result of the greater attention to and compliance of patients with recurrent ulcers with respect to blood glucose control.

The limitation of our study is that this was a cross-sectional study, so the strength of the evidence is considered low. Moreover, in the selection of infection indicators, the Wagner grading system can only be used to evaluate the impact of infection depth on ulcer recurrence, which is not as comprehensive as the IWGDF/Infectious Disease Society of America scoring system.

**Conclusion**

In our comparison of recurrent ulcers and initial ulcers, we identified that diabetes duration, callus formation, history of vascular intervention, and amputation were independent risk factors for recurrent DFUs. Callus formation can be diagnosed during a foot examination and resolved with callus treatment in a specialized tertiary diabetic foot care center. Therefore, specialist clinicians should focus more on improving foot pressure, to effectively prevent ulcer recurrence. Our results also suggest that defects exist in the prevention and management of foot ulcers at our center.

### Table 3. Multiple factor logistic regression analysis.

| Variable                          | β    | SE (β) | P    | OR   | 95% CI (OR) |
|-----------------------------------|------|--------|------|------|-------------|
| Duration                          | 0.004| 0.001  | 0.002| 1.004| 1.001–1.006 |
| History of vascular intervention  |      |        |      |      |             |
| No                                |      |        |      |      |             |
| Yes                               | 1.468| 0.378  | < 0.001| 2.824| 1.782–4.474 |
| Amputation                        |      |        |      |      |             |
| No                                |      |        |      |      |             |
| Yes                               | 3.103| 0.403  | < 0.001| 22.256| 10.108–49.003 |
| Callus                           |      |        |      |      |             |
| No                                |      |        |      |      |             |
| Yes                               | 1.038| 0.235  | < 0.001| 2.769| 1.772–4.327 |

SE: standard error; OR: odds ratio; CI: confidence interval.
For example, we should strengthen efforts to reasonably reduce blood sugar and more effectively carry out foot care education for patients. This study presents the characteristics of recurrent DFUs in China and clearly reflects the current deficiencies of our center regarding diabetic foot care and the diagnosis and treatment of diabetic foot disease. In the future, we will follow the IWGDF guidelines and gradually standardize the grading, prevention and management of DFUs.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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