AnnalsofClinicalandMedical Case Reports

ResearchArticle ISSN2639-8109Volume10

Study On Clinical Features and Pathogenetic FactorsAssociated with Diabetic Foot Gangrene

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Received:11Nov2022
Accepted: 05 Dec 2022
Published:13Dec2022
JShort Name:ACMCR

Citation:

Ye-min C, Cheng Z, Study On Clinical Features and PathogeneticFactorsAssociatedwithDiabeticFootGangrene. Ann Clin Med Case Rep. 2022; V10(9): 1-6

Keywords:

Diabetic Foot Gangrene; Dry Gangrene; Wet Gangrene;ClinicalFeatures;CorrelationStudies

1. Abstract

Objectivetoexplorethedifferencesinclinicalfeatures,lesionlocation,andpathomechanismbetweendifferenttypesofdiabeticfoot gangrene and provide evidence-based evidence for the choice of clinicaltreatmentoptions.MethodsAcross-sectionalsurveystudy was conducted to collect 266 patients with incipient diabetic foot who were hospitalized in the vasculopathy Department of ShanghaiIntegratedTraditionalChineseandWesternmedicinehospital, 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,neuropathyandpainscores,andlowerlimbvascularexamination were collected, and all data were entered into spss21.0 forstatisticalanalysis.ResultsPatientsinthewetgangrenegroup 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 heavierthanthoseinthewetgangrenegroupinBMI,WHR,NRS pain score,ABI, popliteal artery flow rate, and all had significant differences (P<0.05). ConclusionWetgangrenehas asignificant positivecorrelationwithinfection,inflammation,neuropathy,and localdebridementshouldnotbedelayedatanearlytime;Drygangrenehasasignificantpositivecorrelationwithvasculopathy,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 neuropathyandvariousdegreesofperipheralvasculardisease[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 Timingselection,thecurrentclassificationstilllacksclinicalguidingsignificance,andcannoteffectivelyjudgetheprognosis,which plagues the choice of treatment methods and timing in clinical treatment.

This study intends to explore clinical rules and provide evidence-basedbasisforclinicaltreatmentthroughthestudyofclinicalfeatures,lesionsitesandpathologicalmechanismsofdifferent types of diabetic foot gangrene. Therefore, it is clear whether to choosethedebridementsurgeryprogramorthevascularinterven- tion program, and to determine the order of use of the two pro- grams.

2. InformationandMethods

General information adopts cross-sectional survey research method. From January 2018 to December 2018, consecutive pa- tients with diabetic foot gangrene admitted to the Department of Vascular Diseases, Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, affiliated to Shanghai Universi- ty ofTraditional 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 CommitteeofShanghaiHospitalofIntegratedTraditionalChinese 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)inthedrygangrenegroup,85malesand42females. There was no statistical difference in gender and age between the two groups (P>0.05).

Diagnostic criteria for the diagnosis of diabetes, refer to the relevantstandardsinthe“GuidelinesforthePreventionandTreat- mentofType2DiabetesinChina(2013Edition)”bytheDiabetes Society of the Chinese MedicalAssociation [3], and for the diag- nosis of diabetic foot, refer to the “IDF diabetes Relevant stand- ards in Foot Clinical Practice Recommendations [4].

Inclusion criteria ①meet the diagnostic criteria for diabetic foot; ②appear diabetic foot for the first time; ③meet the diag- nosticcriteriaforwetgangreneanddrygangreneofdiabeticfoot; ④obtaintheconsentofthepatienthimselfandsigntheinformed consent form.

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 inflamma- toryindicatorssuchaswhitebloodcellsandC-reactiveprotein; ②withseverehеart,brain,etc.1.Kidneydysfunctionorfailure;3. Incompleteclinicaldata,whichaffectsthejudgmentoftheresults; 4.Patientsortheirfamilymembersdisagree.

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, gastrocnemiustendernesstest,etc.;(2)Infectionandinflammation 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 andpainscores:TorontoClinicalScoringSystem(TCSS),Numer- ical Pain Scale (NRS), etc.; (4) Lower extremity vascular exami- nation: ankle-brachial index (ABI), popliteal artery velocity, etc.

StatisticalmethodsStatisticalandanalysiswereperformedon the enteredresultsby IBM SPSS21.0 software.The measurement dataareuniformlyrepresentedby($\bar{x} \pm s$).Firstly,thenormality andhomogeneityofvariancetestsarecarriedoutonthedata,and the Student-t test is used for the data satisfying the normal distri- bution,andtheSatterthwaiteapproximatettestisusedforthedata 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,andχ^2testwasusedasthemethod;theranksumtestwas usedfortherankdata;theSpearmanrankcorrelationanalysiswas usedtostudytherelationshipbetweentheindicators.Thetestlevel α=0.05, P<0.05 is statistically significant.

3. Results

Comparisonofsymptomsandsignsbetweenthetwogroupsof patients(Table1-4):Comparedwiththewetgangrenegroup（W- group）, the dry gangrene group（D-group）had higher BMI and WHR, while the wet gangrene group had higher body tem- perature, abnormal skin temperature of the affected calf, The ab- normal 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.

Comparisonofinfectionandinflammationindicatorsbetween the two groups: (Table 5) shows that WBC, NEUT, CRP, ESR, PCT,andIL-6inthewetgangrenegroupweresignificantlyhigher than those in the dry gangrene group (P<0.01), and the difference was statistically significant learning meaning.

Comparison of neuropathy and pain scores between the two groups(Table6-7)showsthattherearestatisticallysignificantdif- ferences in the comparison of TCSS scores and NRS pain scores between the two groups (P<0.01). The abnormal TCSS scores of patientsinthedrygangrenegroupweremainlyconcentratedin6-8 points,accountingfor28.3%ofthetotalnumber,andtheabnormal NRS scores were mainly concentrated in 4-6 points, accounting for68.5%ofthetotalnumberofpatients.Mainlyconcentrated in 9~11 points, accounting for 42.4% of the total number, NRS abnormalities mainly concentrated in 1~3 points, 4~6 points, ac- counting for 28.8% and 34.5% of the total number, respectively, theincidenceofDPNinthewetgangrenegroupThepatientsinthe dry gangrene group were more obvious, and the pain degree was lower than that of the patients in the dry gangrene group.

Comparisonofvascularlesionsinthelowerextremitiesofthe two groups (Table 8) shows that theABI and popliteal artery ve- locityofthepatientsinthewetgangrenegroupweresignificantly higherthanthoseinthedrygangrenegroup(P<0.01),andthedif-

ferencewasstatisticallysignificant.Amongthepatientsinthewet gangrenegroupThemeanvaluesofABIandpoplitealarteryflow velocitywere1.00and56.63respectively,andthemeanvaluesof ABIandpoplitealteryflowvelocityindrygangrenegroupwere 0.53 and 41.69, respectively.

Spearmancorrelationanalysisbetweendifferenttypesofdia- betic foot gangrene and various clinical features (Table 9) shows that through Spearman correlation analysis, the wet gangrene groupismoderatelypositivelycorrelatedwithWBC,NEUT,CRP, IL-6,ABI, andTCSS scoresThere was a low positive correlation withbodytemperature,abnormalrateofaffectedcalf(skintemperature, circumference, and gastrocnemius tenderness), PCT, ESR,andpoplitealarterybloodflowvelocity,andanegativecorrelationwithBMI,WHR,andNRSscore(P<0.01),thedifference was statistically significant.

Table1: ComparisonofBMI,WHR,and bodytemperaturebetweenthe twogroups($\bar{x}\pm s$).

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

Table2: Comparisonofskintemperaturedifferencebetweentwogroupsofpatients.

SkinTemperatureofAffectedLeg（Comparisonwith healthyside）					
Group	**Number**	**Normal**	**Skintemperature difference≤1℃**	**1℃＜Skintemperature difference≤2℃**	**Skintemperature difference＞2℃**
D-group	127	94	21	10	2
W-group	139	40	52	42	5
Statistical Results			Z=-7.22; P＜0.01		

Table3: Comparisonofcircumferencedifferencebetweentwogroupsofpatients.

	CircumferentialDiameterofAffectedLeg(Comparisonwithhealthyside)				
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		

Table4: Comparisonofgastrocnemiustendernessintheaffectedcalfbetweenthetwogroups.

	TendernessofAffectedGastrocnemius				
Group	**Number**	**Nothing**	**Pressingitagainwillcausepain**	**Lightpressingcausespain**	**Ithurtsnottopress**
D-group	127	84	30	11	2
W-group	139	47	59	24	9
Statistical Results			Z=-5.20; P＜0.01		

Table5: Comparisonofgeneralinformationandclinicalbiochemistryofpatientsinthetwogroups($\bar{x}\pm s$).

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

Table6: ComparisonofTCSSscoresbetweenthetwogroupsof patients.

			TCSSScoringsystem		
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			

Table7: ComparisonofNRSpainscoresbetweenthetwo groups.

NRSPainRating					
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			

Table8: ComparisonofABIandpoplitealarterybloodflowvelocitybetweenthetwogroupsofpatients($\bar{x}\pm s$).

Group	Number	ABI	PoplitealArteryVelocity
		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

Table9: Correlationbetweendifferenttypesofdiabeticfootgangreneandvariousclinicalfeatures.

DifferentTypesofGangrene		
Clinical Features	**Rvalue**	**Pvalue**
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
Calfgastrocnemiustenderness	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
TCSSscore	0.594	＜0.01
NRSscore	-0.456	＜0.01
ABI	0.759	＜0.01
Poplitealarterybloodflowvelocity	0.407	＜0.01

4. Discussion

The occurrence and development of diabetes are closely relatedto 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 foundthattheBMIandWHRofpatientsinthedrygangrenegroup were significantly higher than those in the wet gangrene group, and the difference was statistically significant. The proportion of obeseandoverweightpatientsinthegangrenegroupisalsohigher, 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.areallimportantindica- tors of infection and inflammation in the body, and they are also the most widely used clinical markers of infection and inflammation.WBCisanimportantcellforthebodytoresistexternalinfections and produce immunity. CRP appears earlier than WBC and NEUT.Itisanacutephaseproteinsynthesizedbylivercellswhen thebodyisstimulatedbyinflammation.Itisgenerallyconsidered tobeaverysensitiveinflammationandtissuedamage.Marker[7], also involved in the whole process of inflammatory response [8]; IL-6canstimulateandimprovetheproliferationanddifferentiation of cells involved in immune response, including stimulating CRP PCTisanearlyinflammatorymarkerofbacterialinfection,andit iswidelyusedinthediagnosisandtreatmentofinfectiousdiseases [9], it is useful for the monitoring of diabetic foot infection and thepredictionofamputation/toeriskimportantvalue[10].ESRis a test index that reflects the aggregation of erythrocytes, and ESR will increase rapidly under various pathological conditions such asinflammation,tissuedamage,andnecrosis.Thereasonsforthe increaseofESRarecomplexandoftennon-specific,buttherewill beasignificantincreaseintheactivephaseofinflammationand

injury [11], so it can be used as a marker for judging the activi-ty and prognosis of diabetic foot gangrene lesions an important indicator. This study found that WBC, NEUT, CRP, ESR, PCT, andIL-6inthewetgangrenegroupweresignificantlyhigherthan those in the dry gangrene group. The abnormal rate and gastrocnemius tenderness rate were also significantly higher than thosein 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 higherThe dry gangrene group also showedthatthewetgangrenegrouphadawiderangeofinfection andnecrosis,suggestingthatthediabeticfootwetgangrenetypeis 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.

TheAmericanDiabetesAssociation(ADA)recommendsthatdiabeticpatientsshouldbescreenedforDPNatleastonceayear[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 usedclinically.Itissuitableforelderlypatients[13]andhasahigh 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 gangrenegroupweresignificantlyhigherthanthoseinthedrygangrene 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 significantlyheavierthanthatinthedrygangrenegroup,especial- ly for pain Sensation of sensation and temperature is weaker than thatofthedrygangrenegroup,andtheresponsetoexternalstimuli is more sluggish, and skin lesions and ulcers are more likely to occurduetovariousinducements.Atthesametime,duetoneuron damage, the neurotrophic supply of DPN patients becomes poor. Atrophy of the limbs, gradual prominence and deformity of the bonesofthefoot,andmorepronetofrictionandulceration,which in turn leads to the occurrence and development of diabetic foot [14].

ABIisoftenusedtoassesstheseverityoflowerextremityarterial ischemia,whichissimple,inexpensive,effective,andspecific,and is often used in the screening of lower extremity arterial lesions. TheresultsofthisstudyshowedthatthemeanvalueofABIinthe wet gangrene group reached 1.0, which belonged to the normal range, while the mean value of ABI in the dry gangrene group was0.53,whichbelongedtomoderatestenosis.ABIandpopliteal arteryvelocitywerealsosignificantlyhigherthanthoseinthedry gangrene group (P<0.01), and the difference was statistically significant. It can be seen thatABI 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 differentclinicalfeaturesofdiabeticfootgangreneandpathogen- ic factors (infection, vascular disease, neuropathy, etc.). It can be consideredthatwetgangrenehasasignificantpositivecorrelation with infection, inflammation, and neuropathy, and dry gangrene has a significant positive correlation with vascular disease, obesity, and pain.

ThelatefamousdoctorXiJiuyisummedupdecadesofexperience 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,inflammationandotherchangesdidnotsignificantlyaffectthe nerves,tendons,fasciaandothertissuesofthefoot,sothenecrosis 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’simmunecellsandimmunefactorsarealsodifficulttoreach thelocalareatoproducecorrespondinginflammationduetopoor blood supply reaction. In thisstudy, the symptoms, signs, clinical tests, imaging and other indicators of diabetic foot gangrene were collectedthroughalargesampletoclarifythepathologicalmechanism 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, localdebridementshouldbedonesoonerratherthanlater.Incision anddrainage,removalofputridtendonsandothernecrotictissues are possible to remove degenerated and necrotic tendons and oth- er 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 thanearly,andvascularinterventionaltherapycanbedoneifnecessary. Keep the dry gangrene stable, pay attention to local disinfection,keepthewoundsurfaceandperwounddry,andafterthe

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

The work was supported by the National Science and Technology Major Project (2019ZX09201004-002-091), Shanghai 13th Five-Year Key Clinical Specialist (TCM Surgery), National Natural Science Foundation of China (82174382), Science and Technology Innovation Action Plan of Shanghai Science and Technology Commission (20Z21900200), Shanghai Clinical Research Project (20224Y0387), Hongkou District Scientific Research Project of Traditional Chinese Medicine (HKQGYQY-ZYY-2022-05).

6. Competing Interests

The authors have declared that no competing interests exist.

References

1. Ingelfinger JR, Armstrong DG, Boulton A, Bus SA. Diabetic Foot Ulcers and Their Recurrence. New England Journal of Medicine. 2017; 376(24): 2367.
2. Schaper NC, Apelqvist J, Bakker K. The International Consensus and practical guidelines on the management and prevention of the diabetic foot. Diabetes/metabolism Research & Reviews. 2012;28(S1):225-231.
3. Diabetes Branch of Chinese Medical Association. Guidelines for Prevention and Treatment of Type 2 Diabetes in China (2013 Edition). Chinese Journal of Diabetes. 2014; 6(7): 447-498.
4. Ammar I. IDF Clinical Practice Recommendation on the Diabetic Foot: A guide for healthcare professionals. Diabetes Research & Clinical Practice. 2017; 127; 285-287.
5. Talaei M, Sadeghi M, Marshall T. Anthropometric indices predicting incident type 2 diabetes in an Iranian population: the Isfahan Cohort Study. Diabetes & metabolism. 2013; 39(5): 424-431.
6. Qihan Z, Feixia S, TingtingY. Waist-to-height ratio is an appropriate index for identifying cardiometabolic risk in Chinese individuals with normal body mass index and waist circumference. Journal of Diabetes. 2015; 6(6): 527-534.
7. Pepys M. Acute phase proteins with special reference to C-reactive protein and related proteins (Pentaxins) and serum amyloid A pro-tein. Adv Immunol. 1983; 34: 141-142.
8. Lavery LA, XiY, Peters EJG. The Role of Biomarkers to Diagnose Diabetic Foot Osteomyelitis. A Meta-analysis. Current Diabetes Re-views. 2015; 12(4): 396-402.
9. Qu J, XL, Liu Y. Evaluation of procalcitonin, C-reactive protein, interleukin-6 & serum amyloid A as diagnostic biomarkers of bacteri-al infection in febrile patients. Indian Journal of Medical Research. 2015; 141(3): 315.
10. Rongya Z, Penghua W, Jinghang Z. The predictive value of serum procalcitonin on the risk of amputation in patients with diabetic foot infection. International Journal of Endocrinology and Metabolism. 2015; 35(6): 370-373.
11. Wang Tinghuai, Zhu Danian. Physiology [M]. 8th Edition. Beijing: People's Health Publishing House, 2013:61-62.
12. Boulton AJ, Vinik AI, Arezzo JC. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005; 28(4):956-962.
13. Feldt KS, Ryden MB, Miles S. Treatment of pain in cognitively impaired compared with cognitively intact older patients with hip-fracture. Journal of the American Geriatrics Society. 1998;46(9):1079-1085.
14. Xiaojun L. Risk factors and pathogenesis of diabetic foot. Journal of Internal Medicine Emergency and Critical Care. 2002;8(1): 28-31.
15. Yuzhen W, FeiS, ChengZ, LiJi, Yemin C. Cao Yemin's experience in treating diabetic foot gangrene (gangrenous type). Shanghai Jour- nal of Traditional Chinese Medicine. 2021; 55(03): 35 -38.