

# The effect of an intensive patients' education program on anxiety, depression and patient global assessment in diabetic foot ulcer patients with Wagner grade 1/2

## A randomized, controlled study

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### Abstract

This study aimed to synthetically evaluate the impact of intensive patients' education program (IEP) on anxiety, depression and patient global assessment (PGA) in diabetic foot ulcer (DFU) patients.

One hundred eighty DFU patients with Wagner grade 1 and Wagner grade 2 were consecutively recruited in this randomized, controlled study and randomly assigned to IEP group (N=90) or control group (N=90) as 1:1 ratio. In the IEP group, patients received the IEP and usual care, and patients in the control group received usual care only. IEP included educating patients and their family members, supervising patients' harmful habits and diets, psychological care for the patients and establishing a patient-physician-nurse WeChat group. Hospital Anxiety and Depression Scale-anxiety/depression (HADS-A/D) and Zung Self-Rating Anxiety/depression Scale (SAS/SDS) were applied to assess anxiety/depression at M0-M3. PGA score was also assessed at M0-M3.

For anxiety assessment, IEP group presented decreased HADS-A/SAS scores at M2/M3 and increased HADS-A/SAS score changes (M3-M0) compared to control group. For depression assessment, IEP group displayed reduced HADS-D/SDS scores at M2/M3 and raised SDS score change (M3-M0) compared to control group. Moreover, IEP group exhibited reduced PGA score at M1/M2/M3 and elevated PGA score change (M3-M0) compared to control group. Further subgroup analyses disclosed that IEP reduced HADS-A/SAS/HADS-D/PGA scores at M3 and elevated these score changes (M3-M0) in patients with Wagner grade 2 but not Wagner grade 1.

IEP ameliorates anxiety, depression and PGA in DFU patients with Wagner grade 2 but not Wagner grade 1.

**Abbreviations:** DFU = diabetic foot ulcer, PGA = patient global assessment, DM = diabetes mellitus, DPN = diabetic peripheral neuropathy, HADS = Hospital Anxiety and Depression Scale, HADS-A = HADS anxiety, HADS-D = HADS depression, IEP = intensive patients' education program, ITT = intent-to-treat, LEA = lower extremity amputation, LOCF = last observation carried forward, M0 = baseline, M1 = first month, M2 = second month, M3 = third month, SAS = Zung Self-Rating Anxiety Scale, SDS = Zung Self-Rating Depression Scale.

**Keywords:** anxiety, depression, diabetic foot ulcer, intensive patients' education program, PGA, Wagner grade

### 1. Introduction

Diabetes is known as one of the most prevalent chronic diseases and the fifth leading cause of death worldwide.<sup>[1]</sup> It is estimated that the prevalence of diabetes is 382 million population during 2013, which is predicted to rise to 592 million by 2035 worldwide.<sup>[2]</sup> Among which, China possesses the largest number

of diabetics accounting for a quarter of all global cases, as well as high incidences of diabetes complications including diabetic foot ulcer (DFU), diabetic peripheral neuropathy (DPN) and diabetic hypertension.<sup>[3,4]</sup> As one of serious diabetic complications, DFU presents with annual incidence ranging from 1% to 4%, and the lifetime incidence as high as 25% in all diabetic cases, which is

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characterized as foot ulceration in diabetic patients due to distal nerve abnormalities in the lower extremities and different degrees of vascular disease.<sup>[3–5]</sup> In addition, DFU is difficult to be fully recovered, and its poor healing state usually leads to infection and gangrene, ultimately resulting in more severe consequences, such as lower extremity amputation (LEA), or even death.<sup>[3,4]</sup> Although individualized treatment has achieved good efficacy on physical impairment in DFU patients, partly due to unbearable clinical symptoms, long-term hospitalization or big economic burden, DFU patients are at high risk to occur psychological disorders such as depression as well as anxiety, which could lead to disease deterioration, ulcers recurrence or even suicidal tendency.<sup>[6–17]</sup> Hence, it is necessary to explore additional approaches to relieve psychological disorders, sequentially improving prognosis in DFU patients.

Knowing the negative influences of depression and anxiety on prognosis in DFU patients, a series of interventions have been carried out, such as supportive psychotherapy treatment and foot care education program.<sup>[18,19]</sup> However, most of previous studies focus on education or training for self-management as well as self-care-focused psychoeducational interventions to manage depression and anxiety, while little attention has been paid to comprehensively intensive education program involving not only patients' education but also family members' education in DFU patients.<sup>[18,20–22]</sup> Hence, this study designed a novel intensive patients' education program (IEP) composing of 5 items including:

- (1) educating the patients,
- (2) educating the patients' family members,
- (3) supervising patients' harmful habits and diets,
- (4) psychological care,
- (5) establishing a patient-physician-nurse WeChat group, and we aimed to synthetically evaluate the impact of IEP on anxiety, depression as well as patient global assessment (PGA) in DFU patients.

## 2. Methods

### 2.1. Patients

One hundred eighty patients with DFU who were treated from Jan 2015 and Jun 2017 were consecutively recruited in this randomized, controlled study. The inclusion criteria were as follows:

- (1) diagnosed as diabetes mellitus (DM) according to American Diabetes Association criteria;
- (2) with a diagnosis of DFU confirmed by clinical and vascular Imaging examinations and classified as Wagner grade I or II;
- (3) age above 18 years old;
- (4) able to understand the study contents and complete the questionnaires of anxiety and depression;
- (5) able to be regularly followed up, which was evaluated by the investigator.

Following patients were excluded:

- (1) underwent antidepressant or antianxiety therapies within 3 months;
- (2) complicated with severe mental illness (except for depression and anxiety) such as schizophrenia, dementia and so on;
- (3) complicated with poorly controlled hypertension or hyperlipidemia;

- (4) complicated with uncontrolled heart, liver or renal disease;
- (5) with a history of malignancies;
- (6) pregnant or breast-feeding women.

The present study was approved by Institutional Review Board of our hospital and conducted in compliance with applicable regulatory requirements in accordance with the provisions of the Declaration of Helsinki and in adherence to Good Clinical Practice. All participants provided the written informed consents before enrollment.

### 2.2. Randomization and grouping

Using the block randomization method, patients were randomly assigned to IEP group (N=90) or control group (N=90) as a 1:1 ratio after enrollment. Randomization procedure was performed by a statistical analyzer who was no involvement in other part of this study. And the randomization sequence was generated with the use of SAS 9.1 statistical software (Statistical Analysis System, USA). The documents of randomization codes were kept in Shanghai Qeejen Bio-tech Company (Shanghai, China). When the eligibility of a patient was confirmed by investigator and the informed consent was provided from the patient, investigator would contact the Company and then a code was provided from the randomized list.

### 2.3. IEP interventions

In the IEP group, patients received the IEP and usual care, and patients in the control group received usual care only. IEP was performed by nurses and physicians in the hospital, which included five items: education to the patients, education to the family members of patients, supervision of patients' harmful habits and diets, psychological care for the patients and establishment of a patient-physician-nurse WeChat group. After enrollment, patients were given a pamphlet on how to perform the care in the first week, then IEP was conducted weekly and mainly carried out in the form of educational sessions (lasted 3 hours each time) for three months. The details of the 5 items of IEP were as follows:

- (1) Education of the patients: in this part, patients were educated how to take care of the diabetic foot, prevent the development and the formation of new ulcers, keep appropriate diet and intake of food and exercise the leg and foot. (Detailed contents of education were shown in the Supplementary Table 1, <http://links.lww.com/MD/D585>).
- (2) Education of the patients' family members of: As for this part, patients' family members were asked to understand the patient, assist the patient from all aspects, supervise patients to abstain from harmful habits such as smoking and drinking, keep the patient in the warmth of the family, help patients set up the confidence to defeat the disease and let patients actively cooperate with treatment.
- (3) Supervision of patients' harmful habits and diets: after receiving the pamphlet for care in the first week, patients' family members were asked to keep a detailed record of patients' daily diet, smoking and drinking. During each educational session, patients' family members were required to report the diet, smoking and alcohol consumption of patients for nearly a week according to the records, then nurses or physicians would give advice to help patients develop healthy eating programs and formulate strategies for smoking cessation and alcohol abstinence.

- (4) Psychological care: In the part of psychological care, nurses would communicate with patients sincerely, try their best to resolve patients' troubles, enlighten and persuade the patients to stick to correct treatment and diet, mobilize patients' enthusiasm and strengthen their courage to fight with disease.
- (5) Establishment of a patient-physician-nurse WeChat group: in the first week after enrollment, patients or their family members were invited to join a WeChat group where patients or their family members could communicate with each other or with physicians and nurses for timely help.

#### 2.4. Usual care

Usual care was given to all patients, which included the instructions about the way and time of measuring blood glucose, the proper way of insulin injections, regular examination, emergency procedures in the disease as well as attentions. Furthermore, according to the disease conditions, all patients received usual therapies such as metabolic management using insulin or statins, rehabilitation therapy of lower extremities, vasodilatation therapy or antiplatelet therapy.

#### 2.5. Data collection and assessments of anxiety and depression

Baseline characteristics of patients were collected after enrollment, which included age, gender, highest education, occupation status, marry status, smoke, drink, duration of DM, wound area, and Wagner grade. The Wagner grade was assessed by experienced physician according to the Wagner system. Assessments of anxiety and depression were carried out at baseline (M0), first month (M1), second month (M2), and third month (M3) after the start of the intervention. Because each self-rating scale had its own defects, in order to accurately assess the effect of intervention on anxiety and depression, we applied 2 scales to validate it. Anxiety of patients was assessed by using of Hospital Anxiety and Depression Scale (HADS) and the Zung Self-Rating Anxiety Scale (SAS), and depression of patients was evaluated with the use of HADS and the Zung Self-Rating Depression Scale (SDS). Moreover, PGA score was also assessed at M0, M1, M2, and M3 using a visual analogue scale (0–10 cm, scored 0–10 points, higher score indicated poorly controlled disease status). All scales were independently filled by patients on the basis of full understanding of the contents of the scales, then the HADS anxiety (HADS-A) score, SAS score, HADS depression (HADS-D) score, SDS score and PGA score were calculated by nurses.

#### 2.6. Definitions

Both HADS-A and HADS-D consisted of 7 questions which were scored as 0–3 points individually, resulting in 0–21 points and being classified as: 0–7, no anxiety/depression; 8–10, light anxiety/depression; 11–14, moderate anxiety/depression; 15–21, severe anxiety/depression.<sup>[2,3]</sup> Similarly, both SAS and SDS consist of 20 questions which were scored as 1–4 points individually, ranging from “none or a little of the time” to “most or all of the time”, resulting in 20–80 raw score, subsequently standard scores were calculated by  $\text{int}(1.25 * \text{raw score})$  and classified as: 25–49, no anxiety/depression; 50–59, light anxiety/depression; 60–69, moderate anxiety/depression; 70–100, severe anxiety/depression.<sup>[2,4,25]</sup>

#### 2.7. Statistical analysis

An intent-to-treat (ITT) principle was used for all analyses. All patients who were randomized after enrollment were included into the analyses. For missing assessments, the last observation carried forward (LOCF) method was used. Statistical analysis was performed using SPSS 22.0 software (IBM, USA) and Graphpad Prism 6.01 software (GraphPad Software Inc, USA). Normal distributed continuous variable was presented as mean value  $\pm$  standard deviation, skewed distributed continuous variable was presented as median (25th–75th quantiles), and categorized variable was presented as count (percentage). Comparison between 2 groups was determined by Student *t* test, Wilcoxon rank sum test or Chi-square test. Reported statistical significance levels were all 2-sided, and *P* value  $< .05$  was considered significant.

### 3. Results

#### 3.1. Study flow

In the beginning, 324 DFU patients were invited, among which 58 patients were excluded, including 46 patients missing invitation and 12 patients declining to attend pre-screening procedure. Then, 266 patients were left for screening, and 86 patients were excluded, including 69 patients who did not meet inclusion criteria and 17 patients who disagreed to signed informed consents. The remaining 180 patients were recruited and randomized as a 1:1 ratio into IEP group (N=90) or control group (N=90). For IEP group, there were 14 withdrawals including 8 patients losing follow up and 6 patients withdrawing from the study due to severe complications. As to control group, there were 15 withdrawals consisting of 8 patients losing follow up and 7 patients withdrawing from the study due to severe complications. Assessments were performed at M0/M1/M2/M3 and all 90 patients in each group were included into analysis with ITT principle (Fig. 1).

#### 3.2. Baseline characteristics

The mean age of DFU patients was  $59.4 \pm 10.1$  years in IEP group and  $59.9 \pm 11.1$  years in control group ( $P = .790$ ) (Table 1). There were 53 males and 37 females in IEP group, and 59 males as well as 31 females in control group ( $P = .356$ ). The median duration of DM was 6.0 (4.0–8.3) years in IEP group and 6.0 (5.0–9.0) years in control group ( $P = .343$ ). As to wound area, the median value was 3.8 (1.5–5.4)  $\text{cm}^2$  in IEP group and 4.0 (1.9–6.1)  $\text{cm}^2$  in control group ( $P = .494$ ). IEP group had 56 (62.2%) patients with Wagner grade 1 and 34 (37.8%) patient with Wagner grade 2, meanwhile, there were 51 (56.7%) patients diagnosed as Wagner grade 1 and 39 (43.3%) patients diagnosed as Wagner grade 2 in control group ( $P = .448$ ). Other detailed baseline characteristics were shown in Table 1.

#### 3.3. Anxiety, depression and PGA score at baseline

At baseline, there was no difference between IEP group and control group in HADS-A score ( $P = .933$ ), anxiety status by HADS-A ( $P = .545$ ), anxiety severity by HADS-A score ( $P = .108$ ), SAS score ( $P = .774$ ), anxiety status by SAS score ( $P = .762$ ), anxiety severity by SAS score ( $P = .755$ ), HADS-D score ( $P = .933$ ), depression status by HADS-D score ( $P = .104$ ), depression severity by HADS-D score ( $P = .935$ ), SDS score

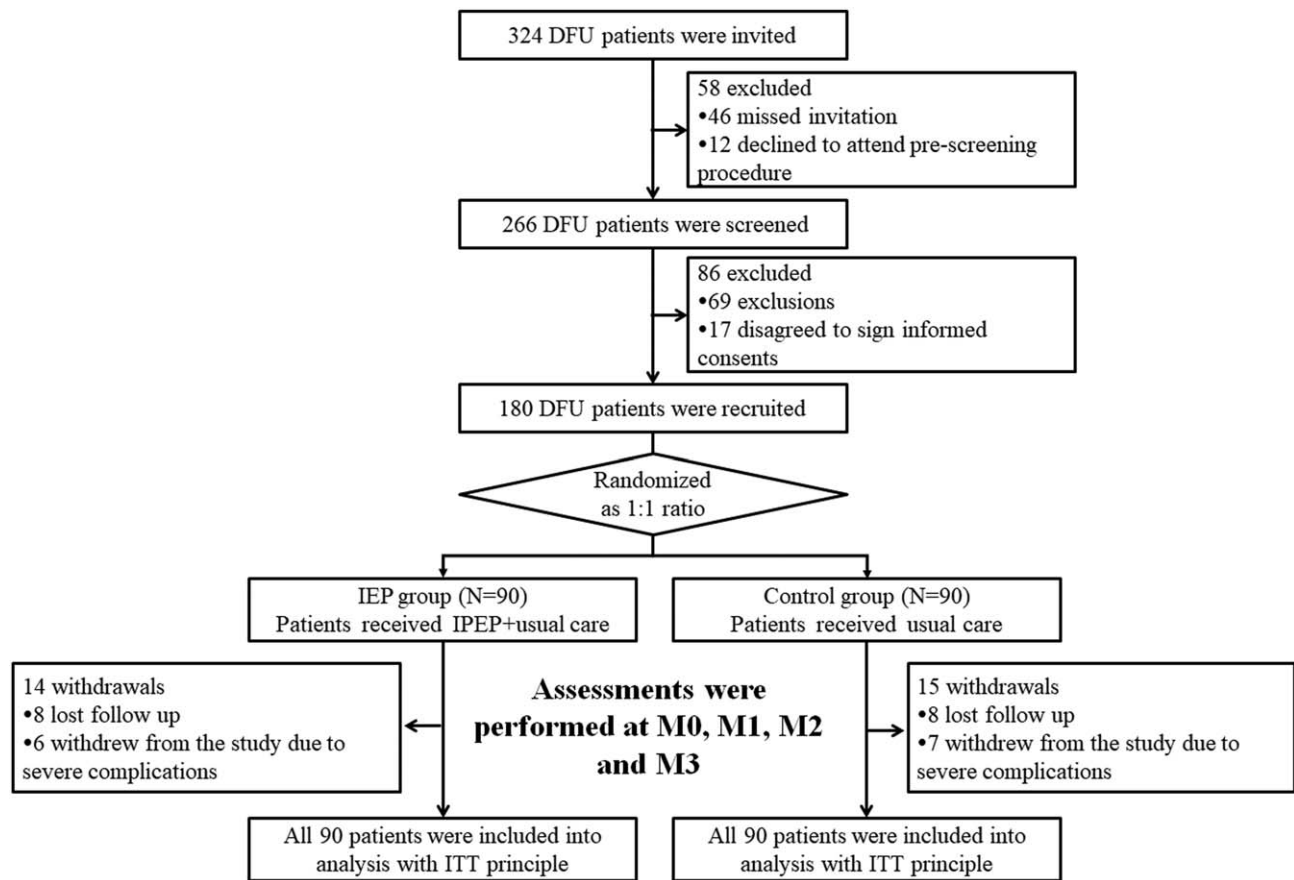


Figure 1. Flow chart.

**Table 1**  
Baseline characteristics of DFU patients in IEP group and control group.

Items	IEP group (N=90)	Control group (N=90)	P value
Age (years)	59.4±10.1	59.9±11.1	.790
Gender (male/female)	53/37	59/31	.356
BMI (kg/m <sup>2</sup> )	26.0±2.9	26.3±3.2	.507
Highest education (n/%)			1.000
Primary school or less	11 (12.2)	11 (12.2)	
High school	37 (41.2)	37 (41.2)	
Undergraduate	31 (34.4)	31 (34.4)	
Graduate or above	11 (12.2)	11 (12.2)	
Occupation status (n/%)			.551
Unemployed	43 (47.8)	47 (52.2)	
Employed	47 (52.2)	43 (47.8)	
Marriage status (n/%)			.065
Single	8 (8.9)	19 (21.1)	
Married	69 (76.6)	62 (68.9)	
Divorced	8 (8.9)	3 (3.3)	
Widowed	5 (5.6)	6 (6.7)	
Smoke (n/%)	20 (22.2)	25 (27.8)	.389
Drink (n/%)	28 (31.1)	30 (33.3)	.750
Duration of DM (years)	6.0 (4.0–8.3)	6.0 (5.0–9.0)	.343
Wound area (cm <sup>2</sup> )	3.8 (1.5–5.4)	4.0 (1.9–6.1)	.494
Wagner grade (n/%)			.448
Grade 1	56 (62.2)	51 (56.7)	
Grade 2	34 (37.8)	39 (43.3)	

Data were presented as mean value ± standard deviation, count (percentage) or median (25th–75th quantiles). Comparison was determined by student *t* test, Chi-square test or Wilcoxon rank sum test. *P* value < .05 was considered significant (in bold). BMI = body mass index, DFU = diabetic foot ulcer, DM = diabetes mellitus, IEP = intensive education program.

(*P* = .900), depression status by SDS score (*P* = .876), depression severity by SDS score (*P* = .821) or PGA score (*P* = .871) (Table 2).

#### 3.4. Comparison of anxiety between IEP group and control group

According to HADS-A, lower HADS -A score at M3 (*P* < .05) (Fig. 2A) and higher HADS-A score changes (M3-M0) (*P* = .046) (Fig. 2B) were discovered in IEP group compared to control group, while there was no difference of anxiety rate (*P* = .078) (Fig. 2C) and anxiety severity (*P* = .543) (Fig. 2D) evaluated by HADS-A between 2 groups. As to SAS, decreased SAS score at M2/M3 (both *P* < .01) (Fig. 2E) and increased SAS score change (M3-M0) (*P* = .045) (Fig. 2F) were shown in IEP group compared to control group, whereas there was no difference in anxiety rate (*P* = .456) (Fig. 2G) and anxiety severity (*P* = .539) (Fig. 2H) assessed by SAS between 2 groups. These evidences suggested that anxiety was relieved in IEP group compared to control group.

#### 3.5. Comparison of depression between IEP group and control group

In regard to HADS-D, DFU patients in IEP group presented with decreased HADS-D score at M3 (*P* < .05) (Fig. 3A) compared to control group, while there was no difference in HADS-D score change (M3-M0) (*P* = .096) (Fig. 3B), depression rate (*P* = .178) (Fig. 3C) and depression severity (*P* = .986) (Fig. 3D) between 2



**Table 2**  
**Baseline anxiety, depression and PGA of patients in IEP group and control group.**

Items	IEP group (N=90)	Control group (N=90)	P value
HADS-A score	6.7 ± 3.2	6.7 ± 3.9	.933
Anxiety status by HADS-A score			.545
No anxiety (HADS-A score 0–7, n/%)	51 (56.7)	55 (61.1)	
Anxiety (HADS-A score 8–21, n/%)	39 (43.3)	35 (38.9)	
Anxiety severity by HADS-A score			.108
Light (HADS-A score 8–10, n/%)	32 (82.1)	23 (65.7)	
Moderate (HADS-A score 11–14, n/%)	5 (12.8)	8 (22.9)	
Severe (HADS-A score 15–21, n/%)	2 (5.1)	4 (11.4)	
SAS score	48.1 ± 11.4	48.5 ± 10.9	.774
Anxiety status by SAS score			.762
No anxiety (SAS score 25–49, n/%)	54 (60.0)	52 (57.8)	
Anxiety (SAS score 50–100, n/%)	36 (40.0)	38 (42.2)	
Anxiety severity by SAS score			.755
Light (SAS score 50–59, n/%)	22 (61.1)	22 (57.9)	
Moderate (SAS score 60–69, n/%)	10 (27.8)	12 (31.6)	
Severe (SAS score 70–100, n/%)	4 (11.1)	4 (10.5)	
HADS-D score	6.6 ± 3.0	6.7 ± 4.0	.933
Depression status by HADS-D score			.104
No depression (HADS-D score 0–7, n/%)	68 (75.6)	58 (64.4)	
Depression (HADS-D score 8–21, n/%)	22 (24.4)	32 (35.6)	
Depression severity by HADS-D score			.935
Light (HADS-D score 8–10, n/%)	12 (54.6)	17 (53.1)	
Moderate (HADS-D score 11–14, n/%)	7 (31.8)	11 (34.4)	
Severe (HADS-D score 15–21, n/%)	3 (13.6)	4 (12.5)	
SDS score	45.6 ± 11.1	45.8 ± 11.4	.900
Depression status by SDS score			.876
No depression (SDS score 25–49, n/%)	58 (64.4)	59 (65.6)	
Depression (SDS score 50–100, n/%)	32 (35.6)	31 (34.4)	
Depression severity by SDS score			.821
Light (SDS score 50–59, n/%)	21 (65.6)	19 (61.3)	
Moderate (SDS score 60–69, n/%)	7 (21.9)	9 (29.0)	
Severe (SDS score 70–100, n/%)	4 (12.5)	3 (9.7)	
PGA score	5.5 ± 1.7	5.5 ± 2.0	.871

Data were presented as mean value ± standard deviation or count (percentage). Comparison was determined by student *t* test, Chi-square test or Wilcoxon rank sum test. *P* value < .05 was considered significant (in bold). PGA = patient global assessment, IEP = intensive education program, HADS-A score = Hospital Anxiety and Depression Scale anxiety score, SAS = Zung Self-Rating Anxiety Scale, HADS-D score = Hospital Anxiety and Depression Scale depression score, SDS = Zung Self-Rating Depression Scale.

groups. In terms of SDS, reduced SDS score at M2/M3 (both  $P < .05$ ) (Fig. 3E) and increased SDS score change (M3-M0) ( $P = .049$ ) (Fig. 3F) were shown in IEP group compared to control group, whereas depression rate ( $P = .062$ ) (Fig. 3G) and depression severity ( $P = .115$ ) (Fig. 3H) did not differ between 2 groups. These results demonstrated that depression was attenuated in IEP group compared to control group.

### 3.6. Comparison of PGA between IEP group and control group

Compared to control group, lessened PGA score at M1 ( $P < .05$ ), M2 ( $P < .05$ ) and M3 ( $P < .01$ ) (Fig. 4A) as well as elevated PGA score change (M3-M0) ( $P = .006$ ) (Fig. 4B) were discovered in IEP group, which indicated that PGA was ameliorated in IEP group compared to control group.

### 3.7. IEP attenuated anxiety, depression and PGA in DFU patients with Wagner grade 2 but not Wagner grade 1

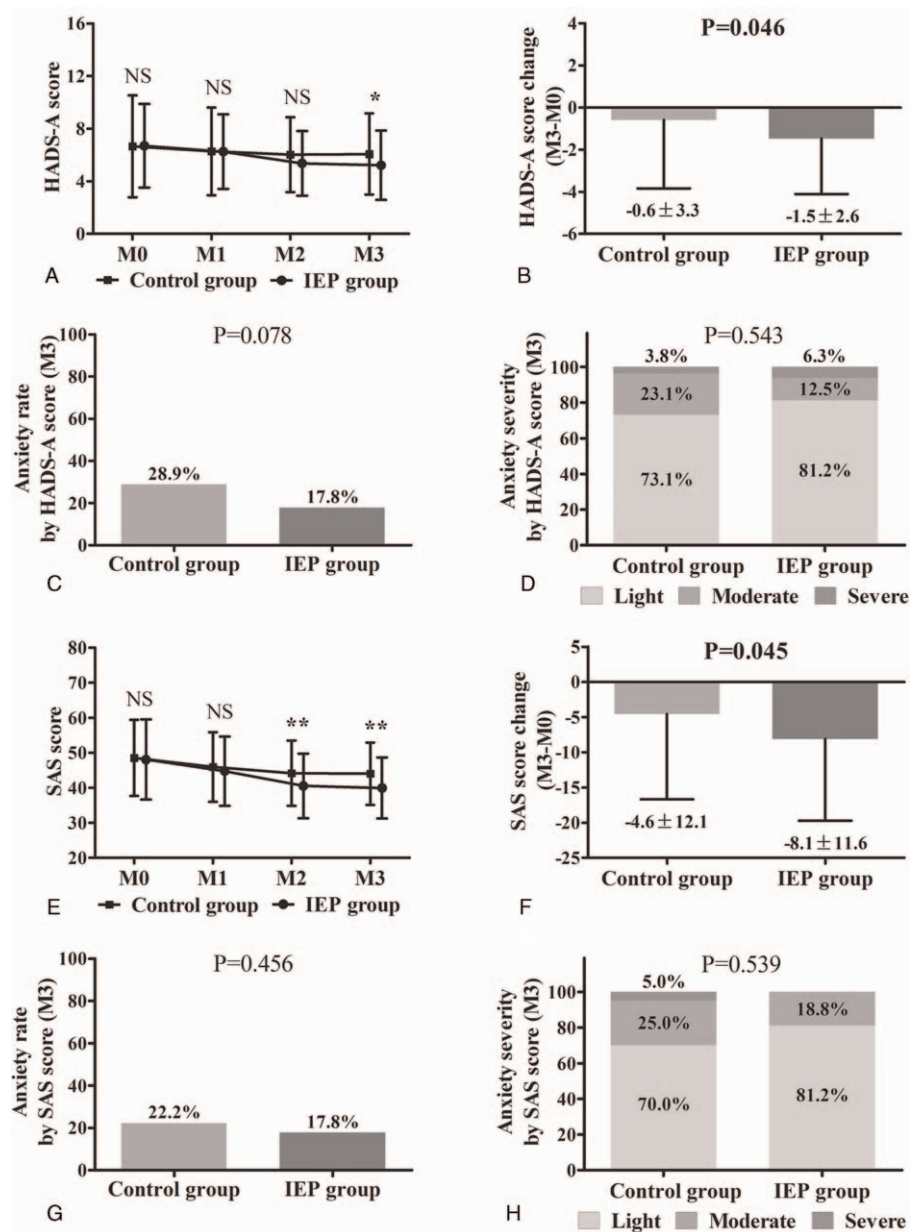
In order to further investigate the efficacy of IEP in DFU patients with different Wagner grades, subgroup analysis was performed. For DFU patients with Wagner grade 1, there was no

difference of HADS-A, SAS, HADS-D, SDS and PGA scores at M3, as well as the change (M3-M0) of these scores (All  $P > .05$ ) between IEP group and control group (Fig. 5). Regarding to DFU patients with Wagner grade 2, reduced scores of HADS-A ( $P = .011$ ), SAS ( $P = .001$ ), HADS-D ( $P = .008$ ) and PGA ( $P = .001$ ) at M3, and elevated score changes (M3-M0) of HADS-A ( $P = .014$ ), SAS ( $P = .008$ ), HADS-D ( $P = .042$ ), SDS ( $P = .036$ ) as well as PGA ( $P = .001$ ) (Fig. 6) were uncovered in IEP group compared to control group.

## 4. Discussion

In this study, we observed that: DFU patients in IEP group exhibited reduced anxiety, depression and PGA compared to control group, and further subgroup analysis disclosed that IEP effectively decreased anxiety, depression and PGA scores in patients with Wagner grade 2 but not Wagner grade 1.

DFU patients often complicate with physiological disorders, such as depression and anxiety, which might derive from several causes as follows: long treatment duration and frequent relapse of DFU, impairment of mobility and productivity, economic burden of lengthy treatment and hospitalization. Subsequently, physiological disorders react on DFU prognosis, which leads to

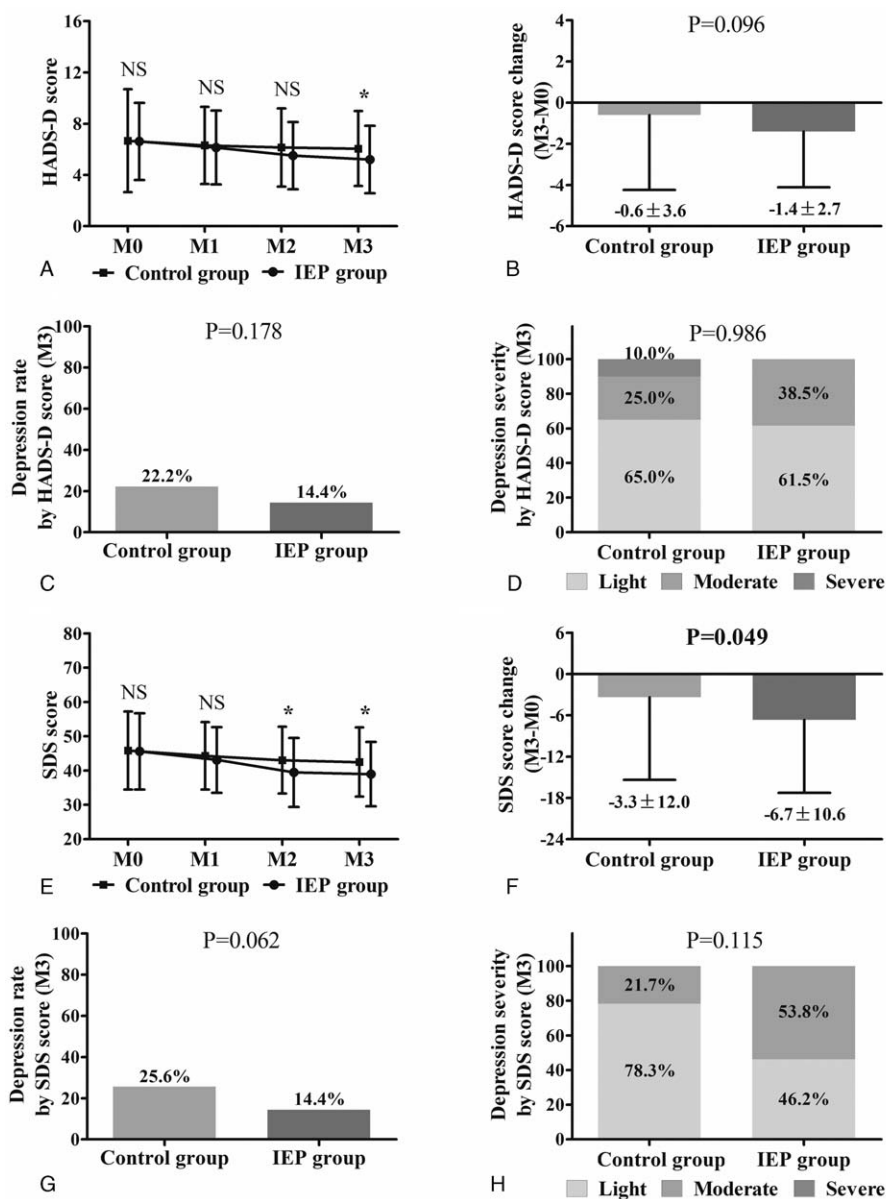


**Figure 2.** Anxiety score, score change (M3-M0), anxiety rate and severity assessed by HADS and SAS in DFU patients. For anxiety assessed by HADS, lower anxiety score at M3 (A) and no difference of anxiety change (B), rate (C) as well as severity (D) were observed in IEP group compared to control group. For anxiety evaluated by SAS, reduced anxiety score at M2/M3 (E) and no difference of anxiety change (F), rate (G) as well as severity (H) were discovered in IEP group compared to control group. Comparison was determined by *t* test, Chi-square test or Wilcoxon rank sum test. \*\*= $P < .01$ . M (month), \*= $P < .05$ , DFU=diabetic foot ulcer, HADS=Hospital Anxiety and Depression Scale, IEP=intensive patients' education program, NS=not significant, SAS=Zung Self-Rating Anxiety Scale.

poor ulcer healing and progression of DFU to higher Wagner grades.<sup>[6-17]</sup> In clinical practice, education programs targeting health care providers and patients have been considered as effective tactics for remission of physiological disorders in diabetes or relevant complications, such as DFU and diabetic neuropathy.<sup>[18,21,22]</sup> For example, a previous study illuminates that a 3-month educating program involving all aspects of diabetes effectively prevents physiological disorders and occurrence of new ulcers and improves patients' self-efficacy as well as their foot ulcers care rate.<sup>[26]</sup> In addition, direct psychotherapeutic intervention is another approach to treat physiological

disorders in DFU patients. For instance, a former study reveals that psychotherapy alone during hospitalization is associated with decreased total number of diabetic foot patients with anxiety, depression (assessed by HADS) and reduced diabetes-related problems (assessed by Problem Areas in Diabetes Scale).<sup>[18]</sup> These 2 aforementioned approaches represent the mainstream of physiological disorders treatment in DFU patients, but the treatment efficacy is often limited, which results from:

- (1) diverse contents and forms of the education program might lead to different treatment adherence and feedback;



**Figure 3.** Depression score, score change (M3-M0), depression rate and severity assessed by HADS and SDS in DFU patients. For depression assessed by HADS, decreased depression score at M3 (A) and no difference of depression change (B), rate (C) as well as severity (D) were uncovered in IEP group compared to control group. For depression evaluated by SDS, lower depression score at M2/M3 (E) and no difference of depression change (F), rate (G) as well as severity (H) were shown in IEP group compared to control group. Comparison was determined by *t* test, Chi-square test or Wilcoxon rank sum test. \* = *P* < .05. M (month), DFU = diabetic foot ulcer, HADS = Hospital Anxiety and Depression Scale, IEP = intensive patients' education program, NS = not significant, SDS = Zung Self-Rating Depression Scale.

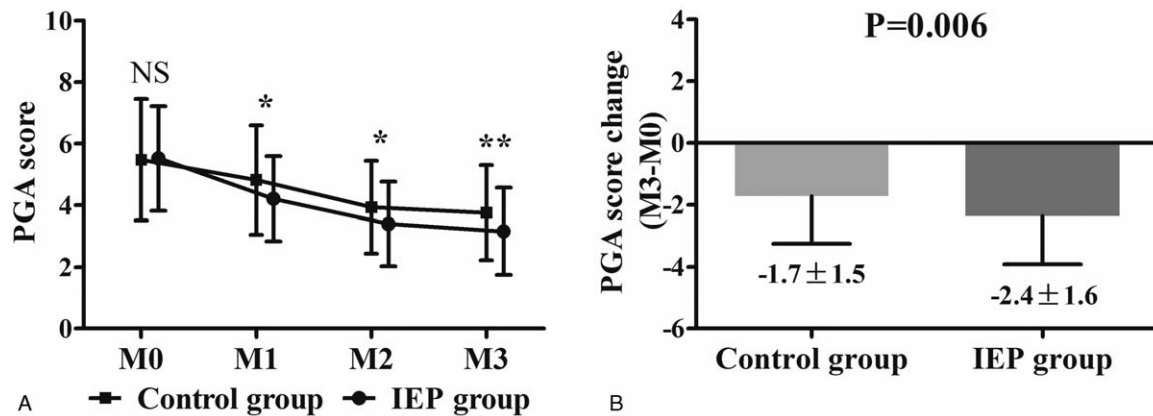
(2) single psychotherapy might do not improve glycemic control and self-management, causing progression of foot ulcer, thereby, physiological disorders would not get relieved.

Therefore, in our study, comprehensive IEP was proposed and put into practice to test its efficacy of treating anxiety and depression in DFU patients, and we discovered that IEP could ameliorate anxiety and depression (assessed by HADS, SAS and SDS), as well as improve PGA in DFU patients. The possible explanations might be that:

(1) Educating patients and their family members made them acquire in-depth knowledge of DFU development process,

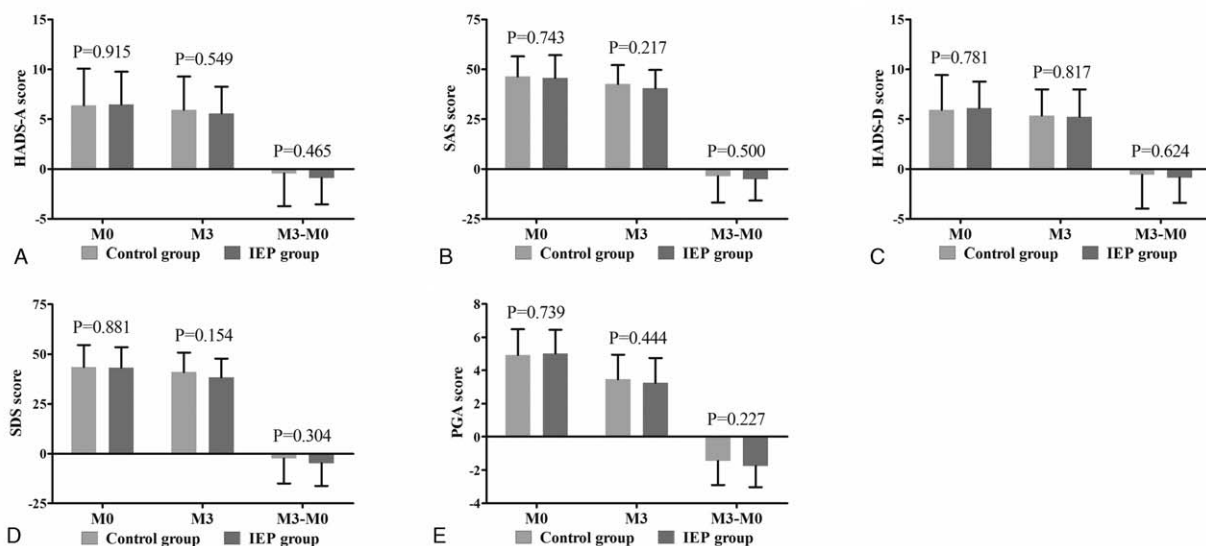
which might be conducive to effective self-management, more family support and better home care;

- (2) supervising patients' harmful habits and diets made DFU patients in IEP group achieve healthier lifestyle, which excluded them from DFU risk factors such as smoke habits and glycemia;
- (3) psychological care supplied professional psychotherapeutics targeting depression and anxiety in DFU patients;
- (4) most importantly, patient-physician-nurse WeChat group was set up to offer interaction among DFU patient, physician and nurse, which contributed to quicker treatment feedback from DFU patients and patients' access to professional medical care as soon as possible.



**Figure 4.** PGA score and PGA score change (M3-M0) in DFU patients. Compared to control group, lower PGA scores at M1/M2/M3 were observed in IEP group (A), while there was no difference of PGA score change (M3-M0) between two groups (B). Comparison was determined by *t* test. \*\*= $P < .01$ . M (month), \*= $P < .05$ , DFU=diabetic foot ulcer, IEP=intensive patients' education program, NS=not significant, PGA=patient global assessment.

## Patients with Wagner grade 1



**Figure 5.** Anxiety, depression and PGA in DFU patients with Wagner I. For anxiety, no difference of HADS-A (A) and SAS (B) scores at M3, or score change (M3-M0) was discovered between IEP group and control group. For depression, no difference of HADS-D(C) and SDS (D) scores at M3, or score change (M3-M0) was shown between 2 groups. Additionally, there was no difference of PGA score (E) at M3 or score change (M3-M0) between 2 groups. Comparison was determined by *t* test. DFU=diabetic foot ulcer, HADS-A/D=Hospital Anxiety and Depression Scale-Anxiety/Depression, IEP=intensive patients' education program, PGA=patient global assessment, SAS=Zung Self-Rating Anxiety Scale, SDS=Zung Self-Rating Depression Scale.

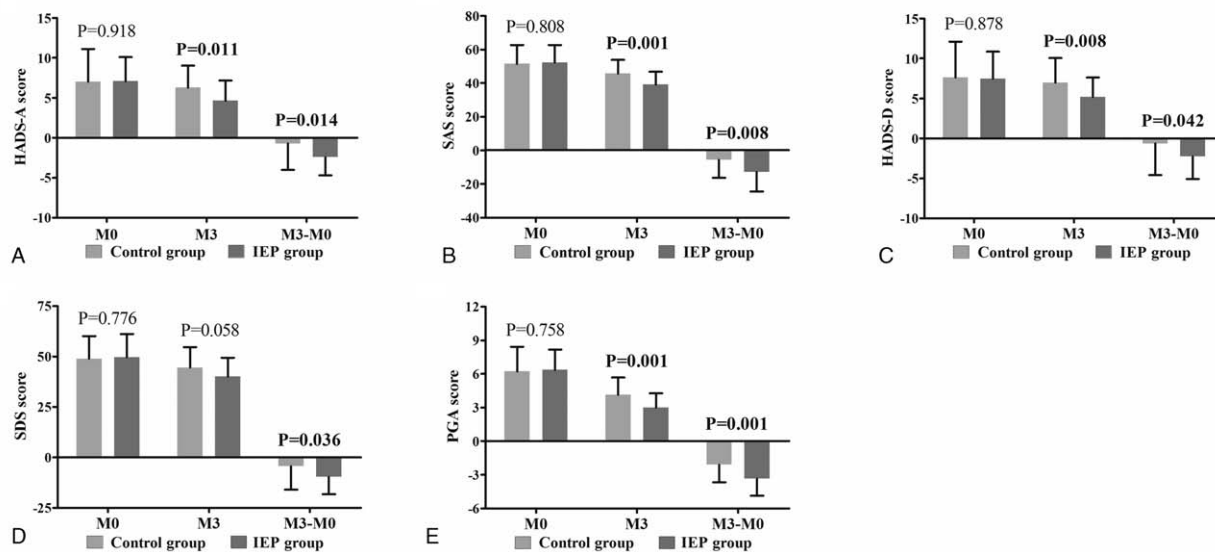
Briefly, IEP provided relatively comprehensive and integrated care for DFU patients, meanwhile, DFU patients received great support from family, nurse and physician, thus patients in IEP group exhibited better psychological status.<sup>[17]</sup> Moreover, the improvement of PGA in DFU patients might be due to indirect impact of relieved physiological disorders or direct impact of ameliorated DFU-related symptoms including numbness or tingling in acra and muscle pain, tenderness, or weakness.

In order to further understand the effect of IEP on psychological disorders and PGA in DFU patients with different Wagner grade, we performed subgroup analyses, which disclosed that for DFU patients with Wagner grade 2, psychological disorders and PGA were alleviated in IEP group compared to

control group, but not in DFU patients with Wagner grade 1. The inspiring finding in our study for DFU patients with Wagner grade 2 indicated that IEP might assist those patients in delay or prevention of foot ulcer progression. The result in our study might be explained by that: DFU patients with Wagner grader 2 displayed more severe ulceration and often complicated with infection compared to DFU patients with Wagner grader 1, which caused those DFU patients had stronger urge to improve psychological status and PGA, leading to better adherence to IEP, thereby more effectively maintaining self-management and more voluntarily cooperated with family members, nurses and physicians, eventually, DFU patients with Wagner grader 2 benefiting from IEP to a greater extent.



## Patients with Wagner grade 2



**Figure 6.** Anxiety, depression and PGA in DFU patients with Wagner II. For anxiety, lower HADS-A (A) and SAS (B) scores at M3 as well as higher both scores change (M3-M0) were observed in IEP group compared to control group. For depression, decreased HADS-D (C) score at M3 and increased both scores change (M3-M0) (C, D) were discovered in IEP group compared to control group. Moreover, there were reduced PGA score at M3 and elevated score change (M3-M0) (E) in IEP group compared to control group. Comparison was determined by *t* test. DFU=diabetic foot ulcer, HADS-A/D=Hospital Anxiety and Depression Scale-Anxiety/Depression, IEP=Intensive patients' education program, PGA=patient global assessment, SAS=Zung Self-Rating Anxiety Scale, SDS=Zung Self-Rating Depression Scale.

Several limitations existed in the present study. Firstly, the cost of IEP in various aspects were not calculated, such as the labor cost from medical professionals, including diabetologist, psychologist, nurses, educators and rehabilitation team, hence, the cost-effectiveness of implementing IEP was still not explored. Secondly, the follow-up duration was relatively short, long-term effect of IEP on DFU patients was not confirmed. Thirdly, DFU patients with Wagner grade  $\geq 3$  were not enrolled in this study, therefore, the function of IEP in these sorts of patients was not explored.

### 5. Conclusion

In brief, IEP ameliorates anxiety, depression and PGA in DFU patients with Wagner grade 2 but not Wagner grade 1.

### Author contributions

Huifen Chen and Cong Cai conceived this study. Huifen Chen, Cong Cai and Jun Xie collected, investigated and analysis the data. All authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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