

# Effect of Preoperative Level of Glycemic Control with Pulsed Radiofrequency on the Incidence of Postherpetic Neuralgia in Patients with Herpes Zoster Combined with Type 2 Diabetes Mellitus: A Cohort Study

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**Purpose:** To investigate the correlation between the level of glycosylated hemoglobin (HbA1c) and postherpetic neuralgia (PHN).

**Patients and Methods:** This cohort study included 100 patients with herpes zoster (HZ) undergoing treatment with pulsed radiofrequency (PRF). Patients with comorbid type 2 diabetes mellitus (T2DM) were divided into three groups based on their glycemic control levels: good [ $\text{HbA1c} < 7\%$  (53.01 mmol/mol), group D<sub>1</sub>], fair [ $7\%$  (53.01 mmol/mol)  $\leq$   $\text{HbA1c} < 9\%$  (74.86 mmol/mol), group D<sub>2</sub>], and poor [ $9\%$  (74.86 mmol/mol)  $\leq$   $\text{HbA1c}$ , group D<sub>3</sub>]. The control group (group N) consisted of patients without T2DM. The main outcome measured was the occurrence of PHN in the four groups.

**Results:** A total of 90 patients were included in the cohort. The occurrence of PHN was found to be higher in groups D<sub>2</sub> and D<sub>3</sub> when compared to group N (N vs D<sub>2</sub>,  $P = 0.007$ ; N vs D<sub>3</sub>,  $P < 0.001$ ). Furthermore, the occurrence of PHN was higher in groups D<sub>2</sub> and D<sub>3</sub> in comparison to group D<sub>1</sub> (D<sub>1</sub> vs D<sub>2</sub>,  $P = 0.022$ ; D<sub>1</sub> vs D<sub>3</sub>,  $P < 0.001$ ), with the incidence of PHN in group D<sub>3</sub> being greater than in group D<sub>2</sub> ( $P < 0.001$ ).

**Conclusion:** Preoperative HbA1c predicts the incidence of PHN after PRF in T2DM patients.

**Keywords:** herpes zoster, postherpetic neuralgia, pulsed radiofrequency, type 2 diabetes mellitus, HbA1c

## Introduction

Herpes zoster (HZ) is caused by the reactivation of the varicella-zoster virus (VZV) that lies dormant in sensory ganglia.<sup>1</sup> The virus travels along the affected sensory nerves to the skin, resulting in a distinct blistering rash accompanied by pain.<sup>2,3</sup> Epidemiological data suggests that the risk of developing HZ ranges from 25% to 30%.<sup>4</sup> The most common chronic complication of HZ is postherpetic neuralgia (PHN), characterized by persistent skin pain that lasts for at least 90 days after the onset of the herpes rash.<sup>5</sup> This neuropathic pain, with a prevalence of 15% to 40% in HZ patients, has no definitive cure,<sup>6–8</sup> and the enduring and intense pain associated with it significantly impacts the patient's emotional well-being, sleep, and overall quality of life.<sup>9</sup> Moreover, managing PHN also places a financial and social burden on patients, with some individuals even experiencing suicidal thoughts.<sup>10</sup> Therefore, emphasis should be placed on preventing the development of PHN.

Current treatment aims to alleviate symptoms and typically involves medication, physical therapy, and minimally invasive interventional procedures.<sup>11,12</sup> Pulsed Radiofrequency (PRF) involves using high-frequency, high-voltage electrical currents to create voltage fluctuations in a specific treatment area, resulting in a slight elevation in tissue

temperature, which modulates synaptic activity briefly.<sup>13</sup> PRF can effectively reduce pain related to HZ in around 70% of cases.<sup>14</sup> However, some patients may still develop PHN after PRF treatment, and the factors contributing to this outcome remain unclear. Therefore, further studies are necessary to investigate ways to reduce the occurrence of PHN following PRF.

Recent studies have identified type 2 diabetes mellitus (T2DM) as a risk factor for PHN,<sup>15–17</sup> with diabetic patients being more susceptible to developing PHN than their non-diabetic counterparts.<sup>18,19</sup> Glycosylated hemoglobin (HbA1c) serves as a reliable indicator of average glycemic control over a few months and is used to assess the risk of complications associated with T2DM.<sup>20</sup> The American Diabetes Association (ADA) emphasizes that lowering HbA1c levels could potentially decrease the likelihood of neurological, microvascular, and macrovascular complications associated with T2DM.<sup>21</sup> Currently, clinicians rely on HbA1c levels as a key marker for assessing the severity of diabetes and making management decisions.<sup>22</sup>

However, the relationship between preoperative glycemic control and the incidence of postoperative PHN in HZ patients with T2DM before PRF has not been conclusively determined. This study aims to compare postoperative PHN rates in HZ patients with T2DM across varying levels of preoperative glycemic control under the same treatment conditions, to establish whether a correlation exists. The findings will help elucidate the impact of preoperative glycemic control on postoperative PHN in these patients, providing valuable insights for PHN prevention.

## Materials and Methods

This study included patients diagnosed with HZ who received treatment at the Pain Department of the Affiliated Hospital of Jiaxing University between April 2023 and February 2024. The study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the First Hospital of Jiaxing on March 27, 2023 (2023-KY-066). It was duly registered in the China Clinical Trial Registry ([www.chictr.org.cn](http://www.chictr.org.cn); CTR2300070130; 04/03/2023). Before being enrolled in the study, all patients were duly informed of the potential risks and provided written consent.

## Study Population

The HbA1c levels of the patients were recorded on the day of admission, and their glycemic control was categorized into three groups based on the guidelines of the American Diabetes Association and previous research.<sup>21,23</sup> Multiple studies have shown that maintaining HbA1c levels below 7% (53.01 mmol/mol) can reduce the occurrence of microvascular complications in patients with T2DM,<sup>24,25</sup> while HbA1c levels above 9% (74.86 mmol/mol) indicate poor blood sugar control, putting patients at risk of developing acute metabolic syndrome during the perioperative period.<sup>26</sup> The groups were defined as follows: (1) the good glycemic control group (group D<sub>1</sub>): HbA1c < 7% (53.01 mmol/mol); (2) the general glycemic control group (group D<sub>2</sub>): 7% (53.01 mmol/mol) ≤ HbA1c < 9% (74.86 mmol/mol); (3) the poor glycemic control group (group D<sub>3</sub>): HbA1c ≥ 9% (74.86 mmol/mol). Patients who attended the pain department of our hospital during the same period and did not have T2DM were selected as the control group (group N): HbA1c < 6% (42.08 mmol/mol).<sup>27,28</sup>

Inclusion criteria: (1) HZ patients aged 50–90 years; (2) pre-treatment Numerical Rating Scale (NRS) ≥ 4; (3) disease duration < 90 days; (4) scheduled for pulsed radiofrequency (PRF) treatment (HZ patients meeting the 2018 Chinese Expert Consensus Diagnostic Criteria for HZ);<sup>29</sup> (5) patients with comorbid T2DM, including a history of T2DM, or fasting plasma glucose (FPG) ≥ 11.1 mmol/L, or oral glucose tolerance test (OGTT) 2hPG ≥ 11.1 mmol/L, or HbA1c > 6.5% (47.54 mmol/mol).<sup>30</sup>

Exclusion criteria: (1) skin infection at the puncture site; (2) presence of a pacemaker or other contraindications to PRF treatment; (3) severe cardiac, pulmonary, hepatic, or renal dysfunction; (4) allergy to treatment drugs; (5) other painful conditions or dermatologic disorders complicating HZ diagnosis; (6) abnormal blood clotting time; (7) long-term use of glucocorticoids or immunosuppressants; (8) history of opioid abuse; (9) cognitive and communication disorders; (10) refusal to participate or sign informed consent. Participants who decided to withdraw from the study, did not follow the prescribed treatment, or were unreachable for follow-up were omitted from the study results.

## Treatment

All four groups of patients were treated with the same treatment method, which was categorized into medication and PRF treatment. Pharmacologic therapy: Pregabalin was routinely administered at 150 mg/day prior to receiving PRF. Remedial analgesia: temporary oral aminophenol oxycodone 5 mg. PRF therapy: The patient was placed on a computed tomography (CT) bed, and PRF therapy was performed on the segment with the most severe pain and the three dorsal root ganglia adjacent to the segment. According to CT localization, the corresponding upper edge of the intervertebral foramen was selected as the puncture site. The temperature, time, pulse width and frequency were set to 42°C, 360 s, 20 ms and 2 Hz, respectively.

## Outcome Indicators and Evaluation of Therapeutic Efficacy

Follow-up indicators: (1) Whether PHN occurred or not; (2) Pain level assessment: NRS was used to assess the pain level. 0 was classified as no pain, 1–3 was classified as mild pain, 4–6 was classified as moderate pain, and 7–10 was classified as severe pain. Patients chose the value that matched their own pain level from 0–10; (3) Sleep assessment: The Self-Rating Scale of Sleep (SRSS) was used to assess the quality of sleep. There were 10 items in total, each divided into 5 levels of scoring (1–5). The lowest total score was 10 (indicating no sleep problems) and the highest score was 50 (indicating the most serious sleep problems). The lower the score, the fewer the sleep problems; the higher the score, the more serious the problems; (4) Anxiety and depression assessment: The Hospital Anxiety and Depression Scale (HADS) was used to assess the degree of anxiety and depression. It was divided into an anxiety subscale (A) and a depression subscale (D). There were 14 items, each scored on a scale of 0–3. The higher the score, the more likely the presence of anxiety and depression.

## Data Collection and Outcome Assessment

Data were collected using a standardized form to obtain baseline characteristics from electronic clinical cases. Baseline characteristics data included age, gender, Body Mass Index (BMI), education, smoking, alcohol consumption, history of allergies, site of herpes, pre-operative NRS ( $NRS_0$ ), duration of HZ, and comorbidities. Preoperative ( $T_0$ ) and postoperative immediately ( $T_1$ ) NRS, SRSS, and HADS were evaluated in four patient groups by a non-involved resident. Follow-up assessments of NRS, SRSS, and HADS were conducted at 7 days ( $T_2$ ), 30 days ( $T_3$ ), and 90 days ( $T_4$ ) postoperatively through telephone or outpatient reviews to determine efficacy. The use of remedial medications and the presence of critical blood glucose values ( $>22$  mmol/L) were recorded during hospitalization for the four groups of patients.

The primary outcome of this study was whether PHN occurred in patients with HZ. PHN was defined as skin pain that persisted for at least 90 days after the appearance of a herpes rash in HZ.<sup>5</sup> Secondary outcome measures included the NRS, SRSS, and HADS at  $T_1$ ,  $T_2$ ,  $T_3$ , and  $T_4$ . The efficacy of these measures was calculated by the weighted value of the postoperative 90-day NRS. Efficacy evaluation was determined by the formula:  $[(\text{preoperative NRS} - \text{postoperative 90-day NRS}) / \text{preoperative NRS}] \times 100\%$ . A good prognosis was defined as an efficacy evaluation of 50% to 100%, while a poor prognosis was defined as an efficacy evaluation of less than 50%.

## Sample Size Estimation

Based on preliminary findings (unpublished data), the incidence of PHN was observed to be 25% in group N ( $n = 8$ ), 30% in group  $D_1$  ( $n = 10$ ), 50% in group  $D_2$  ( $n = 10$ ), and 100% in group  $D_3$  ( $n = 10$ ). Sample size calculation was conducted using PASS 15 software for a multi-group rate comparison, with a two-sided  $\alpha=0.05$  and a confidence level of 90%. This calculation determined a total sample size of 41 cases for the study. Considering a 20% failure rate, the total sample size required was adjusted to 52 cases, with 13 cases allocated to each group. To enhance the precision of the study results, consultation with statistical experts led to a final determination of a sample size of 100 cases, with 25 cases in each group.

## Statistical Analysis

Continuous variables were assessed for normal distribution using the Shapiro–Wilk test. For variables that followed a normal distribution, data were presented as Mean  $\pm$  SD and group comparisons were conducted using the independent

samples *t*-test. Non-normally distributed variables were presented as M (Q1, Q3) and group comparisons were made using the Mann–Whitney *U*-test. Repeated-measures data were analyzed using generalized estimating equations. Categorical data were presented as n (%) and analyzed using the chi-square test or Fisher's exact test. Statistical analysis and graphing were performed using SPSS 23.0 and GraphPad Prism 9.0. Differences with a *p*-value of less than 0.05 were considered statistically significant.

## Results

From March 2023 to February 2024, initial evaluations were conducted on 127 patients. Out of these, 100 patients met the inclusion criteria and were categorized into groups N, D<sub>1</sub>, D<sub>2</sub>, and D<sub>3</sub> based on their HbA1c levels. Ten patients were lost to follow-up, resulting in a final analysis of 23 patients in group N, 23 patients in group D<sub>1</sub>, 23 patients in group D<sub>2</sub>, and 21 patients in group D<sub>3</sub> (Figure 1). The baseline characteristics of the four groups were largely balanced (Table 1).

## Comparison of PHN incidence

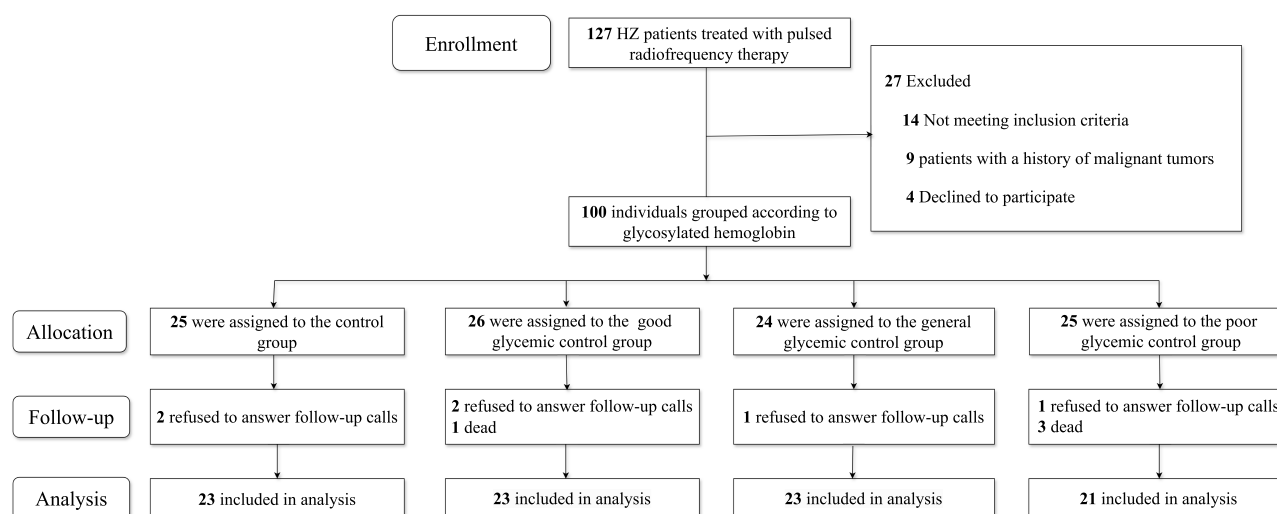
The incidence of PHN was 8.70% in group N, 13.04% in group D<sub>1</sub>, 43.48% in group D<sub>2</sub>, and 100% in group D<sub>3</sub>, with a statistically significant difference observed across the groups ( $P < 0.001$ ). The incidence of PHN was notably higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group N (N vs D<sub>2</sub>,  $P = 0.007$ ; N vs D<sub>3</sub>,  $P < 0.001$ ), while there was no significant difference between group D<sub>1</sub> and group N. Additionally, the incidence of PHN was significantly higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group D<sub>1</sub> (D<sub>1</sub> vs D<sub>2</sub>,  $P = 0.022$ ; D<sub>1</sub> vs D<sub>3</sub>,  $P < 0.001$ ), and the incidence of PHN in group D<sub>3</sub> was significantly higher compared to group D<sub>2</sub> ( $P < 0.001$ ) (Figure 2).

## Comparison of efficacy

The good prognosis was 91.3% in group N, 86.96% in group D<sub>1</sub>, 52.17% in group D<sub>2</sub>, and 4.76% in group D<sub>3</sub>. There was a statistically significant difference among the four groups ( $P < 0.001$ ), with worse efficacy in groups D<sub>2</sub> and D<sub>3</sub> compared to group N (N vs D<sub>2</sub>,  $P = 0.003$ ; N vs D<sub>3</sub>,  $P < 0.001$ ). However, the difference in efficacy with group D<sub>1</sub> was not statistically significant. Groups D<sub>2</sub> and D<sub>3</sub> had worse efficacy compared to group D<sub>1</sub> (D<sub>1</sub> vs D<sub>2</sub>,  $P = 0.010$ ; D<sub>1</sub> vs D<sub>3</sub>,  $P < 0.001$ ). Additionally, group D<sub>3</sub> had worse efficacy than group D<sub>2</sub> ( $P < 0.001$ ) (Figure 3).

## Comparison of NRS at various time points

The preoperative NRS of each group was corrected as a covariate. Analysis of generalized estimating equations showed that in intragroup comparisons, there was no statistically significant difference in NRS among groups N, D<sub>1</sub>, and D<sub>2</sub> at T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> time points ( $P > 0.05$ ). The difference in NRS at T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> time points was statistically

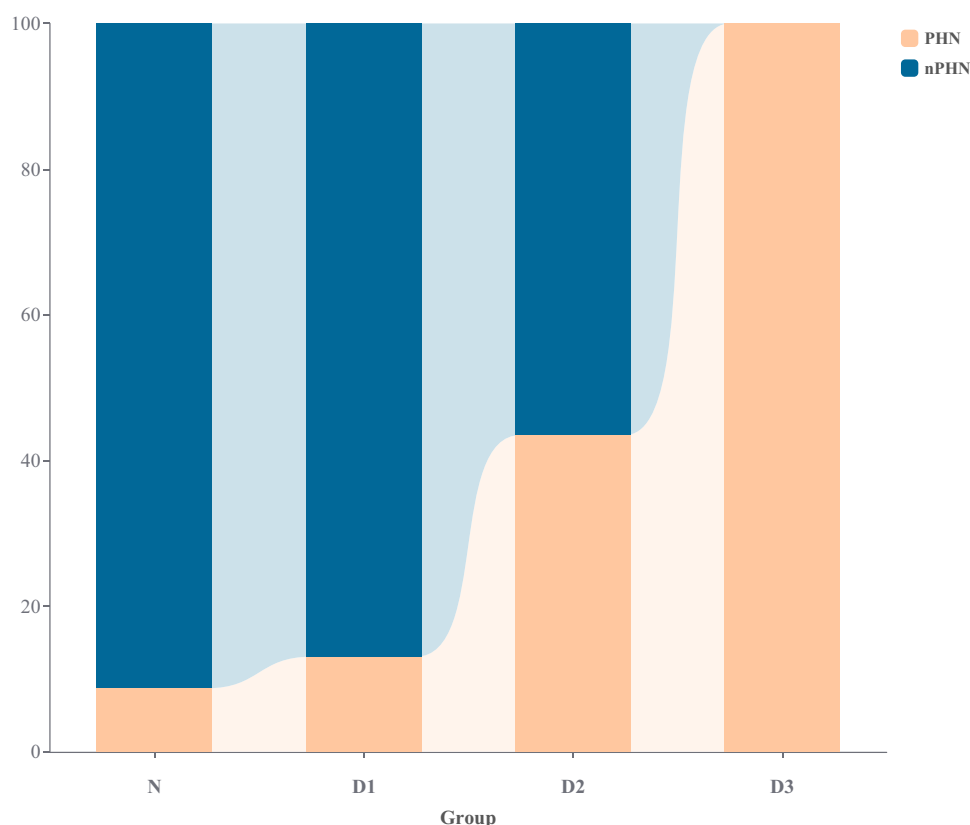


**Figure 1** Flow diagram of the cohort study.

**Table I** Clinical Characteristics of Four Groups

Variables	N (n = 23)	D <sub>1</sub> (n = 23)	D <sub>2</sub> (n = 23)	D <sub>3</sub> (n = 21)	P
Age, n (%)					0.070
≤ 65	11 (47.83)	3 (13.04)	9 (39.13)	6 (28.57)	
> 65	12 (52.17)	20 (86.96)	14 (60.87)	15 (71.43)	
Male, n (%)	7 (30.43)	10 (43.48)	12 (52.17)	14 (66.67)	0.106
BMI, n (%)					0.831
BMI < 18.5	2 (8.70)	1 (4.35)	1 (4.35)	2 (9.52)	
18.5 ≤ BMI < 24	13 (56.52)	13 (56.52)	9 (39.13)	10 (47.62)	
24 ≤ BMI < 28	4 (17.39)	6 (26.09)	10 (43.48)	7 (33.33)	
28 ≤ BMI	4 (17.39)	3 (13.04)	3 (13.04)	2 (9.52)	
Educational, n (%)					0.203
Illiteracy	7 (30.43)	6 (26.09)	7 (30.43)	3 (14.29)	
Elementary school	10 (43.48)	8 (34.78)	10 (43.48)	10 (47.62)	
Junior high school	4 (17.39)	2 (8.70)	5 (21.74)	7 (33.33)	
High school or above	2 (0.00)	7 (13.04)	1 (0.00)	1 (4.76)	
Smoking, n (%)	3 (13.04)	6 (26.09)	3 (13.04)	4 (19.05)	0.648
Drinking, n (%)	2 (8.70)	3 (13.04)	2 (8.70)	4 (19.05)	0.721
History of allergy, n (%)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	1.000
The site of the herpes, n (%)					0.816
Upper limbs	0 (0.00)	2 (8.70)	2 (8.70)	0 (0.00)	
Lower limbs	1 (4.35)	2 (8.70)	3 (13.04)	1 (4.76)	
Head and face	4 (17.39)	3 (13.04)	5 (21.74)	2 (9.52)	
Chest and back	14 (60.87)	11 (47.83)	9 (39.13)	11 (52.38)	
Waist and abdomen	4 (17.39)	5 (21.74)	4 (17.39)	6 (28.57)	
Neck and shoulders	0 (0.00)	0 (0.00)	0 (0.00)	1 (4.76)	
The course of HZ (days), n (%)					0.139
≤ 30	12 (52.17)	13 (56.52)	19 (82.61)	14 (66.67)	
> 30	11 (47.83)	10 (43.48)	4 (17.39)	7 (33.33)	
NRS <sub>0</sub> , M (Q <sub>1</sub> , Q <sub>3</sub> )	6.0 (5.0,7.0)	7.0 (6.0,7.0)	6.0 (5.5,7.0)	6.0 (5.0,6.0)	0.153
Rheumatoid arthritis, n (%)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	1.000
Hypertension, n (%)	9 (39.13)	12 (52.17)	16 (69.57)	11 (52.38)	0.229
Cerebral infarction, n (%)	0 (0.00)	2 (8.70)	1 (4.35)	0 (0.00)	0.613
Hyperthyroidism, n (%)	0 (0.00)	1 (4.35)	0 (0.00)	0 (0.00)	1.000

**Abbreviations:** M, Median; Q<sub>1</sub>, 1st Quartile; Q<sub>3</sub>, 3st Quartile; BMI, Body Mass Index; HZ, Herpes zoster; NRS<sub>0</sub>, Pre-operative numerical rating scale.



**Figure 2** Percentage stacked histogram of PHN incidence in 4 groups of patients.

**Notes:** The incidence of PHN was notably higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group N (N vs D<sub>2</sub>,  $P = 0.007$ ; N vs D<sub>3</sub>,  $P < 0.001$ ). Additionally, the incidence of PHN was significantly higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group D<sub>1</sub> (D<sub>1</sub> vs D<sub>2</sub>,  $P = 0.022$ ; D<sub>1</sub> vs D<sub>3</sub>,  $P < 0.001$ ), and the incidence of PHN in group D<sub>3</sub> was significantly higher compared to group D<sub>2</sub> ( $P < 0.001$ ).

**Abbreviations:** PHN, postherpetic neuralgia; nPHN, non- postherpetic neuralgia.

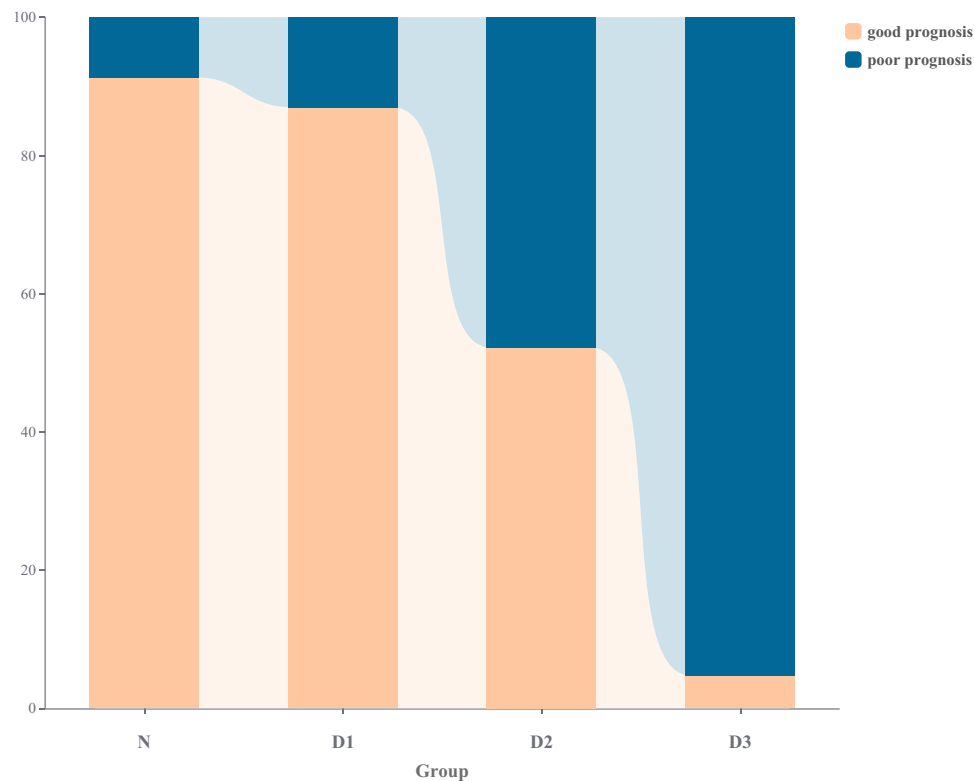
significant only in group D<sub>3</sub> ( $P < 0.001$ ). In intergroup comparisons, at T<sub>2</sub>, NRS were significantly higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group N (N vs D<sub>2</sub>,  $P = 0.035$ ; N vs D<sub>3</sub>,  $P < 0.001$ ). At T<sub>3</sub>, NRS were significantly higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group N (N vs D<sub>2</sub>,  $P = 0.016$ ; N vs D<sub>3</sub>,  $P = 0.004$ ). At T<sub>4</sub>, NRS were significantly higher in groups D<sub>2</sub> and D<sub>3</sub> compared to group N (all  $P < 0.001$ ). There was no statistically significant difference between group N and group D<sub>1</sub> at T<sub>1</sub>-T<sub>4</sub> ( $P > 0.05$ ) (Figure 4). There was an interaction effect between time and group.

## Comparison of SRSS at various time points

The SRSS was utilized as a metric to measure sleep quality, with higher scores indicating lower sleep quality. The preoperative SRSS of each group was corrected as a covariate. Analysis of generalized estimating equations showed that in within-group comparisons, the differences in SRSS at the T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> time points were statistically significant in groups N, D<sub>2</sub>, and D<sub>3</sub> (N:  $P = 0.035$ , D<sub>2</sub>:  $P = 0.033$ , D<sub>3</sub>:  $P < 0.001$ ), and not statistically significant for SRSS at the T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> time points in group D<sub>1</sub>. In intergroup comparisons, at the T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> time points, SRSS was significantly higher in the D<sub>3</sub> group compared to the N group (all  $P < 0.001$ ). The differences between the N group and the D<sub>1</sub> and D<sub>2</sub> groups were not statistically significant at all postoperative time points (Figure 5). There was an interaction effect between time and group.

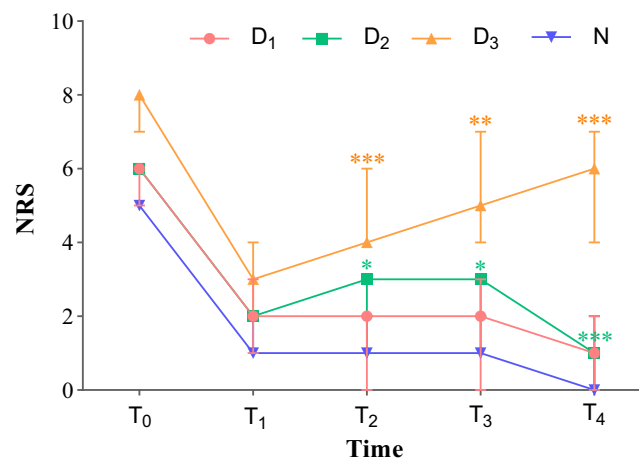
## Comparison of HADS at various time points

The preoperative HADS scores of each group were used as covariates. Analysis of generalized estimating equations showed that in intragroup comparisons, there was no statistically significant difference in HADS(A) among groups N, D<sub>1</sub>, and D<sub>2</sub> at times T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> ( $P > 0.05$ ). However, the difference in HADS(A) among the D<sub>3</sub> group at time



**Figure 3** Stacked Histogram of Percentage of Patients in 4 Groups with Good Prognosis vs Poor Prognosis.

**Notes:** With worse efficacy in group D<sub>2</sub> and D<sub>3</sub> compared with group N (N vs D<sub>2</sub>,  $P = 0.003$ ; N vs D<sub>3</sub>,  $P < 0.001$ ); compared with group D<sub>1</sub>, groups D<sub>2</sub> and D<sub>3</sub> had worse efficacy (D<sub>1</sub> vs D<sub>2</sub>,  $P = 0.010$ ; D<sub>1</sub> vs D<sub>3</sub>,  $P < 0.001$ ); group D<sub>3</sub> had worse efficacy than group D<sub>2</sub> ( $P < 0.001$ ).



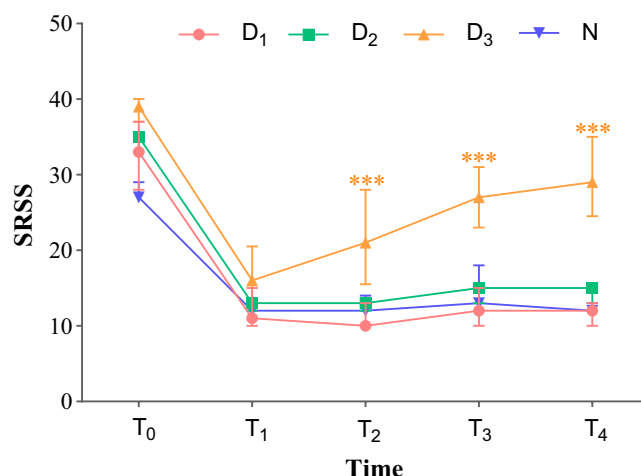
**Figure 4** Line graphs of NRS over time for the 4 groups of patients.

**Notes:** \*  $P < 0.05$  compared with group N; \*\*  $P < 0.01$  compared with group N; \*\*\*  $P < 0.001$  compared with group N; NRS: Numerical Rating Scale; D<sub>1</sub>: good glycemic control group: HbA<sub>1c</sub> < 7% (53.01 mmol/mol); D<sub>2</sub>: general glycemic control group: 7% (53.01 mmol/mol) ≤ HbA<sub>1c</sub> < 9% (74.86 mmol/mol); D<sub>3</sub>: poor glycemic control group: HbA<sub>1c</sub> ≥ 9% (74.86 mmol/mol); (N) control group: HbA<sub>1c</sub> < 6% (42.08 mmol/mol); T<sub>0</sub>: preoperative; T<sub>1</sub>: postoperative immediately; T<sub>2</sub>: post-operative day 7; T<sub>3</sub>: post-operative day 30; T<sub>4</sub>: post-operative day 90.

points T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> was statistically significant ( $P = 0.027$ ). In intergroup comparisons, at time points T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub>, HADS(A) was significantly higher in the D<sub>3</sub> group compared to the N group (all  $P < 0.05$ ) (Figure 6).

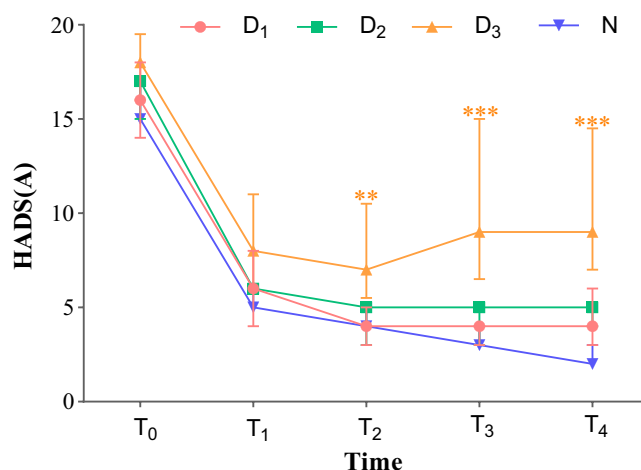
Overall, the difference between groups D<sub>1</sub> and D<sub>3</sub> in HADS(D) at T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> times was statistically significant (D<sub>1</sub>,  $P = 0.016$ ; D<sub>3</sub>,  $P < 0.001$ ). The difference in HADS(D) between group N and group D<sub>2</sub> at T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> time points was not statistically significant ( $P > 0.05$ ). In intergroup comparisons, HADS(D) were significantly higher in the





**Figure 5** Line graphs of SRSS over time for the 4 groups of patients.

**Notes:** \*\*\*  $P < 0.001$  compared with group N; SRSS: Self-Rating Scale of Sleep; D<sub>1</sub>: good glycemic control group: HbA1c < 7% (53.01 mmol/mol); D<sub>2</sub>: general glycemic control group: 7% (53.01 mmol/mol) ≤ HbA1c < 9% (74.86 mmol/mol); D<sub>3</sub>: poor glycemic control group: HbA1c ≥ 9% (74.86 mmol/mol); (N) control group: HbA1c < 6% (42.08 mmol/mol); T<sub>0</sub>: preoperative; T<sub>1</sub>: postoperative immediately; T<sub>2</sub>: postoperative day 7; T<sub>3</sub>: postoperative day 30; T<sub>4</sub>: postoperative day 90.



**Figure 6** Line graphs of Hads(A) over time for the 4 groups of patients.

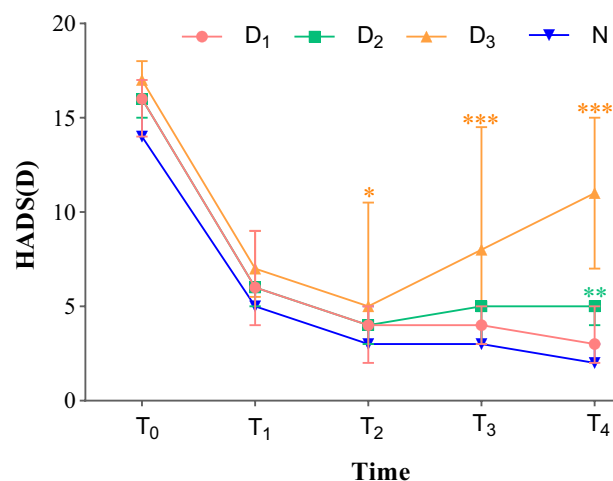
**Notes:** \*\*  $P < 0.01$  compared with group N; \*\*\*  $P < 0.001$  compared with group N; HADS(A): Hospital Anxiety and Depression Scale (anxiety subscale); D<sub>1</sub>: good glycemic control group: HbA1c < 7% (53.01 mmol/mol); D<sub>2</sub>: general glycemic control group: 7% (53.01 mmol/mol) ≤ HbA1c < 9% (74.86 mmol/mol); D<sub>3</sub>: poor glycemic control group: HbA1c ≥ 9% (74.86 mmol/mol); (N) control group: HbA1c < 6% (42.08 mmol/mol); T<sub>0</sub>: preoperative; T<sub>1</sub>: postoperative immediately; T<sub>2</sub>: postoperative day 7; T<sub>3</sub>: postoperative day 30; T<sub>4</sub>: postoperative day 90.

D<sub>3</sub> group compared to the N group at the T<sub>2</sub> and T<sub>3</sub> time points (all  $P < 0.05$ ). HADS (D) were also significantly higher in the D<sub>2</sub> and D<sub>3</sub> groups compared to the N group at the T<sub>4</sub> time point (N vs D<sub>2</sub>,  $P = 0.006$ ; N vs D<sub>3</sub>,  $P < 0.001$ ) (Figure 7). There was an interaction effect between time and group.

## Comparison of the use of remedial drugs and the presence of glycemic crisis values during hospitalization

None of the patients in group N used remedial analgesic drugs during hospitalization. In group D<sub>1</sub>, 4.35% of patients used remedial analgesic drugs, while in group D<sub>2</sub> and D<sub>3</sub>, the percentages were 21.74% and 42.86% respectively. The overall difference in drug usage among the four groups was statistically significant ( $P < 0.001$ ). Specifically, the differences in drug usage between group N and D<sub>1</sub>, N and D<sub>2</sub>, D<sub>1</sub> and D<sub>2</sub>, as well as D<sub>2</sub> and D<sub>3</sub> were not statistically significant. However, the number of patients using remedial analgesic drugs in group D<sub>3</sub> was significantly higher compared to both group N and D<sub>1</sub> (N vs D<sub>3</sub>,  $P = 0.002$ ; D<sub>1</sub> vs D<sub>3</sub>,  $P = 0.007$ ).





**Figure 7** Line graphs of Hads(D) over time for the 4 groups of patients.

**Notes:** \*  $P < 0.05$  compared with group N; \*\*  $P < 0.01$  compared with group N; \*\*\*  $P < 0.001$  compared with group N; HADS(D): Hospital Anxiety and Depression Scale (depression subscale); D<sub>1</sub>: good glycemic control group: HbA1c  $< 7\%$  (53.01 mmol/mol); D<sub>2</sub>: general glycemic control group:  $7\%$  (53.01 mmol/mol)  $\leq$  HbA1c  $< 9\%$  (74.86 mmol/mol); D<sub>3</sub>: poor glycemic control group: HbA1c  $\geq 9\%$  (74.86 mmol/mol); (N) control group: HbA1c  $< 6\%$  (42.08 mmol/mol); T<sub>0</sub>: preoperative; T<sub>1</sub>: postoperative immediately; T<sub>2</sub>: postoperative day 7; T<sub>3</sub>: postoperative day 30; T<sub>4</sub>: postoperative day 90.

No patients in group N and group D<sub>1</sub> experienced glycemic crisis values during hospitalization. 21.74% of patients in group D<sub>2</sub> exhibited glycemic crisis values during hospitalization, while 80.95% of patients in group D<sub>3</sub> had glycemic crisis values. The overall difference among the four groups was statistically significant (all  $P < 0.001$ ). There was no statistically significant difference in the frequency of glycemic crisis values during hospitalization between group D<sub>1</sub> and group D<sub>2</sub>, as well as between group D<sub>1</sub> and group N. However, the number of patients in group D<sub>3</sub> with glycemic crisis values during hospitalization was significantly higher than that of group N and group D<sub>1</sub> (all  $P < 0.001$ ). Additionally, there was no statistically significant difference in the frequency of glycemic crisis values during hospitalization between group D<sub>1</sub> and D<sub>2</sub>, and between group D<sub>1</sub> and N (Table 2).

## Discussion

In this cohort study, we investigated the occurrence of PHN following PRF treatment in patients with HZ and varying levels of glycemic control indicated by HbA1c levels. Our results demonstrated a significant increase in PHN incidence among HZ patients with T2DM whose HbA1c levels exceeded 7% (53.01 mmol/mol), underscoring the impact of poor glycemic control.

Recent studies have identified T2DM as a risk factor for PHN.<sup>19,31,32</sup> HZ patients with T2DM exhibit a worse prognosis and longer recovery period compared to non-diabetic individuals.<sup>19</sup> T2DM, a metabolic disorder, can lead to widespread organ damage, particularly when poorly controlled, potentially leading to diabetic peripheral neuropathy.<sup>19</sup>

When coupled with HZ, diabetes can exacerbate symptoms and increase the likelihood of nerve damage, further elevating the risk of PHN. Studies indicate a higher prevalence of PHN in T2DM patients compared to non-diabetic individuals.<sup>15</sup> Our findings align with this, showing a markedly increased PHN occurrence in HZ patients with T2DM compared to those without ( $P < 0.001$ ). In individuals with T2DM, microvascular damage can trigger neuronal stress

**Table 2** Comparison of the Use of Remedial Drugs and the Occurrence of Glycemic Crisis Values During Hospitalization in 4 Groups of Patients

Variables	N (n=23)	D <sub>1</sub> (n=23)	D <sub>2</sub> (n=23)	D <sub>3</sub> (n=21)
Number of cases of remedial pains, n (%)	0(0%)	1(4.3%)	5(21.7%)	9(42.9%) <sup>##</sup>
Critical blood glucose level, n (%)	0(0%)	0(0%)	5(21.7%)	17(81.0%) <sup>##</sup>

**Notes:** \* Statistically different from group N; <sup>#</sup> Statistically different from D<sub>1</sub> group.

responses, leading to VZV reactivation and increasing the risk of PHN.<sup>33–35</sup> Prolonged hyperglycemia can activate the polyol pathway, disrupting cellular function and increasing susceptibility to PHN.<sup>36</sup> Furthermore, T2DM-related weakened immune responses, particularly in polymorphonuclear cells and monocyte macrophages, make diabetic patients more prone to developing PHN compared to non-diabetic individuals.<sup>37</sup>

Currently, the relationship between glycemic control levels and the incidence of PHN in patients with both HZ and T2DM remains unclear. Our study seeks to clarify this connection, suggesting that better preoperative glycemic control is associated with a reduced incidence of PHN. Specifically, we found that patients with HbA1c levels exceeding 7% (53.01 mmol/mol) exhibited a higher incidence of PHN, as well as poorer treatment outcomes and sleep quality. This trend aligns with a large population-based observational study by Hirji et al<sup>38</sup> which identified a strong correlation between higher HbA1c levels and infection risk in T2DM, particularly when HbA1c levels surpassed 8% (63.93 mmol/mol).

Cell-mediated immunity (CMI) plays a crucial role in preventing VCV reactivation.<sup>31,39</sup> In T2DM patients with poor glycemic control, persistent hyperglycemia hinders CMI, affecting processes such as phagocytosis, memory CD4+ cells, cytotoxic CD8+ T cells, and cytokines activation.<sup>40</sup> A cohort study conducted in Spain revealed that elevated HbA1c levels were associated with reduced CD4+ T cells and memory CD4+ responses,<sup>41</sup> potentially explaining the higher PHN incidence in patients with poor glycemic control. Additionally, VZV damages to A $\delta$ , A $\beta$ , and C sensory nerve fibers, resulting in the varied pain experienced in PHN.<sup>46</sup> T2DM also leads to damage of A $\delta$  and C nerve fibers, contributing to painful neuropathy.<sup>42</sup> This could elucidate why patients in group D<sub>3</sub> required more pain-relieving medication than those in the other groups. Although the NRS scores of patients in group D<sub>3</sub> were initially lower after treatment, they gradually increased during follow-up, consistently surpassing scores in groups N, D<sub>1</sub>, and D<sub>2</sub>. This trend suggests that poor glycemic control heightens the risk of neuropathic pain, underscoring the importance of stable glycemic management for effective pain control.<sup>43,44</sup>

This study observed higher SRSS and HADS scores in the D<sub>3</sub> group compared to the N group at time points T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub>. MONTI et al<sup>45</sup> highlighted the impact of T2DM on neurotransmitters in the central nervous system, leading to autonomic dysfunction that affects sleep. DEPIETRO et al<sup>46</sup> found that hyperglycemia in hospitalized patients resulted in both shorter sleep duration and reduced sleep quality. Another case-control study revealed an independent association between shorter rapid eye movement sleep duration and poorer blood glucose levels.<sup>47</sup> Furthermore, a large cohort study indicated that individuals with T2DM had a nearly 22% higher risk of developing depression compared to controls.<sup>48</sup> Hyperglycemia is linked to increased oxygen electron transfer and reactive oxygen species (ROS) production,<sup>49,50</sup> contributing to neuropathic pain and potentially triggering anxiety and depression in patients.<sup>33,51</sup> Therefore, maintaining good glycemic control in patients with comorbid HZ and T2DM can enhance sleep quality and decrease the likelihood of anxiety and depression.

This study has several limitations. Firstly, it is a single-center observational cohort study with a small sample size. To further confirm the findings, a multicenter prospective randomized controlled study with a larger sample size is necessary. Secondly, the study only collected HbA1c levels of patients with HZ before PRF treatment and did not adequately consider how HbA1c levels 2–3 months post-operation could impact the incidence of PHN. Lastly, the study focused on HZ patients treated with PRF, which may not be representative of all HZ patients undergoing different treatment modalities.

## Conclusion

In patients undergoing PRF treatment for HZ combined with diabetes mellitus, having a preoperative HbA1c level above 7% (53.01 mmol/mol) significantly raises the risk of developing postoperative PHN. Therefore, in future research, it may be beneficial to consider increasing the sample size, collecting more data, and comparing the effects of different treatment methods on the incidence of PHN to further validate the results of this study. Additionally, the impact of HbA1c levels 2–3 months post-surgery on the occurrence of PHN should also be taken into account to more comprehensively assess the risk of diabetic patients in HZ treatment. Overall, the results of this study suggest that diabetic patients should pay more attention to blood sugar control during HZ treatment to reduce the incidence of PHN.

## Acknowledgments

The authors would like to thank all of the patients who participated in this study and all of the clinicians who assisted with patient recruitment.

## Funding

This study was supported by the National Natural Science Foundation of China (82171216), Zhejiang Provincial Traditional Chinese Medical Innovation Team (No. 2022-19), Key Discipline Established by Zhejiang Province and Jiaxing City Jointly—Pain Medicine (2019-ss-ttyx), Jiaxing Key Laboratory of Neurology and Pain Medicine, and Zhejiang Provincial Clinical Key Specialties-Anesthesiology (2023-ZJZK-001).

## Disclosure

The author(s) report no conflicts of interest in this work.

## References

- O'Connor KM, Paauw DS. Herpes zoster. *Med Clin North Am*. 2013;97(4):503–522. doi:10.1016/j.mcna.2013.02.002
- Cohen JI. Clinical practice: herpes zoster. *N Engl J Med*. 2013;369(3):255–263. doi:10.1056/NEJMcpl302674
- Weller TH. Varicella and herpes zoster. Changing concepts of the natural history, control, and importance of a not-so-benign virus. *N Engl J Med*. 1983;309(23):1434–1440. doi:10.1056/NEJM198312083092306
- Szucs TD, Kressig RW, Papageorgiou M, et al. Economic evaluation of a vaccine for the prevention of herpes zoster and post-herpetic neuralgia in older adults in Switzerland. *Hum Vaccin*. 2011;7(7):749–756. doi:10.4161/hv.7.7.15573
- Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med*. 2014;371(16):1526–1533. doi:10.1056/NEJMcpl403062
- Yang F, Yu S, Fan B, et al. The epidemiology of herpes zoster and postherpetic neuralgia in china: results from a cross-sectional study. *Pain Ther*. 2019;8(2):249–259. doi:10.1007/s40122-019-0127-z
- Niv D, Maltzman-Tseikhin A. Postherpetic neuralgia: the never-ending challenge. *Pain Pract*. 2005;5(4):327–340. doi:10.1111/j.1533-2500.2005.00035.x
- Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine*. 2001;19(23–24):3076–3090. doi:10.1016/S0264-410X(01)00044-5
- Flor H. Painful memories. Can we train chronic pain patients to ‘forget’ their pain? *EMBO Rep*. 2002;3(4):288–291. doi:10.1093/embo-reports/kvf080
- Hope-Simpson RE. Postherpetic neuralgia. *J R Coll Gen Pract*. 1975;25(157):571–575.
- Tang J, Zhang Y, Liu C, Zeng A, Song L. Therapeutic strategies for postherpetic neuralgia: mechanisms, treatments, and perspectives. *Curr Pain Headache Rep*. 2023;27(9):307–319. doi:10.1007/s11916-023-01146-x
- Lin CS, Lin YC, Lao HC, Chen CC. Interventional treatments for postherpetic neuralgia: a systematic review. *Pain Physician*. 2019;22(3):209–228. doi:10.36076/ppj.2019.22.209
- Racz GB, Ruiz-Lopez R. Radiofrequency procedures. *Pain Pract*. 2006;6(1):46–50. doi:10.1111/j.1533-2500.2006.00058.x
- Peng Z, Guo J, Zhang Y, et al. Development of a model for predicting the effectiveness of pulsed radiofrequency on zoster-associated pain. *Pain Ther*. 2022;11(1):253–267. doi:10.1007/s40122-022-00355-3
- Heymann AD, Chodick G, Karpati T, et al. Diabetes as a risk factor for herpes zoster infection: results of a population-based study in Israel. *Infection*. 2008;36(3):226–230. doi:10.1007/s15010-007-6347-x
- Queenan JA, Farahani P, Ehsani-Moghadam B, Birtwhistle RV. The prevalence and risk for herpes zoster infection in adult patients with diabetes mellitus in the Canadian Primary Care Sentinel Surveillance Network. *Can J Diabetes*. 2018;42(5):465–469. doi:10.1016/j.cjcd.2017.10.060
- Saadatian-Elahi M, Bauduceau B, Del-Signore C, Vanhems P. Diabetes as a risk factor for herpes zoster in adults: a synthetic literature review. *Diabet Res Clin Pract*. 2020;159:107983. doi:10.1016/j.diabres.2019.107983
- Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain*. 2016;157(1):30–54. doi:10.1097/j.pain.0000000000000307
- Suaya JA, Chen SY, Li Q, Burstin SJ, Levin MJ. Incidence of herpes zoster and persistent post-zoster pain in adults with or without diabetes in the United States. *Open Forum Infect Dis*. 2014;1(2):ofu049. doi:10.1093/ofid/ofu049
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2000;23 Suppl 1:S4–19.
- Bantle JP, Wylie-Rosett J, Albright AL, et al.; American Diabetes Association. Nutrition recommendations and interventions for diabetes: a position statement of the American diabetes association. *Diabetes Care*. 2008;31 Suppl 1:S61–78. doi:10.2337/dc08-S061
- Zghebi SS, Panagioti M, Rutter MK, et al. Assessing the severity of Type 2 diabetes using clinical data-based measures: a systematic review. *Diabet Med*. 2019;36(6):688–701. doi:10.1111/dme.13905
- Rodbard HW, Jellinger PS. The American association of clinical endocrinologists/American College of Endocrinology (AAACE/ACE) algorithm for managing glycaemia in patients with type 2 diabetes mellitus: comparison with the ADA/EASD algorithm. *Diabetologia*. 2010;53(11):2458–2460. doi:10.1007/s00125-010-1905-7
- DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986. doi:10.1056/NEJM199309303291401

25. GROUP UK PROSPECTIVE DIABETES STUDY. Intensive blood group with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
26. Cheisson G, Jacqueminet S, Cosson E, et al. Perioperative management of adult diabetic patients preoperative period. *Anaesth Crit Care Pain Med*. 2018;37 Suppl 1:S9–S19.
27. Naravadi V, Balasubramanian G, Molnar J, Gray J, Anand K. Mo1020 association between elevated hemoglobin A1c(HbA1C) and the colorectal neoplasms in patients with type-2 diabetes mellitus. *Gastroenterology*. 2012;142(5, Supplement 1):S–574. [ISSN 0016-5085]. doi:10.1016/S0016-5085(12)62202-1
28. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–412. doi:10.1136/bmj.321.7258.405
29. Liu BT, Xue K, Fan BF, Cui Y. Interpretation of the expert consensus on the whole-process management of herpes zoster-associated pain. *Zhonghua Yi Xue Za Zhi*. 2022;102(40):3156–3159. doi:10.3760/cma.j.cn112137-20220415-00814
30. Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group; Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Society. Geriatric endocrinology and metabolism branch of Chinese Geriatric Health Care Society; Geriatric Professional Committee of Beijing Medical Award Foundation; National Clinical Medical Research Center for Geriatric Diseases (PLA General Hospital). [Clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition)]. *Zhonghua Nei Ke Za Zhi*. 2022;61(1):12–50. doi:10.3760/cma.j.cn112138-20211027-00751
31. Okamoto S, Hata A, Sadaoka K, Yamanishi K, Mori Y. Comparison of varicella-zoster virus-specific immunity of patients with diabetes mellitus and healthy individuals. *J Infect Dis*. 2009;200(10):1606–1610. doi:10.1086/644646
32. Kalra S, Chawla A. Herpes zoster and diabetes. *J Pak Med Assoc*. 2016;66(8):1042–1043.
33. Kaiserman I, Kaiserman N, Nakar S, Vinker S. Herpetic eye disease in diabetic patients. *Ophthalmology*. 2005;112(12):2184–2188. doi:10.1016/j.opthta.2005.07.014
34. Kaze AD, Santhanam P, Erqou S, Ahima RS, Bertoni A, Echouffo-Tcheugui JB. Microvascular disease and incident heart failure among individuals with type 2 diabetes mellitus. *J Am Heart Assoc*. 2021;10:e018998. doi:10.1161/JAHA.120.018998
35. Yang CY, Su PF, Hung JY, Ou HT, Kuo S. Comparative predictive ability of visit-to-visit HbA1c variability measures for microvascular disease risk in type 2 diabetes. *Cardiovasc Diabetol*. 2020;19:105. doi:10.1186/s12933-020-01082-9
36. Katsuda Y, Sasase T, Tadaki H, et al. Contribution of hyperglycemia on diabetic complications in obese type 2 diabetic SDT fatty rats: effects of SGLT inhibitor phlorizin. *Exp Anim*. 2015;64:161–169. doi:10.1538/expanim.14-0084
37. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol*. 1999;26:259–265. doi:10.1111/j.1574-695X.1999.tb01397.x
38. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Camirero A. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). *J Diabetes Complications*. 2012;26(6):513–516. doi:10.1016/j.jdiacomp.2012.06.008
39. Vossen MT, Gent MR, Weel JF, de Jong MD, van Lier RA, Kuijpers TW. Development of virus-specific CD4+ T cells on reexposure to Varicella-Zoster virus. *J Infect Dis*. 2004;190(1):72–82. doi:10.1086/421277
40. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. *Lancet Diabetes Endocrinol*. 2016;4(2):148–158. doi:10.1016/S2213-8587(15)00379-4
41. Martinez PJ, Mathews C, Actor JK, et al. Impaired CD4+ and T-helper 17 cell memory response to Streptococcus pneumoniae is associated with elevated glucose and percent glycated hemoglobin A1c in Mexican Americans with type 2 diabetes mellitus. *Transl Res*. 2014;163(1):53–63. doi:10.1016/j.trsl.2013.07.005
42. Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. *Endocrinol Metab Clin North Am*. 2013;42(4):747–787. doi:10.1016/j.ecl.2013.06.001
43. Oyibo SO, Prasad YD, Jackson NJ, Jude EB, Boulton AJ. The relationship between blood glucose excursions and painful diabetic peripheral neuropathy: a pilot study. *Diabet Med*. 2002;19(10):870–873. doi:10.1046/j.1464-5491.2002.00801.x
44. Boulton AJ, Drury J, Clarke B, Ward JD. Continuous subcutaneous insulin infusion in the management of painful diabetic neuropathy. *Diabetes Care*. 1982;5(4):386–390. doi:10.2337/diacare.5.4.386
45. Monti JM. The neurotransmitters of sleep and wake, a physiological reviews series. *Sleep Med Rev*. 2013;17(4):313–315. doi:10.1016/j.smrv.2013.02.004
46. DePietro RH, Knutson KL, Spampinato L, et al. Association between inpatient sleep loss and hyperglycemia of hospitalization. *Diabetes Care*. 2017;40(2):188–193. doi:10.2337/dc16-1683
47. Arriaga-Rodríguez M, Leal Y, Mayneris-Perxachs J, et al. Gut microbiota composition and functionality are associated with REM sleep duration and continuous glucose levels. *J Clin Endocrinol Metab*. 2023;108(11):2931–2939. doi:10.1210/clinem/dgad258
48. Wahlqvist ML, Lee MS, Chuang SY, et al. Increased risk of affective disorders in type 2 diabetes is minimized by sulfonylurea and metformin combination: a population-based cohort study. *BMC Med*. 2012;10:150. doi:10.1186/1741-7015-10-150
49. Gadjeva VG, Goycheva P, Nikolova G, Zheleva A. Influence of glycemic control on some real-time biomarkers of free radical formation in type 2 diabetic patients: an EPR study. *Adv Clin Exp Med*. 2017;26(8):1237–1243. doi:10.17219/acem/68988
50. Wentholt IM, Kulik W, Michels RP, Hoekstra JB, DeVries JH. Glucose fluctuations and activation of oxidative stress in patients with type 1 diabetes. *Diabetologia*. 2008;51(1):183–190. doi:10.1007/s00125-007-0842-6
51. Réus GZ, Carlessi AS, Silva RH, Ceretta LB, Quevedo J. Relationship of oxidative stress as a link between diabetes mellitus and major depressive disorder. *Oxid Med Cell Longev*. 2019;2019:8637970. doi:10.1155/2019/8637970

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