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A correlation study between blood glucose fluctuation and chronic pain in the older people with type 2 diabetes mellitus

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Abstract

Objectives To investigate the correlation between blood glucose fluctuation parameters and other clinical data with chronic pain in older patients (≧60 years) with type 2 diabetes mellitus (T2DM), as well as evaluating the predictive value of risk of these parameters for chronic pain.

Methods Clinical data were collected from 60 older patients with T2DM undergoing chronic pain who were hospitalized in the Department of Geriatric Endocrinology at the First Affiliated Hospital of Anhui Medical University. Pain scores using the numeric rating scale (NRS) were administered to all study participants by a dedicated person. Based on their pain scores, patients were categorized into two groups: mild pain group (NRS ≤ 5, $n = 28$) and severe pain group (NRS > 5, $n = 32$). Blood glucose levels were continuously monitored using the Continuous Glucose Monitoring System (CGMS). *Spearman* correlation analysis was performed to investigate the correlation between pain scores and blood glucose fluctuation parameters, as well as other clinical data of concern. Comparing general clinical information and relevant data recorded by CGMS between the two groups. Binary *logistic* regression was used to identify factors influencing the severity of chronic pain in old patients with T2DM combined with chronic pain. Additionally, the predictive value of Mean Amplitude of Glycemic Excursions (MAGE), Coefficient of Variation (CV), and Time in Range (TIR) for chronic pain severity was assessed using Receiver Operating Characteristic (ROC) curve analysis.

Results *Spearman* correlation analysis revealed positive correlations between pain scores and the following variables: gender, age, duration of diabetes, duration of pain, MAGE, CV, mean blood glucose (MBG), standard deviation (SD), Mean of Daily Differences (MODD), and the highest glucose level. Conversely, pain scores were negatively correlated with red blood cell (RBC) count, hemoglobin (Hb), estimated glomerular filtration rate (eGFR). There were statistically significant differences in gender, age, disease duration, pain duration, Hb, eGFR, MAGE, CV, TIR, MBG, SD, MODD, and highest blood glucose values between the two groups. The gender, age, duration of diabetes, duration of pain, Hb, eGFR, MAGE, TIR, CV, MBG, SD, and MODD were identified as the risk factors for the severity of chronic pain in older T2DM patients by using binary *logistic* regression analysis. ROC curve analysis showed that the area under the curve

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for MAGE was 0.741 (sensitivity: 53.1%, specificity: 89.3%), for CV it was 0.668 (sensitivity: 40.6%, specificity: 89.3%), and for TIR it was 0.763 (sensitivity: 67.9%, specificity: 84%).

Conclusion The chronic pain is strongly correlated with blood glucose fluctuation parameters in older patients with T2DM. This work shows that those indicators of blood glucose fluctuations can be used for predicting chronic pain level in older T2DM patients, providing a potential methodology for rapid evaluation of chronic pain.

Clinical trial number ChiCTR1800019107.

Keywords Geriatrics, type 2 diabetes, blood glucose fluctuation, chronic pain, continuous glucose monitoring, correlation

Introduction

Over the past three decades, the global incidence of T2DM has surged rapidly. Currently, there is a large proportion of older T2DM over 60 years of age among all adult T2DM, and the direct effects of aging on metabolic regulation exacerbate the underlying pathophysiology of the disease in these patients [1]. Chronic pain, which is defined as pain persisting for over one month or recurring over several months to years, significantly affects the life quality of patients. Among older T2DM patients, chronic pain is prevalent due to complications and comorbidities such as lower extremity vascular disease, peripheral neuropathy, osteoporosis, and osteoarthritis. Notably, pain can be neglected easily as an inevitable part of aging by older patients, leading to the underestimation of pain effects.

The etiology of chronic pain in older T2DM patients is multifaceted, often involving an interplay of several overlapping factors, which profoundly impacts their quality of life. This pain can lead to emotional disturbances, sleep disorders, and even heighten the risk of suicide and severe adverse events [2]. Despite its prevalence, there is a notable paucity of research focusing on chronic pain in older T2DM patients. Thus, delving into the causes and mechanisms underlying chronic pain in the older people is important. It can provide deeper clinical insights for early intervention, thereby reducing patients' burden and improving their overall well-being.

Both domestic and international research has highlighted that blood glucose fluctuation may play a crucial role as a risk factor for diabetic complications, acting as an important measurement for blood glucose control apart from glycosylated hemoglobin (HbA1c) [3]. These fluctuations are involved with chronic diabetic complications such as nephropathy, neuropathy, retinopathy, and cardiovascular diseases [4]. They can influence the onset and progression of these diseases by intensifying inflammatory stress responses and altering gene expression [5]. Parameters of blood glucose fluctuation can be tracked and recorded using CGMS. This system provides a comprehensive, continuous, and clear reflection of blood glucose fluctuation patterns, making it a vital clinical tool for assessing these fluctuation parameters. Typically, the evaluation includes metrics such as the MAGE, CV, TIR, MBG, SD of blood glucose, and MODD. MAGE is the mean amplitude of blood glucose fluctuations over 24 h and represents the average of the amplitude of blood glucose fluctuations. CV is the coefficient of variation of blood glucose, which is calculated from the mean and standard deviation of blood glucose over a certain period of hospitalisation, reflecting the degree of dispersion of the patient's blood glucose. TIR refers to the proportion of blood glucose within the target range (usually defined as 3.9 to 10.0 mmol/L) that is achieved. Previous studies have shown a correlation between blood glucose fluctuations in T2DM patients and the occurrence of painful diabetic peripheral neuropathy (PDPN), suggesting that greater fluctuations might increase the risk of PDPN [6]. However, the relationship between blood glucose fluctuations and chronic pain in older T2DM patients still remains unclear. This study was divided into mild pain group (NRS$\leq$5 points, n=28) and severe pain group (>5 points, n=32) according to NRS pain score, *Spearman* correlation analysis of the correlation between pain scores and blood glucose fluctuation parameters and other clinical data, comparison of general clinical data and related data recorded by CGMS between the two groups, binary *logistic* regression to analyse the factors affecting the degree of combined chronic pain of older T2DM, and ROC curve to evaluate the predictive value of MAGE, CV and TIR on the degree of combined chronic pain of older T2DM. The ROC curve was made by plotting sensitivity as the vertical coordinate and sensitivity as the horizontal coordinate, and the area under the ROC curve could judge the diagnostic efficiency of the diagnostic test.

The aim of our study is to investigate the correlation blood glucose fluctuation parameters and pain scores/severity in older patients with T2DM who suffer from chronic pain. The objective is to find potential predictive indicators for chronic pain in older T2DM patients, providing new insights for the early prevention and treatment of chronic pain in the older people.

Subjects and methods

Study subjects

A total of 60 older T2DM patients with chronic pain, who were admitted to the Geriatric Endocrinology Department of the First Affiliated Hospital of Anhui Medical University between August 2020 and February 2022, were selected for this study (Fig. 1). Inclusion criteria: Age≥60 years; Meeting the diagnostic criteria for T2DM [8]; Presence of chronic persistent physical pain lasting more than one month; Stable antidiabetic regimen in the past three months; Relatively ideal mental state and cognitive function; Complete clinical data and high compliance with treatment and care. Exclusion criteria: Patients with type 1 diabetes or other types of diabetes; Patients with severe complications such as diabetic ketoacidosis or hyperosmolar coma. Patients with severe recurrent hypoglycemic events in the past three months; Patients with severe cardiovascular, cerebrovascular diseases, or liver or kidney dysfunction; Patients with factors potentially affecting blood glucose measurements; Patients with malignant tumors or mental disorders. Pain scores for all subjects were assessed using the Numerical Rating Scale (NRS) by a dedicated professional. The study was reviewed and approved by the hospital's ethics committee, and all participants provided informed consent.

Detailed methods

Collection of general and clinical data

General clinical data such as gender, age, duration of diabetes, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were collected from the patients. After hospital admission, patients were required to fast, abstain from smoking, and avoid alcohol for at least 8 h. The following morning, 5 ml of venous blood was drawn from each patient. Relevant biochemical indicators were measured using a fully automated biochemical analyzer, including: triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), RBC count, Hb, fasting plasma glucose (FPG), HbA1c, 2-hour postprandial plasma glucose (2hPG), fasting C-peptide (FC-P), 2-hour postprandial C-peptide (2hC-P), estimated glomerular filtration rate (eGFR), creatinine (Cr).

Assessment of pain scores

Pain scores of older T2DM patients with chronic pain were evaluated by using the NRS, and assessed by a dedicated professional through a detailed inquiry of the patients' medical histories.The NRS involves a straight line divided into 10 equal parts, each represented by a number from 0 to 10, indicating increasing levels of pain, with 0 representing no pain and 10 representing the worst pain imaginable. Patients were asked to rate their pain intensity on this scale, making it a simple, effective,

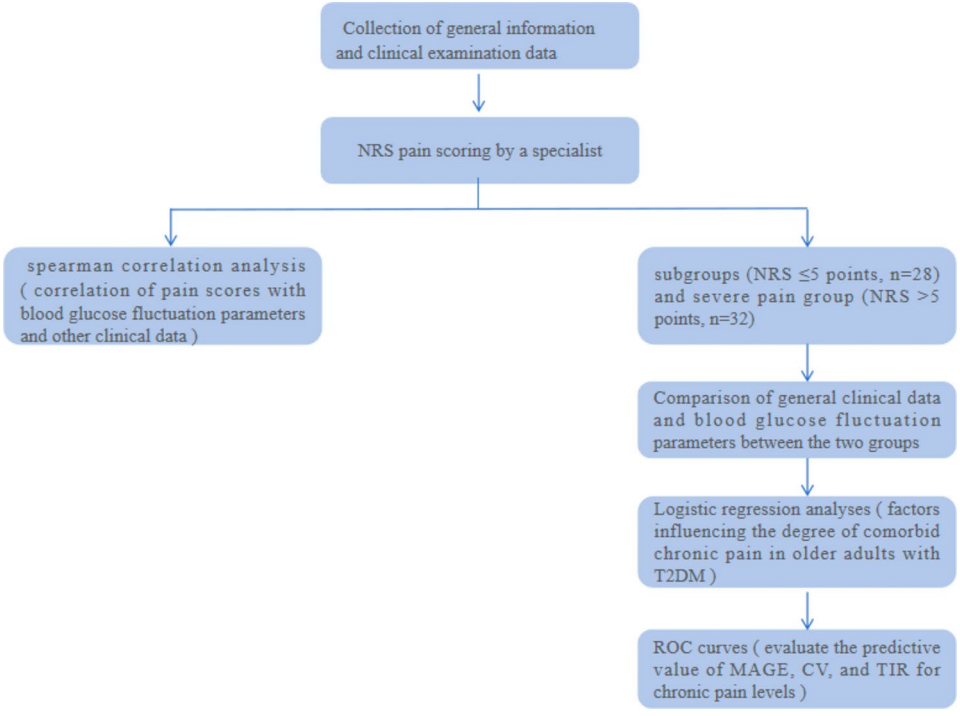

Fig. 1 Technology roadmap

and commonly used method for pain assessment [9]. Based on the pain scores of the 60 study subjects, they were divided into two groups: mild pain group (NRS ≤ 5, $n=28$) and severe pain group (NRS > 5, $n=32$).

Collection of CGM-related parameters

All study subjects wore an Abbott Freestyle Libre H continuous glucose monitoring (CGM) sensor on the lateral side of their upper arm. Intertissue fluid glucose concentrations were read every 15 min and analysed, the sensor measured interstitial glucose concentration every 15 min, providing 96 readings over a 24-hour period. A capillary blood glucose measurement was performed five times daily using a Rapid Blood Glucose Meter (Johnson & Johnson Steinhardt Superior Blood Glucose Meter, USA). The following parameters were calculated based on the glucose readings: MAGE, CV, TIR, MBG, SD, MODD, highest blood glucose value, lowest blood glucose value.

Statistical analysis

Data were statistically analyzed using SPSS version 26.0. Normally distributed quantitative data were shown as mean ± standard deviation ($\bar{x} \pm s$), comparisons between the two groups were made using the *t*-test; while non-normally distributed quantitative data were presented as median and interquartile range *[M (Q1, Q3)]*,using the rank sum test. Categorical data were expressed as *n* (%), using the x^2 test. *Spearman* correlation analysis was constructed to explore the correlation between pain scores and blood glucose fluctuation parameters, as well as other clinical data. Binary *logistic* regression was performed to analyze the factors influencing the severity of chronic pain in older T2DM patients. The ROC curve was utilized to evaluate the predictive value of MAGE, CV, and TIR for the severity of chronic pain. $P<0.05$ was considered statistically significant.

Results

Main characteristics of chronic pain in older T2DM patients

The average pain score for older T2DM patients with chronic pain was 5.47 ± 1.46. The primary pain sites include the lower back, lower limbs, and knee joints, with more than 50% of patients experiencing pain in two or more locations (Table 1).

Table 1 Pain sites in older patients with T2DM combined with chronic pain

Pain Site	Number of Patients	Percentage (%)	Number of Pain Sites	Number of Patients	Percentage (%)
Lower Limbs	31	51.67	One Site	30	50
Lower Back	32	53.33	Two Sites	17	28.33
Knee Joints	29	48.33	Three Sites	13	21.67
Other Sites	9	15			

Correlation of pain scores with general clinical data and blood glucose fluctuation parameters in older T2DM patients with chronic pain

Spearman correlation analysis was used to examine the relationship between pain scores and general clinical data, as well as blood glucose fluctuation parameters. The results indicated that gender, age, duration of diabetes, pain duration, MAGE, CV, MBG, SD, MODD, and highest blood glucose value were positively correlated with pain scores in older T2DM patients with chronic pain. Conversely, RBC, Hb, eGFR, and TIR were negatively correlated with pain scores. The details are presented in Table 2.

Comparison of general clinical data and blood glucose fluctuation parameters between the two groups $[n/\bar{x} \pm s/M(Q_1, Q_3)]$

There was a statistically significant difference in gender, age, duration of disease, duration of pain, Hb, eGFR, MAGE, CV, TIR, MBG, SD, MODD, and highest blood glucose value between patients in mild pain group and severe pain group. The details are presented in Table 3.

Binary *logistic* regression analysis of factors influencing the severity of chronic pain in older T2DM patients.

Binary *logistic* regression analysis was performed by using pain severity as the dependent variable (mild pain = 0, severe pain = 1), taking the factors that differed between the two groups (such as gender, age, duration of diabetes, pain duration, Hb, eGFR, MAGE, CV, TIR, MBG, SD, and MODD) as independent variables. The results indicated that age, duration of diabetes, pain duration, RBC, Hb, eGFR, MAGE, TIR, CV, SD, MBG, and MODD were factors influencing the severity of chronic pain in older T2DM patients (Table 4).

ROC curves to assess the risk-predictive value of MAGE, CV, and TIR on the degree of comorbid chronic pain in older adults with T2DM

Commonly used dynamic glucose monitoring indicators were selected to assess blood glucose fluctuations (MAGE, CV) and blood glucose control status (TIR) to analyze their predictive value for the risk of chronic pain severity in older T2DM patients (Fig. 2). ROC curve analysis is used to graph the true positive rate (also known as sensitivity) as the vertical coordinate and the false positive rate (also known as sensitivity, which is equal to 1 - specificity) as the horizontal coordinate, reflecting the relationship between sensitivity and specificity under different threshold conditions, and the truncation value corresponding to the point closest to the upper-left corner of the coordinate system is the optimal truncation value, and the diagnostic efficiency of the diagnostic test

Table 2 Correlation of *spearman*'s analysis of pain scores with general clinical information and blood glucose fluctuation parameters

	$n/\bar{x} \pm s/M(Q_1, Q_3)$	*r*	*P*
Gender (Male/Female)	47/13	0.325	0.011
Age (years)	74.05 ± 8.72	0.473	<0.001
SBP (mmHg)	133.86 ± 20.55	0.208	0.11
DBP (mmHg)	73.02 ± 10.60	-0.066	0.617
Duration of Diabetes (years)	17.13 ± 9.19	0.271	0.038
Pain Duration (months)	14.00 ± 10.76	0.655	<0.001
WBC(*10^9/L)	6.23 ± 2.62	0.163	0.222
RBC(*10^{12}/L)	4.34 ± 0.52	-0.317	0.017
Hb(g/L)	130.43 ± 16.85	-0.421	0.001
Plt(*10^9/L)	180.93 ± 56.87	-0.037	0.782
FIB(mg/dL)	3.10(2.72, 3.78)	0.177	0.191
Cr(μmmol/L)	82.32 ± 38.23	0.055	0.677
eGFR[ml/(min·1.73m^2)]	81.05 ± 23.74	-0.312	0.016
TCH(mmol/L)	3.79 ± 1.08	-0.055	0.687
TG(mmol/L)	1.14(0.93, 1.73)	0.138	0.307
HDL-C(mmol/L)	1.05 ± 0.30	0.075	0.582
LDL-C(mmol/L)	2.23 ± 0.84	-0.113	0.407
HbA1c(%)	8.67 ± 2.00	0.254	0.069
FPG(mmol/L)	9.38 ± 4.33	0.132	0.405
2hPG(mmol/L)	19.48 ± 5.14	0.177	0.269
FC-P(ng/ml)	1.50 ± 0.90	-0.232	0.139
2 h-CP(ng/ml)	3.58 ± 1.93	-0.227	0.154
MAGE(mmol/L)	6.22 ± 1.64	0.516	<0.01
CV(%)	31.09 ± 5.33	0.306	0.018
TIR(%)	0.61 ± 0.16	-0.465	<0.01
MBG(mmol/L)	9.32 ± 1.48	0.414	0.001
SD(mmol/L)	2.91 ± 0.76	0.467	<0.001
MODD(mmol/L)	2.11 ± 0.72	0.364	0.015
Highest Blood Glucose (mmol/L)	18.05 ± 3.22	0.328	0.032
Lowest Blood Glucose (mmol/L)	3.25(2.41, 4.11)	-0.079	0.611

is judged by calculating the area under the ROC curve [7]. It showed the following results: MAGE: The area under the ROC curve (AUC) for predicting pain severity was 0.741 (*95% CI*: 0.630 ~ 0.876), with a cutoff value of 0.626, sensitivity of 53.1%, and specificity of 89.3%. CV: The AUC for predicting pain severity was 0.668 (*95% CI*: 0.530 ~ 0.806), with a cutoff value of 0.620, sensitivity of 40.6%, and specificity of 89.3%. TIR: The AUC for predicting pain severity was 0.763 (*95% CI*: 0.637 ~ 0.890), with a cutoff value of 0.461, sensitivity of 67.9%, and specificity of 84%.

Discussion

Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage by the International Association for the Study of Pain (IASP) [8]. Chronic pain is defined as pain that persists for more than one month. As a common health issue among the older people, pain significantly affects their quality of life. Previous studies have shown that the prevalence of chronic pain among old residents in long-term care facilities ranges from 45 to 80% [9]. Between 2009 and 2021, there will be a dramatic increase in the number of people suffering from pain worldwide. This dramatic increase can be seen in all other population groups, including high- and low-income countries [10], and chronic pain is one of the most common and important diseases of older persons. In terms of pain sites, studies have shown that the most common sites of chronic pain in older people are the lower back and lower limbs, and the most common types are musculoskeletal pain and joint pain [11]. Those pain sites are often involved with common pain-related diseases in the older people, such as osteoarthritis, osteoporosis, peripheral neuropathy, and lower limb arteriosclerosis. In this study, the average pain score of the enrolled subjects was 5.47 ± 1.46, with pain primarily located in the lower back, lower limbs, and knee joints, which is consistent with previous findings. Among the subjects, 50% experienced pain in one site, 28.33% in two sites, and 21.67% in three sites, indicating a significant presence and widespread distribution of chronic pain in older T2DM patients. Given that older T2DM patients are more likely to suffer from chronic physical diseases and severe pain,

Table 3 Comparison of general clinical data and blood glucose fluctuation parameters between the two groups $[n/\bar{x} \pm s/M(Q_1, Q_3)]$

	Mild pain group	Severe pain group	*P*
Gender (Male/Female)	24/4	19/13	0.021
Age (years)	68.93 ± 6.85	78.53 ± 7.70	<0.001
SBP (mmHg)	129.18 ± 15.87	137.94 ± 23.40	0.092
DBP (mmHg)	73.96 ± 9.09	72.19 ± 11.84	0.514
Duration of Diabetes (years)	14.50 ± 8.42	19.52 ± 9.35	0.035
Pain Duration (months)	7.89 ± 6.70	19.24 ± 10.86	<0.001
WBC(*10^9/L)	5.55 ± 1.37	6.79 ± 3.22	0.054
RBC(*10^{12}/L)	4.49 ± 0.52	4.21 ± 0.50	0.051
Hb(g/L)	137.00 ± 14.41	125.10 ± 17.01	0.006
Plt(*10^9/L)	185.35 ± 48.55	177.34 ± 63.37	0.598
FIB(mg/dL)	3.93(2.61, 3.54)	3.21(2.86, 4.04)	0.164
Cr(μmmol/L)	73.12 ± 35.91	90/08 ± 38.96	0.090
eGFR[ml/(min·1.73m^2)]	92.70 ± 20.50	71.21 ± 21.20	<0.001
TCH(mmol/L)	3.81 ± 0.81	3.78 ± 1.28	0.897
TG(mmol/L)	1.12(0.86, 1.41)	1.30(1.02, 1.80)	0.262
HDL-C(mmol/L)	1.01 ± 0.17	1.08 ± 0.37	0.324
LDL-C(mmol/L)	2.34 ± 0.77	2.14 ± 0.89	0.386
HbA1c(%)	8.30 ± 2.23	8.99 ± 1.75	0.219
FPG(mmol/L)	8.97 ± 4.44	9.89 ± 4.26	0.500
2hPG(mmol/L)	18.53 ± 4.96	20.71 ± 5.26	0.181
FC-P(ng/ml)	1.57 ± 0.88	1.42 ± 0.94	0.587
2 h-CP(ng/ml)	3.69 ± 1.67	3.44 ± 2.26	0.695
MAGE(mmol/L)	5.574 ± 1.300	7.01 ± 1.64	<0.001
CV(%)	29.446 ± 4.980	32.53 ± 5.28	0.024
TIR(%)	0.684 ± 0.162	0.55 ± 0.14	<0.001
MBG(mmol/L)	8.676 ± 1.382	9.99 ± 1.36	0.001
SD(mmol/L)	2.556 ± 0.607	3.22 ± 0.75	<0.001
MODD(mmol/L)	1.912 ± 0.602	2.37 ± 0.79	0.034
Highest Blood Glucose (mmol/L)	17.172 ± 2.783	19.15 ± 3.47	0.045
Lowest Blood Glucose (mmol/L)	3.40(2.55, 4.05)	3.20(2.40, 4.11)	0.713

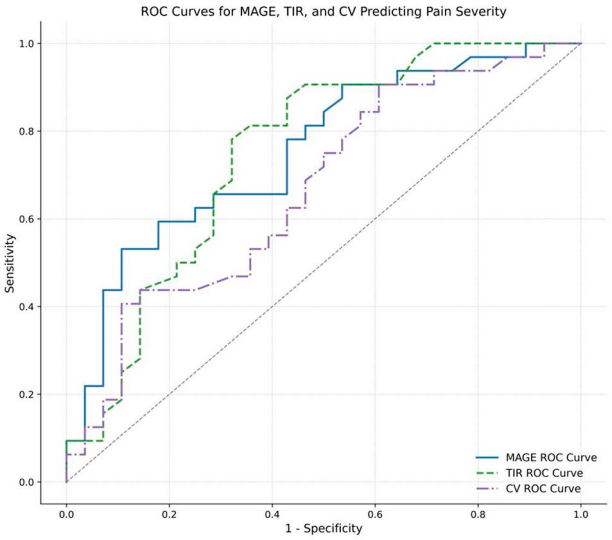

Fig. 2 ROC curves to assess the risk predictive value of MAGE, CV, and TIR for chronic pain severity

identifying risk factors for chronic pain in this population could offer new perspectives and directions for their treatment.

In this study, s*pearman* correlation analysis showed that gender, age, disease duration, pain duration, RBC, Hb, eGFR, MAGE, CV, TIR, MBG, SD, MODD, and highest blood glucose values were significantly correlated with pain scores, which was similar to the statistically significant results of the comparison between the two groups and the results of the binary logistic regression analysis, suggesting that that the overall fluctuation of blood glucose had a more pronounced effect on pain, with the severe pain group having greater fluctuations in blood glucose than the mild pain group.It is worth mentioning that this study also found a correlation between pain scores and RBC, Hb, and eGFR. By searching for

Table 4 Binary *logistic* regression analysis of factors influencing the degree of comorbid chronicity in older T2DM patients

	β	SE	Wald χ2	OR	95%CI	*P*
Gender	1.412	0.649	4.735	4.105	1.151 ~ 14.648	0.03
Age (years)	0.176	0.048	13.49	1.192	1.085 ~ 1.309	<0.001
Duration of Diabetes (years)	0.066	0.032	4.139	1.068	1.068 ~ 1.138	0.042
Pain Duration	0.172	0.05	11.981	1.187	1.077 ~ 1.308	< 0.001
RBC	-1.09	0.576	3.584	0.336	0.109 ~ 1.039	0.058
Hb	-0.05	0.02	6.369	0.951	0.915 ~ 0.989	0.012
eGFR	-0.049	0.016	9.942	0.924	0.924 ~ 0.982	0.002
MAGE	0.662	0.214	9.566	1.939	1.274 ~ 2.95	0.002
CV	0.123	0.057	4.651	1.131	1.011 ~ 1.264	0.031
TIR	-6.275	2.078	9.122	0.002	0 ~ 0.11	0.003
MBG	0.669	0.231	8.404	1.952	1.242 ~ 3.068	0.004
SD	1.511	0.49	9.505	4.531	1.734 ~ 11.839	0.002
MODD	0.962	0.475	4.094	2.617	1.031 ~ 6.643	0.043
Highest Blood Glucose	0.216	0.114	3.597	1.241	0.993 ~ 1.552	0.058

findings, Huang CT found that erythropoietin (EPO) reduces neuropathic pain by decreasing glutamate release from afferent nerves, inhibiting microglia Mitogen-activated protein kinase (MAPK) activation and proinflammatory cytokine production [12]. Brandow AM found that between 30% and 40% of patients with sickle cell anaemia had combined chronic pain. Patients with sickle cell anaemia have comorbid chronic pain [13]. In addition, most older patients with T2DM have concomitant renal insufficiency and diabetic nephropathy. Factors such as iron metabolism disorders, impaired synthesis of active vitamin D, and renal osteodystrophy associated with renal function impairment may be related to the occurrence of pain. This provides new directions for future research on chronic pain. Chang KC [14] found that greater glycaemic fluctuations were associated with an increased risk of PDPN in patients with T2DM during the 6-year follow-up period, which supports the role of glycaemic fluctuations in the development of painful PDPN. However, no literature was retrieved on glycaemic fluctuations and chronic pain, suggesting that our study provides unique insights into glycaemic and pain management in older patients with T2DM combined with chronic pain.

The mechanisms of chronic pain in older patients with T2DM are complicated and not yet fully understood. It is widely accepted that chronic pain in the older people may be related to hyperglycemia, inflammatory stress responses caused by lipid metabolism disorders, ion channel alterations, central and peripheral sensitization, and microglial activation [15]. Additionally, it is also associated with age-related conditions such as osteoarthritis, osteoporosis, and fasciitis due to aging and degeneration. In diabetic patients, glucose metabolism disorders include not only chronic persistent hyperglycemia, such as elevated FPG, postprandial glucose, and HbA1c, but also the recently highlighted blood glucose fluctuations. These fluctuations may play an important role in the pathogenesis of chronic pain in older T2DM patients.

It has been reported that there is a significant correlation between fluctuations of blood glucose levels and the onset of pain. Fluctuations in blood glucose appear to inflict more severe damage to neuronal cells than sustained hyperglycemia, with particular vulnerability observed in unmyelinated and thinly myelinated neurons, which are prone to direct damage. Under stable high glucose conditions, cells exhibit a certain degree of adaptability, maintaining relatively stable morphological and functional integrity. However, glucose fluctuations compromise this adaptability, leading to the generation of pain impulse signals [6], which may correlate with the incidence of pain. Sudden increases in blood glucose also promote the production of nitric oxide in the body, which facilitates the transmission of nociceptive neurotransmitters and the expression of information in both peripheral and central nervous systems, thus inducing pain [16, 17]. Conversely, sudden drops in blood glucose and recurrent hypoglycemia damage microvascular neurons, leading to peripheral neurodegeneration and neuronal apoptosis. This results in diffuse damage to unmyelinated and lightly myelinated nerve fibers, manifesting as a loss of epidermal nerve fibers and consequently, the perception of pain [18]. These observations suggest potential underlying mechanisms linking glucose variability with pain manifestation.

Currently, CGMS are an essential tool for self-monitoring blood glucose in diabetes patients, providing more comprehensive data on glucose fluctuations than HbA1c. In this study, binary *logistic* regression analysis indicated that MAGE, TIR, CV, SD, MBG, and MODD are factors influencing the severity of chronic pain in older T2DM patients. MAGE is the mean of the magnitude of blood glucose fluctuations after removing all fluctuations that do not exceed a certain threshold magnitude (statistically generally 1 standard deviation); MAGE < 3.9 mmol/L is considered the normal reference value [19]. Among these parameters, MAGE is considered as the "gold standard" for reflecting blood glucose fluctuations due to its advantages from the design principle to its relationship with oxidative stress and chronic diabetic complications, and it has become a key indicator in researching diabetes-related complications. Xu F investigated the relationship between glycaemic fluctuations and DPN in T2DM patients with well-controlled HbA1c (HbA1c < 7.0%) and suggested that glycaemic variability assessed by MAGE was the most significant independent risk factor for DPN [20]. CV is an objective indicator of blood glucose stability, calculated from the mean and standard deviation of blood glucose during a certain period of hospitalisation. It can monitor changes in serum glucose, assess the degree of blood glucose disorders, and more accurately reflect changes in blood glucose by eliminating the effects of the magnitude of hyperglycemia and hypoglycemia changes during hospitalisation compared with the traditional calculation of blood glucose data at a single point in time [19]. It mainly reflects the degree of blood glucose dispersion. A higher CV indicates greater blood glucose fluctuations. The "International Consensus on TIR" recommends CV as a primary indicator of blood glucose variability, with a CV of 36% being the cutoff point between stable and unstable blood glucose. Jia Y highlights CV as a potential indicator of DPN progression and advocates its inclusion in diabetes management strategies to reduce the risk of DPN [18]. TIR refers to the proportion of blood glucose within the target range (usually defined as 3.9–10.0 mmol/L), which is a new blood glucose management indicator recommended by

the American Diabetes Association and the Chinese Diabetes Society, suggests that higher TIR values indicating longer period of time to reach the overall blood glucose target. TIR has been found to serve as a reference indicator of short-term glycaemic control, strongly reflecting clinical glycaemic regulation and predicting the risk of microvascular complications of diabetes (such as retinopathy, nephropathy, and neuropathy) [21]. To investigate the predictive value of blood glucose fluctuations for the severity of chronic pain in older T2DM patients, MAGE, CV, and TIR which are widely recognised indicators, were selected. ROC curve analysis showed that MAGE, CV, and TIR are applicable and accurate predictors of the severity of chronic pain in older T2DM patients.

There are only a few studies on the correlation between chronic pain and blood glucose fluctuations in diabetes. Most previous research on blood glucose fluctuations and pain in diabetes focuses on diabetic peripheral neuropathy. Our study showed that chronic pain in older T2DM patients is multifactorial and multi-etiological, which poses a significant challenge in seeking the best treatment for older diabetic patients with pain.

For the treatment of T2DM patients, especially the older T2DM patients with chronic pain, we should not only control the blood glucose standard, but also maintain the blood glucose stability and reduce the fluctuation of blood glucose, especially in the course of the disease to do the early intervention, and control the blood glucose fluctuation while controlling the blood glucose standard, in order to control the complications of T2DM in the older people, to reduce the occurrence of the development of pain, and to improve the quality of life.This can be achieved by increasing patients blood glucose monitoring and using longer half-life glucose-lowering medications with stabilising properties. CGM is a commonly used 24 h blood glucose monitoring system in clinical practice, and the data derived from it can reflect patients blood glucose fluctuations and overall glycemic control, and detect hidden hyperglycemia and hypoglycemia that are difficult to detect with traditional blood glucose monitoring methods, including the dawn phenomenon, Somogyi phenomenon, etc. In addition, some oral hypoglycaemic agents can also reduce blood glucose fluctuations, such as DPP-4 inhibitors can improve β-cell function and thus reduce glucose fluctuations, and SGLT2 inhibitors can reduce blood glucose fluctuations in patients with diabetic nephropathy [22]. In addition, regularity of life, regularity of food, reasonable combination of meals, and regular exercise time can significantly improve the fluctuation of blood glucose. Therefore, for the older patients with T2DM combined with chronic pain, it is necessary to carry out relevant diabetes education, and on the basis of regular diet, according to the patient's glycaemic characteristics, formulate a comprehensive, systematic and individualised glucose-lowering programme to effectively maintain glycaemic stability, which is an important role in slowing down the progression of pain and other complications.

Conclusion

Older T2DM patients with chronic pain exhibit severe pain and multiple pain sites. Among the CGMS monitoring indicators, MAGE, CV, TIR, SD, MBG, and MODD are factors influencing the severity of chronic pain in these patients. MAGE, CV, and TIR can serve as potential indicators for predicting the severity of chronic pain in older T2DM patients. Therefore, in the treatment of older T2DM patients with chronic pain, it is crucial to not only achieve target blood glucose levels but also to focus on controlling blood glucose fluctuations to achieve better clinical outcomes.

Abbreviations

T2DM	Type 2 diabetes mellitus
CGMS	Continuous Glucose Monitoring System
MAGE	Mean Amplitude of Glycemic Excursions
CV	Coefficient of Variation
TIR	Time in Range
ROC	Receiver Operating Characteristic
MBG	Nean blood glucose
SD	Standard deviation
MODD	Mean of Daily Differences
RBC	Red blood cell count
Hb	Hemoglobin
eGFR	Estimated glomerular filtration rate
HbA1c	Glycosylated hemoglobin
PDPN	Painful diabetic peripheral neuropathy
NRS	Numerical Rating Scale
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
TG	Triglyceride
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
FPG	Fasting plasma glucose
2hPG	2-hour postprandial plasma glucose
FC-P	Fasting C-peptide
2hC-P	2-hour postprandial C-peptide
Cr	Creatinine
CGM	Continuous glucose monitoring
AUC	Area under the ROC curve
IASP	International Association for the Study of Pain
EPO	Erythropoietin
MAPK	Mitgen-activated protein kinase)
DPN	Diabetic peripheral neuropathy

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Author contributions

YS and QH contributed to conceptualization, funding acquisition, data collection, data curation, formal analysis, writing the original draft, and review and editing of the paper. MC, YY, CH and YCcontributed to data collection, data curation. SW, XH and XY contributed to conceptualization, supervision, and review and editing of the paper. XS, TT, XZ and LL contributed to conceptualization, supervision, and review and editing of the paper. All authors have read and approved the manuscript.

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Data availability
The datasets generated and analyses performed during the current study are not publicly available due to the consent requirement of participants, all data generated or analysed during this study are included in this published Article.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University, and all study subjects (or their guardians) have given their informed consent.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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