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The Association Between 8- OHdG Levels and Diabetic Neuropathy Patients from Sensory Functioning and Neurological Symptoms

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ABSTRACT

Objective: This clinical study aims to evaluate the association between the levels of urine 8-hydroxy-2-deoxyguanosine (8-OHdG) and neuropathic symptoms and nervous sensory signs in patients with diabetic peripheral neuropathy (DPN).

Methods: A total of 81 individuals with DPN participated in this clinical investigation. According to patients' symptoms, the neuropathy symptom scores (NSS) and their neuropathy deficit scores (NDS) category, four symptom clusters were allocated: no symptoms, mild symptoms, moderate symptoms, and severe symptoms. The four neurological function categories were defined as no signs, mild signs, moderate signs and severe signs. We used an enzyme-linked immunosorbent assay kit to measure the levels of urine 8-OHdG. All statistical tests were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM-SPSS, Chicago, IL, USA).

Results: Based on the results of the ordinary logistic regression, it can be concluded that neuropathic sensory function deficits were not related to neuropathic symptoms in patients with DPN; age was associated with neuropathic function deficits in DPN patients; and the level of urine 8-OHdG has no correlation with neuropathic symptoms in patients with DPN.

Conclusion: In this clinical study, it can be deduced that the level of urinary 8-OHdG has no association with the development of neuropathic symptoms in patients with DPN.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common and serious long-term complications of diabetes mellitus (DM) and is estimated to occur in more than half of type 1 and type 2 diabetes mellitus patients Vinik et al. (2003), Dyck et al. (1999). As of 2010, there were approximately 132 million people with DN worldwide Theo et al. (2012). In 2030, 366 million (4.4% of the world's population) people suffered from DM Wild et al. (2004). DPN is characterized by the progressive loss of peripheral nerve axons, which may be associated with neuropathic pain, foot ulceration and gangrene, and in severe cases, lower extremity amputation Vinik et al. (2000). Nontraumatic lower extremity amputations in DM typically lead to an impaired quality of life and add to the financial burden of healthcare provision for patients with this condition Ebata-Kogure et al. (2017). DPN can be classified according to a combination of pathological, phenomenological, neurophysiological and aetiological parameters Martyn et al. (1997). Symptoms of DPN can be divided into sensory and motor manifestations. The most common are an abnormal or loss of sensation in the limb, e.g., tingling Valensi et al. (2005), Yuen et al. (2002); pain and burning sensations Jensen et al. (2006), Weintraub et Al. (2003); numbness, weakness of the limbs; and hyperalgesia and allodynia in the toes and feet Rauck et al. (2013). Changes in sensation and nervous system reflexes, which initially arise in the toes and then extend superiorly, are recognized as the classical "glove and stocking" distribution of numbness, sensory loss, dysesthesia and neuropathic pain at night. Diabetic neuropathic pain can feel like a burning, pricking, achy or dull sensation. Loss of proprioception occurs in the early stages of diabetic neuropathy. Consequently, patients have a high risk of developing ulcers and infections on the feet and legs, which can lead to gangrene and even amputation of the lower extremity. Neuropathic pain is prevalent in DPN patients and importantly, causes a detrimental effect on the DPN patient's physical and mental health Zis et al. (2017), utimately leading to a poor quality of life. Amputations in DPN not only have a devastating influence on quality of life but also lead to an increase in mortality Icks et al. (2011). Nerve conduction studies (NCS) and questionnaires, such as neuropathy symptom scores (NSS) and neuropathy deficit scores (NDS), are among the most common procedures used for diagnosing and assessing DPN in the clinical literature Rauck et al. (2013). Most clinical studies rely on the presence of

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patient-reported symptoms and physical signs for the diagnosis of DPN. DPN is most likely if the patient experiences neuropathic pain in the legs or feet as described above, so it is important for a physician to estimate the patient's degree of discomfort when performing a clinical assessment. NSS and NDS are typically utilised as diagnostic tools for determining the presence of DPN in DM patients, depending on their symptoms and physical signs. This is important for the prevention of foot ulceration and lower extremity amputation in this patient cohort. The disease processes underlying the onset and progression of DPN are still not clearly defined Yuen et al. (2002) Gorst et al. (2015) Jun et al. (2015). Although there now exists a long history of research that demonstrates the pathophysiology of DPN, it has recently become widely accepted that the onset and development of DPN is not only a result of hyperglycaemia but also associated with several other vascular, metabolic and genetic factors Allen et al. (1997). Among these, hyperglycaemia-induced oxidative stress is considered to be a vital driver of diabetic complications and organ dysfunction in patients with DPN Giacco et al. (2010). 8-hydroxy-2-deoxyguanosine (8-OHdG) as a biomarker for DNA oxidative damage is one of the most widely studied oxidized metabolites Kasai et al. (1997), Beckman et al. (1997). The interaction of the hydroxyl radical, the most important oxygen-free radical, with the nucleobases of the DNA strand, such as guanine, leads to the formation of 8-OHdG Valavanidis et al. (2009). It is stable for measuring urinary 8-OHdG Barregard et al. (2013) and its excretion is likely to reflect the oxidative DNA damage Zanolin et al. (2015).

Thus, a clinical study was performed to assess the association between the levels of 8-OHdG and DPN symptoms and sensory nerve signs. It additionally provides special treatment for the early stages of DM to prevent the occurrence of diabetic complications and organ dysfunction. It would therefore be more effective for approaches to DPN to focus on decelerating DPN development through better glycaemic control and pain management, according to neuropathy pain treatment recommendations Dermanovic Dobrota et al. (2014), Kim et al. (2014). This would assist DPN patients who are receiving appropriate treatment and care in accordance with recommendations from the clinical literature.

METHODS

A cross-sectional clinical study was undertaken to evaluate the level of the 8-OHdG associated with sensory functioning and neurological symptoms in patients with DPN. Eighty-one individuals with DPN, with an age range of 18 to 75 years, were recruited to participate in the study from the Geriatrics Department of Lanzhou University Second Hospital. Inclusion criteria for the study were as follows: (1) All patients were diagnosed according to the guidelines of the American Diabetes Association (ADA) in 2011.American Diabetes Association. et al. (2011); (2) patients were asked to provide details of symptoms and signs at the time of diagnosis; (3) laboratory results of all patients were evaluated; and (4) details of participants' family histories were obtained to exclude maturity-onset diabetes of the young. Exclusion criteria included liver or kidney failure, malignancy, chronic alcohol abuse, spinal canal stenosis or prolapsed discs, systemic or neurological diseases or medication that could potentially induce polyneuropathy, and any other causes of polyneuropathy. Study procedures were performed in accordance with the guidelines of the Declaration of Helsinki, 2013. Each patient agreed to participate and provided written informed consent. The study procedures were approved by the ethics committee of Lanzhou University Second Hospital (number 2022A-571).

The NSS and NDS were based on the symptoms of patients with DPN, which included pain, numbness, burning, tingling, cramps and weakness. The peripheral nervous system of each patient was assessed using the NSS and NDS; these are frequently utilised techniques for the diagnosis and appraisal of DPN in clinical practice Young et al. (1993), Ziegler et al. (2014). The NSS category was defined in accordance with symptom occurrence: no symptoms, 0-2 points; mild symptoms, 3-4 points; moderate symptoms, 5-6 points, and severe symptoms, 7-10 points. Symptom quality and pathological findings were categorized to provide the NDS, i.e. no deficit, 0-2 points; mild deficit, 3-5 points; moderate deficit, 6-8 points, and severe deficit, 9-10 points. The details of the NSS and NDS categories are shown in Figure 1. Ziegler et al. (2005). According to patients' symptoms, NSS and their NDS category, four symptom clusters were allocated: no symptoms, mild symptoms, moderatesymptoms, and severe symptoms. The four neurological nerve function categories were defined as no signs, mild signs, moderate signs and severe signs, a classification based on the neuropathic signs category.

The medical histories of the study participants were requested and reviewed, after which experienced physicians performed routine physical examinations. The medical history obtained included basic information (age, gender, weight, height), duration of diabetes, diabetic mellitus in the family, previous medical history (hypertension, cardiovascular diseases, malignancy and spinal diseases), smoking and alcohol consumption behaviours, diabetic complications (diabetic retinopathy, nephropathy), drug history (anti-hypertensive agents and statins) and current hypoglycaemic treatments (lifestyle and diet interventions, insulin injections, insulin secretagogues, metformin or thiazolidinediones). Somatometric parameters included weight, size, body mass index, waist-hip ratio, systolic blood pressure (SBP) and diastolic blood pressure (DBP), among others. Blood samples were obtained from each participant in the morning and immediately sent to the Central Laboratory

of the Lanzhou University Second Hospital to determine the participants' biochemical indicators. Serum glucose (oxidase method), triglycerides (colorimetry), total cholesterol (cholesterol oxidase technique), low-density lipoprotein (LDL) cholesterol (selective melt method), high-density lipoprotein (HDL) cholesterol (chemistry modify enzyme method) and uric acid (uricase-peroxidase assay) were analysed. The glycosylated hemoglobin (HbA1c) level was calculated using ionic exchange HPLC in the D-10 hemoglobin analysis system (Bio-Rad). Urinary albumin (mg) was measured using immunoturbidimetry (Image 800, Beckman Coulter). Creatinine (g) titres and the urinary albumin: creatinine ratio (UACR) was also evaluated. We used an enzyme-linked immunosorbent assay kit (Human 8-hydroxy-2-deoxyguanosine; Cat. # m1057433V, Shanghai Enzyme Union, China) according to the manufacturer's instructions. The collected urine samples were stored at -80°C until just before measurement. First, the urine sample, enzyme immunoassay (EIA) buffer, standards, and 8-OHdG-AChE tracer were added to all the wells except for the blank. Then, we added 100 µL of 8-OHdG antibody labelled with HRP and incubated the plate for 60 min at 37°C. The plate was washed with 350 µL washing fluid for 1 min five times, and 50 µL termination fluid was added to each well. The optical density was read at 450 nm, and the levels of 8-OHdG were reported in nanograms per millilitre.

Continuous parameters were summarized as the mean ± standard error (SE). Categorical parameters were expressed as absolute and relative frequencies. Variance that was equal or uniform was tested by the homogeneity test of variance. The p-value represents the comparison of patients with 8-OHdG in DPN patients. Continuous parameters were analysed using one-way analysis of variance (ANOVA) for normally distributed values and the Kruskal-Wallis test for non-normally distributed values. The Pearson chi-square test was used when 0 cells had an expected count of less than 5. Where this criterion was not fulfilled, Fisher's exact test for categorical variables was utilised. Ordinal logistic regression models were deployed to quantify the association between 8-OHdG and DPN sensory symptoms and signs in study participants.

Multivariate logistic regression was used if the p-value of the parallel line test was < 0.05 following ordinal logistic regression. All statistical tests were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM-SPSS, Chicago, IL, USA). A p-value of <0.05 was assumed to be significant.

RESULTS

Baseline clinical characteristics of patients with type 2 diabetes

Eighty-one patients with DPN were recruited to take part

Figure 1: NSS and NDS.

Abbreviations: NSS, neuropathy symptom score; NDS, neuropathy deficit score.

in the study. Table 1 compares the participants' clinical characteristics according to the neuropathic symptoms and NSS and the NDS category in patients with DPN. The 11 individuals with no symptoms among the DPN patients were aged 60.00±3.95 years; the 38 subjects with mild symptoms among the DPN patients were aged 58.39±1.68 years; the moderate symptoms among the DPN patients were 25 individuals who were aged 60.44±2.18 years; and there were 10 subjects with severe symptoms among the DPN patients who were aged 60.00±2.87 years. Regarding the most important DNA damage indicators, there were no siginifcant differences in 8-OHdG in the DPN patients according to the sensory symptom classification Table 1 and Figure 2

Figure 2: There was no correlation between the 8-ohdG level and DPN symptoms classify.

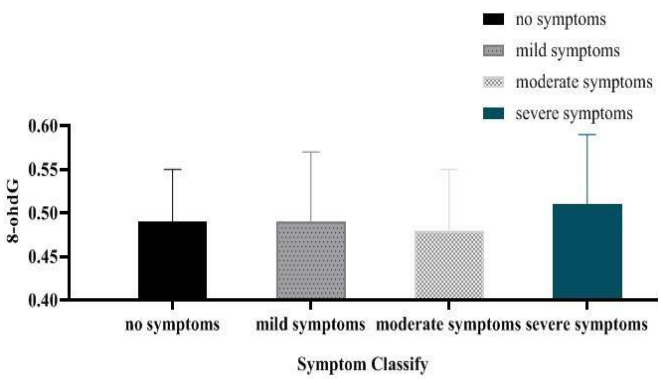


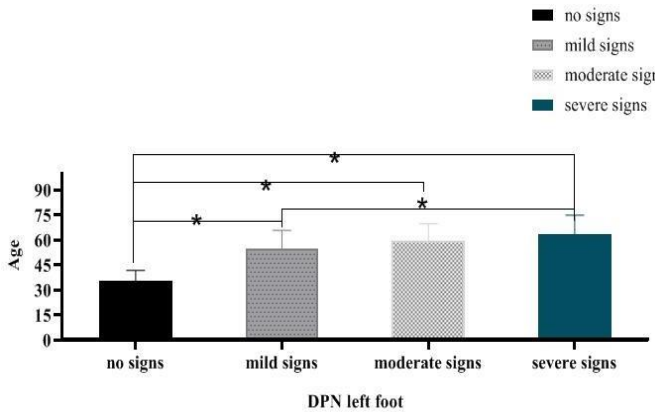
Table 1: Symptom classify and the clinical parameters.

	No (n=11)	Mild (n=38)	Moderate(n=25)	Severe (n=7)	P
Age (year)	60.00±3.95	58.39±1.68	60.44±2.18	60.00±2.87	0.889
Diabetes (year)	9.95±2.71	8.98±1.09	10.63±1.74	9.86±1.98	0.862
Hypertension (year)	9.20±5.93	1.70±0.62	5.42±1.67	6.14±4.10	0.085
Weight (kg)	71.33±2.73	70.00±2.80	68.93±2.88	66.67±5.04	0.917
Hemoglobin (g/l)	148.80±8.21	148.16±3.80	151.72±4.28	153.14±5.79	0.906
FBG (mmol/l)	10.53±1.00	9.94±0.73	9.41±0.67	9.33±1.15	0.864
HbA1C (%)	9.61±0.77	8.54±0.38	9.21±0.39	9.09±0.83	0.471
Insulin (mU/dL)	13.78±5.61	13.13±2.01	10.35±1.49	10.78±2.31	0.760
Urea (mmol/l)	7.09±0.74	6.11±0.25	7.20±0.49	5.60±0.53	0.080
Creatinine (umol/l)	70.55±9.88	62.17±2.15	75.60±7.01	59.41±4.23	0.151
Uric Acid (umol/l)	333.90±32.88	311.27±11.15	341.80±23.06	312.00±24.80	0.580
Albumin (g/l)	41.96±0.94	41.39±1.13	42.02±0.82	43.36±1.33	0.848
Cholesterol (mmol/l)	3.81±0.36	4.21±0.21	4.43±0.20	4.57±0.40	0.458
Triglycerides (mmol/l)	2.37±0.61	1.65±0.20	1.55±0.15	1.55±0.21	0.295
HDL (mmol/l)	0.99±0.06	1.15±0.03	1.12±0.48	1.27±0.09	0.086
LDL (mmol/l)	2.36±0.22	2.68±0.16	2.88±0.15	3.00±0.30	0.330
UMALB (mg/l)	101.57±37.62	60.11±14.40	85.00±19.92	55.71±41.09	0.552
24h UTP (g/24h)	0.56±0.18	0.33±0.06	0.96±0.61	0.49±0.29	0.587
8-OhdG (ng/ml)	0.48±0.01	0.49±0.02	0.48±0.02	0.51±0.02	0.803

Data are mean ± SE. Abbreviations: FBG, Fasting blood glucose; HbA1C, glycated hemoglobin; HDL, high density lipoprotein, LDL, low density lipoprotein; UMALB, Urine microalbumin; 24h UTP, 24-hour urine pritein;8-OhdG, 8-hydroxy-2-deoxyguanosine.

The four neurological nerve function categories were defined as no signs, mild signs, moderate signs and severe signs, a classification based on the neuropathic signs category. There were 2 subjects with no signs, aged 35.50±4.50 years; 13 individuals with mild signs aged 54.00±2.76 years; 34 with moderate signs, aged 57.41±1.38 years; and 32 subjects with mild symptoms among the patients with DPN aged 65.91±1.71 years. Age was significantly different between the four categories of DPN patients in relation to the assessment of nerve function on the left foot Table 2 and Figure 3.

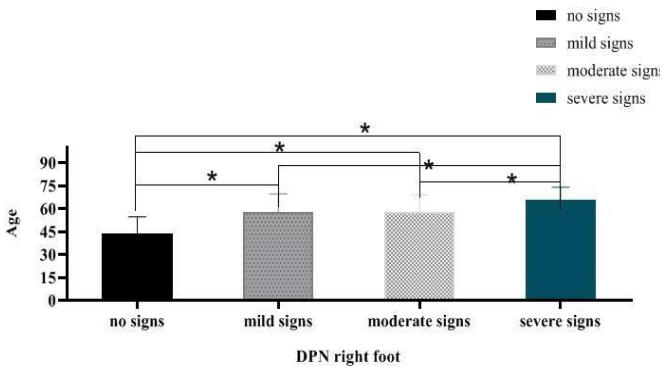
Figure 3: The age has a siginifcant differences between the four categories of DPN neuropathic sensory function of left foot.



Abbreviations: DPN, diabetic peripheral neuropathy.

On the right foot, the 5 individuals with no symptoms among the DPN patients were aged 44.00±4.80 years; the 14 subjects with mild symptoms among the DPN patients were aged 54.86±2.52 years; the moderate symptoms among the DPN patients were 31 individuals aged 57.55±1.47 years; and there were 31 subjects with severe symptoms among the DPN patients aged 66.52±1.63 years. Patients with lower ages were more likely to have no signs among the four categories of DPN patients (Table 3 and Figure 4).

Figure 4: The age was related to the four categories of DPN neuropathic sensory function on right foot.



Abbreviations: diabetic peripheral neuropathy.

Table 2: DPN neuropathic sensory function of left foot and the clinical paremeters.

	No (n=2)	Mild (n=13)	Moderate (n=34)	Severe (n=32)	P
Age (year)	35.50±4.50	54.00±2.76	57.41±1.38	65.91±1.71	0.001
Diabetes (year)	3.00±1.005	10.54±2.75	7.34±0.96	12.24±1.26	0.037
Hypertension (year)	0.00±0.00	8.24±3.22	2.10±0.71	5.42±2.05	0.157
Weight (kg)	70.18±1.45	70.06±2.36	70.92±4.25	68.02±2.12	0.746
Hemoglobin (g/l)	167.50±6.50	153.00±4.21	156.15±3.78	140.25±3.93	0.014
FBG (mmol/l)	5.62±0.15	11.15±1.55	9.18±0.53	10.19±0.64	0.155
HbA1C (%)	9.40±2.20	8.86±0.62	8.54±0.40	9.35±0.36	0.501
Insulin (mU/dL)	4.24±0.52	15.28±4.79	9.04±0.97	14.46±2.16	0.12
Urea (mmol/l)	6.39±0.49	6.08±0.47	5.99±0.23	7.31±0.44	0.043
Creatinine (umol/l)	55.80±9.20	65.01±4.24	63.39±1.95	73.53±6.35	0.339
Uric Acid (umol/l)	331.00±68.00	363.15±34.73	316.36±12.36	313.91±15.57	0.37
Albumin (g/l)	44.55±3.45	42.86±0.96	42.15±1.22	40.87±0.70	0.566
Cholesterol (mmol/l)	4.30±0.47	4.29±0.30	4.18±0.20	4.27±0.22	0.984
Triglycerides (mmol/l)	2.77±1.49	1.62±0.30	1.52±0.13	1.83±0.26	0.421
HDL (mmol/l)	1.04±0.13	1.13±0.05	1.11±0.04	1.16±0.05	0.813
LDL (mmol/l)	2.84±0.42	2.77±0.21	2.65±0.16	2.75±0.16	0.952
UMALB (mg/l)	6.55±1.55	96.75±35.26	60.31±14.07	80.45±18.54	0.495
24h UTP (g/24h)	0.13±0.01	0.57±0.19	0.33±0.05	0.84±0.48	0.666
8-OhdG (ng/ml)	0.48±0.02	0.51±0.02	0.47±0.01	0.49±0.01	0.3

Data are mean ± SE. Abbreviations: FBG, Fasting blood glucose; HbA1C, glycated hemoglobin; HDL, high density lipoprotein, LDL, low density lipoprotein; UMALB, Urine microalbumin; 24h UTP, 24-hour urine pritein; 8-OhdG, 8-hydroxy-2-deoxyguanosine.

Table 3: DPN neuropathic sensory function of right foot and the clinical parameter.

	No (n=5)	Mild (n=14)	Moderate (n=31)	Severe (n=31)	P
Age (year)	44.00±4.80	54.86±2.52	57.55±1.47	66.52±1.63	0
Diabetes (year)	6.67±2.03	5.41±0.96	9.66±1.26	12.22±1.48	0.026
Hypertension (year)	2.20±2.20	1.21±0.55	5.54±1.56	4.92±2.12	0.479
Weight (kg)	65.64±2.01	73.86±6.89	67.87±2.07	68.75±2.10	0.466
Hemoglobin (g/l)	164.60±2.46	155.43±5.98	152.16±4.17	142.10±3.72	0.062
FBG (mmol/l)	8.06±1.34	9.43±0.90	9.74±0.80	10.33±0.64	0.633
HbA1C (%)	9.50±0.94	8.45±0.67	8.54±0.38	9.43±0.38	0.303
Insulin (mU/dL)	8.30±4.07	7.88±0.89	13.48±2.37	13.26±2.13	0.366
Urea (mmol/l)	5.92±0.53	6.08±0.41	6.09±0.37	7.28±0.37	0.065
Creatinine (umol/l)	59.26±5.82	61.79±2.70	66.91±5.46	71.92±4.42	0.521
Uric Acid (umol/l)	357.20±45.34	310.71±16.68	319.16±18.38	327.55±15.37	0.774
Albumin (g/l)	45.64±1.19	42.51±0.60	41.07±1.41	41.62±0.60	0.353
Cholesterol (mmol/l)	4.55±0.28	4.50±0.35	4.10±0.20	4.21±0.22	0.677
Triglycerides (mmol/l)	2.23±0.52	1.28±0.11	1.91±0.25	1.56±0.21	0.247
HDL (mmol/l)	1.08±0.48	1.15±0.06	1.10±0.04	1.16±0.04	0.638
LDL (mmol/l)	3.01±0.24	2.93±0.28	2.56±0.14	2.71±0.16	0.514
UMALB (mg/l)	8.56±1.77	32.21±8.96	96.90±19.68	77.85±19.13	0.076
24h UTP (g/24h)	0.13±0.01	0.30±0.06	0.92±0.47	0.39±0.10	0.512
8-OhdG (ng/ml)	0.48±0.02	0.50±0.01	0.47±0.01	0.50±0.01	0.23

Data are mean ± SE. Abbreviations: FBG, Fasting blood glucose; HbA1C, glycated hemoglobin; HDL, high density lipoprotein, LDL, low density lipoprotein; UMALB, Urine microalbumin; 24h UTP, 24-hour urine pritein;8-OhdG, 8-hydroxy-2-deoxyguanosine.

Risk factors for diabetic peripheral neuropathy with respect to neuropathic sensory function and neurological symptoms

In the ordinary logistic regression analysis, the p-value of the parallel line of the test was 1.000 for the clinical parameters in neuropathic symptoms in patients with DPN. The ordinary logistic regression results showed that 8-OHdG levels (odds ratio (OR), 44.12; 95% confidence intervals (CI), (-4.760, 12.333); P=0.385) and HDL (OR, 45.51; 95% CI, (1.090, 6.545); P=0.006) were no associated with the nerve function symptoms in patients with DPN (Table 4). However, since the 95% CI was close to 1.00, it was assumed that the high HDL had no association with neuropathic sensory symptoms in patients with DPN.

In relation to the nerve function signs on the left foot in subjects with DPN, the p-value of the parallel line of the test was 0.128. The duration of diabetes mellitus, age, Hb and UREA were included in this ordinary logistic regression analysis. The results revealed that older patients with DPN were more likely to develop severe neuropathic sensory function (OR, 1.11; 95% CI (0.049, 0.167); P=0.000) (Table 5). The p-value of the parallel line of the test was 0.115 in the ordinary logistic regression analysis for clinical parameters in neuropathic nerve function on the right foot in patients with DPN. The clinical variables included were age, the time of diabetes mellitus, urea, Hb and UMALB.

The ordinary logistic regression analysis showed that high age (OR, 1.12; 95% CI (0.054, 0.173); P=0.000) was linked with an improvement in neuropathic function of the right foot in patients with DPN (Table 6).

Table 4: Ordinary logistic regression analysis of parameters associated with symptoms classify in DPN patients.

	Exp(B)	95%CI	P
Hypertension (year)	1.03	(-0.026, 0.078)	0.324
Urea Nitrogen (mmol/l)	1.36	(-0.083, 0.700)	0.122
Creatinine (umol/l)	1.01	(-0.025, 0.047)	0.539
HDL (mmol/l)	45.51	(1.090, 6.545)	0.006
8-OHdG (ng/ml)	44.12	(-4.760, 12.333)	0.385
Glucose (mmol/l)	1.021	(-0.224,0.267)	0.865
2h Glucose (mmol/l)	1.029	(-0.110,0.1687)	0.679
HbA1C (%)	0.904	(-0.443,0.242)	0.564

Abbreviations: 8-OhdG, 8-hydroxy-2-deoxyguanosine; HDL, high density lipoprotein.

Table 5: Ordinary logistic regression analysis of parameters associated with DPN left foot in DPN patients.

	Exp(B)	95%CI	P
Age (year)	1.11	(0.049, 0.167)	0
Diabetes (year)	1.01	(-0.058, 0.081)	0.744
Hemoglobin (g/l)	0.99	(-0.030, 0.018)	0.606
Urea (mmol/l)	1.22	(-0.060, 0.455)	0.132

Table 6: Ordinary logistic regression analysis of parameters associated with DPN right foot in DPN patients.

	Exp(B)	95%CI	P
Age (year)	1.12	(0.054, 0.173)	0
Diabetes (year)	1.05	(-0.024, 0.117)	0.196
Hemoglobin (g/l)	0.99	(-0.028, 0.019)	0.703
Urea (mmol/l)	1.07	(-0.189, 0.325)	0.603
UMALB (mg/l)	1	(-0.001, 0.009)	0.123

Abbreviations: UMALB, Urine microalbumin.

DISCUSSION

The aim of this clinical study was to evaluate the association between the levels of 8-OHdG and the neurological symptoms and signs of patients with DPN. According to the clinical study results, the following conclusions could be drawn: 1) the level of 8-OHdG has no relationship with the development of neuropathic symptoms in patients with DPN; 2) age was associated with the development of neuropathic function deficits in DPN patients; and 3) neuropathic sensory function deficits were not related to neuropathic symptoms in patients with DPN.

From this study, it can be demonstrated that neuropathic sensory function was not linked with neuropathic symptoms in diabetic neuropathy patients. Neuropathic symptoms and signs normally do not serve as the only diagnostic criteria for diagnosing diabetic peripheral neuropathy. Kanji documented the useful and rational effects of a clinical examination in the diagnosis of DPN Kanji et al. (2010). Studies have found that nerve conduction tests and NSS may also seldom correlate with the severity of diabetic peripheral neuropathy King et al. (2008). Moreover, in the early stages of type 2 diabetes mellitus, the symptoms and signs were not very obvious in DPN patients; in particular, there were no neuropathic symptoms or signs, such as neuropathic pain, numbness, tingling, and burning, in patients with sDPN. However, there are already nerve sensory function abnormalities Dyck et al. (2011). in patients with sDPN. Consequently, it is necessary to take essential steps to assess neuropathic symptoms and measure neuropathic physical signs for diagnosing diabetic peripheral neuropathy.

In this clinical study, we identified that the level of 8-OHdG has no association with the development of neuropathic symptoms in patients with DPN, as the clinical parameters of age were associated with neuropathic function deficits. The mechanism of diabetic peripheral neuropathy may be associated with the interaction of metabolic disorders such as hyperglycemia toxicity, the aldose reductase-polyol pathway, production of glycosylation end products, oxidative stress, abnormal lipid metabolism, microvascular injury, neurotrophic factor deficiency and abnormal release of cytokines and autoimmune factors. Previous studies have also elaborated that age is correlated with an increase in the prevalence of DPN Moulin et al. (2014). Our results showed that according to the sensory symptom classification, the 8-OHdG level has no relationship with the neuropathic symptoms of DPN. 8 Hydroxy-2′-deoxyguanosine as the product of tissue cell injury under oxidative stress also increase due to smoking, aging, or occupational exposure to physical, chemical, or biological substances Coppey et al. (2012), Singh et al. (2014). In recent years, an increasing number of studies have shown that oxidative stress is the common mechanism of diabetic peripheral neuropathy Sztanek et al. (2016), Himeno et al. (2011).

Peripheral nerve damage is the cause of obstruction in the structural and functional nervous responses in the somatosensory system of DPN patients. Persistent hyperglycemia in diabetic patients increases the damage of oxidative stress, which in turn results in the excessive production of reactive oxygen species (ROS), reducing the body's antioxidant capacity and inhibiting cytokine and cytochrome oxidase release. When nervous damage occurs in sensory neurons, it will lead to positive symptoms and negative symptoms. The distal symmetric polyneuropathy and distal-to-proximal gradient of severity is the most common pattern in patients with DPN, which is not only predominantly of the feet in the clinic but also of the hands Abusoglu et al. (2014). Sensory loss, ongoing spontaneous pain, allodynia, hyperalgesia and evoked pain compose the neuropathic clinical signs in DPN patients Sakano et al. (2009). An imbalance between the oxidation and antioxidant systems in vivo induced different types of tissue stress damage. Neurodegeneration disrupts the connection between the peripheral nerve system and the central nerve system and ultimately leads to sensory loss after peripheral nerve damage. Hence, there are several different types of peripheral diabetic neuropathy, and the neuropathic symptoms and signs may differ from each other depending on the diagnostic tools or measurement criteria Callaghan et al. (2012).

LIMITATIONS

This clinical observational trial had a small sample size and was also carried out with Chinese participants, which largely impacts the generalizability of the findings. Moreover, the research participants were assessed for DPN through a clinical examination and measurement depending on the neuropathic symptoms and sensory function, and their symptoms and signs could be nonspecific. Therefore, future researchers should consider examining the topic using more accurate assessment criteria and measurement methods and larger sample sizes to fully understand the pathology in patients with diabetic peripheral neuropathy.

DECLARATIONS

Ethics approval and consent to participate

A statement to confirm that all methods were carried out in accordance with relevant guidelines and regulations. Study procedures were performed in accordance with the guidelines of the Declaration of Helsinki, 2013. Each patient agreed to participate and provided written informed consent. The study procedures were approved by the ethics committee of Lanzhou University Second Hospital (number 2022A-571).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that there are no conflicts of interest or special relationships with industry in this clinical study.

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Authors' contributions

Li Song is the corresponding author for the clinical study, including designed this study, collected and analyzed data, wrote the manuscript, and made the decision to submit and publish the manuscript. Hong Shi is the first author in the study, and she collected and analyzed data. Li Han is the co-first author of this study. She collected and analyzed data. Jirui He was responsible for the integrity of the data.

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