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PREDICTIVE PERFORMANCE OF SERUM ADIPSIN COMBINED WITH 25(OH)D FOR PERIPHERAL NEUROPATHY IN ELDERLY DIABETIC PATIENTS

PREDIKTIVNA EFIKASNOST SERUMSKOG ADIPSINA U KOMBINACIJI SA 25(OH)D ZA PERIFERNU NEUROPATIJU KOD STARIJIH PACIJENATA SA DIJABETESOM

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Summary

Background: To evaluate the predictive value of serum adipsin and 25-hydroxyvitamin D [25(OH)D] combined detection in elderly diabetic peripheral neuropathy (DPN), aiming to provide new strategies for early intervention.
Methods: Based on the electronic medical records of our hospital from January 2024 to June 2025, 161 elderly patients with T2DM (104 in the DPN group and 57 in the non-DPN group) were enrolled. ELISA detected serum adipsin, and 25(OH)D was measured via liquid chromatography-tandem mass spectrometry (LC-MS/MS). The diagnostic efficacy of the combined detection was confirmed by univariate analysis, logistic regression model, and ROC curves. Disease course and age-stratified subgroup analyses were conducted.
Results: DPN patients showed higher serum adipsin but lower 25(OH)D levels than non-DPN cases ($P<0.05$). Adipsin + 25(OH)D detection exhibited an AUC of 0.831 (sensitivity: 64.42%, specificity: 87.72%), higher than single-index predictions. Subgroup analysis indicated superior predictive efficiency of the combined detection in patients with a disease course of ≥6 years (AUC>0.85). According to correlation analysis, adipsin was positively correlated with FPG, HbA1c, and VPT, and negatively correlated with NCV and SCV, while the opposite was true for 25(OH)D.
Conclusions: Serum adipsin combined with 25(OH)D has high predictive value for elderly DPN, and their synergistic

Kratak sadržaj

Uvod: Cilj je bio da se proceni prediktivna vrednost kombinovanog određivanja serumskog adipsina i 25-hidroksivitamina D [25(OH)D] kod starijih pacijenata sa dijabetesnom perifernom neuropatijom (DPN), u cilju unapređenja strategija za ranu intervenciju.
Metode: Na osnovu elektronskih medicinskih zapisa naše ustanove od januara 2024. do juna 2025. godine, u ispitivanje je uključen 161 stariji pacijent sa T2DM (104 u DPN grupi i 57 u grupi bez DPN). Serumski adipsin je određen ELISA metodom, dok je 25(OH)D meren pomoću tečne hromatografije sa tandem masenom spektrometrijom (LC-MS/MS). Dijagnostička efikasnost kombinovanog određivanja potvrđena je univarijantnom analizom, logističkim regresionim modelom i ROC krivama. Sprovedene su i analize podgrupa prema dužini trajanja bolesti i starosnim kategorijama.
Rezultati: Pacijenti sa DPN su imali više vrednosti serumskog adipsina, ali niže vrednosti 25(OH)D u poređenju sa grupom bez DPN ($P<0,05$). Kombinovano određivanje adipsina i 25(OH)D je pokazalo AUC od 0,831 (osetljivost: 64,42%, specifičnost: 87,72%), što je bolje od pojedinačnih pokazatelja. Analiza podgrupa je ukazala na veću prediktivnu efikasnost kombinovanog određivanja kod pacijenata sa trajanjem bolesti ≥6 godina (AUC>0,85). Prema analizi korelacije, adipsin je bio pozitivno povezan sa FPG, HbA1c i VPT, a negativno sa NCV i SCV, dok je za 25(OH)D zabeležen suprotan odnos.

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effect may be mediated through interconnected pathways involving chronic inflammation, oxidative stress damage, and metabolic dysregulation – collectively termed the 'inflammation-oxidative stress-metabolic disorder' axis.

Keywords: adipsin, 25-hydroxyvitamin D, diabetic peripheral neuropathy, elderly, predictive value

Zaključak: Kombinovano određivanje serumskog adipsina i 25(OH)D ima visoku prediktivnu vrednost za DPN kod stariih pacijenata, a njihov sinergijski efekat može biti izazvan posredstvom međusobno povezanih mehanizmima koji obuhvataju hroničnu inflamaciju, oksidativno oštećenje i metaboličku disregulaciju – osa »inflamacija-oksidativni stress-metabolički poremećaj«.

Ključne reči: adipsin, 25-hidroksivitamin D, dijabetesna periferna neuropatija, stariji pacijenti, prediktivna vrednost

Introduction

With the global ageing, the number of older adults with type 2 diabetes mellitus (T2DM) continues to rise (1). According to epidemiological data, the prevalence rate of DM in the elderly aged over 65 has exceeded 20%, with nearly one-third of T2DM cases complicated with diabetic peripheral neuropathy (DPN) (2). DPN, the most commonly seen DM-associated chronic complication, features distal symmetric polyneuropathy, which can lead to pain, sensory loss, foot ulceration, and even amputation, significantly reducing patients' quality of life and increasing the medical burden (3). Early identification of high-risk groups for timely intervention is the key to delaying DPN progression (4). Nerve conduction velocity (NCV) testing, which is commonly used in clinical practice as the "gold standard," is constrained by its invasiveness, complex operation, and high costs (5). Traditional risk factors (e.g., disease course, HbA1c, dyslipidemia), on the other hand, can only reflect part of the pathological process. Hence, there is an urgent need for highly sensitive and convenient biomarkers for early prediction (6).

Chronic low-grade inflammation and vitamin D deficiency are important drivers of DPN (7). Adipsin (complement factor D), as an inflammatory factor secreted by adipose tissue, can promote islet β cell injury and peripheral nerve inflammation by activating the complement system and regulating macrophage polarisation (8). Serum 25-hydroxyvitamin D [25(OH)D] is not only the core index of vitamin D metabolism, but also participates in the pathological process of DPN through immune response modulation and neurooxidative stress suppression (9). Recent univariate analyses have shown significant elevations in serum adipsin and marked down-regulation of 25(OH)D in DPN patients (10, 11). However, the predictive value of serum adipsin plus 25(OH)D for elderly DPN has not yet been clarified. Moreover, the elderly, characterised by metabolic decline, fat redistribution, and limited sun exposure, may exhibit more distinctive dynamics in adipsin and 25(OH)D levels. The current research mainly focuses on patients of all ages or non-elderly patients with DM (12). Specific evidence for the elderly population is still scarce.

Given current research, this study will primarily focus on the elderly population with DM and explore the diagnostic efficacy of serum adipsin combined with 25(OH)D for DPN, overcoming the limitations of single-factor biomarkers. Meanwhile, by considering the metabolic characteristics of elderly patients, the possible mechanisms of their synergistic effect (such as the inflammatory-immune interaction network) are analysed, providing a new perspective for the early warning of DPN. If it is confirmed that combined testing can efficiently identify high-risk elderly DPN populations, it will help clinicians implement precise interventions (such as vitamin D supplementation, targeted regulation of adipokines, or enhanced metabolic control) before symptoms appear, thereby slowing the progression of nerve damage and reducing the risk of disability.

Materials and Methods

Research design

This study adopted a retrospective cross-sectional study design. Based on the electronic medical records of our hospital's endocrinology department from January 2024 to June 2025, elderly patients with type 2 diabetes mellitus (T2DM) who met the criteria were selected. The predictive value of the adipsin-25(OH)D combination for DPN in the elderly was evaluated by correlating baseline adipsin and 25(OH)D levels with the occurrence of DPN during follow-up. This study was conducted after obtaining ethics committee approval.

Sample size estimation

Based on previous univariate findings (13), we hypothesised that elevated serum adipsin (OR=2.3) and reduced 25(OH)D (OR=0.4) each could independently predict DPN, and that their combination would increase the OR to 3.5 (α=0.05, two-tailed test; statistical power 1-β=0.8). Sample size was calculated by PASS 15.0. Assuming a DPN prevalence of approximately 30% (i.e., comorbid DPN in one-third of elderly T2DM patients) and setting a case (DPN) to non-case (non-DPN) ratio of 1:2, the final estimation indicated a required sample size of 140–160 subjects.

Inclusion and Exclusion Criteria

Inclusion criteria: Aged ≥65 years; meeting the diagnostic criteria for T2DM (FPG≥7.0 mmol/L or 2-hour postprandial blood glucose ≥11.1 mmol/L, or HbA1c≥6.5%, or already on glucose-lowering medication) (14); disease course ≥1 year; complete baseline data (including demographic characteristics, biochemical indicators, and neurological function evaluation) and follow-up (≥6 months) records. Exclusion criteria: Special DM types (e.g., DM secondary to pancreatic diseases); severe hepatic and renal insufficiency; peripheral neuropathy caused by other definite causes; recent (3 months) medication that would affect adipsin or 25(OH)D levels; pregnant/lactating women; unconsciousness or inability to cooperate with neurological function evaluation.

Grouping

DPN diagnosis was established at baseline using Toronto Consensus criteria (15), confirmed by nerve conduction studies within 2 weeks of enrollment. In this study, there were 104 cases in the DPN group and 57 cases in the non-DPN group.

Serum adipsin detection

Fasting blood was collected from patients in the morning before treatment, and serum was separated by centrifugation (stored at -80 °C). Human adipsin ELISA kit was used for detection. The standard samples were diluted at concentrations of 0, 10, 20, 40, 80, and 160 pg/mL and then added to an antibody-coated microplate. Then, serum (100 μL/well) was added for 2 hours of room-temperature incubation. Following liquid removal, the plate was washed 3 times with PBST, incubated with a biotinylated secondary antibody (1:1000 dilution), and incubated at room temperature for 1 hour. Then HRP-labelled streptavidin was added, and colour development was performed in the dark for 15 minutes. A stop solution was then added to terminate the reaction, followed by absorbance measurement at 450 nm wavelength with a microplate reader. For quality control, each plate was equipped with low (20 pg/mL), medium (80 pg/mL), and high (160 pg/mL) concentration quality control products, requiring the coefficient of variation (%) <10%. Human Adipsin ELISA Kit (Cusabio, CSB-E17385h) with inter-assay CV<8%, intra-assay CV<6%. Quality control included three-level controls per plate.

25(OH)D determination

Serum 25-hydroxyvitamin D [25(OH)D] quantification was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The serum samples were processed using a protein precipitation procedure for purification. The supernatant was injected into the LC-MS/MS system for separation and detection. The 25(OH)D concentration was calculated from the peak area ratio of the target analyte to its internal standard, using a calibration curve. Quality control: Quantified by LC-MS/MS (Agilent 6495C) following CLIA certification standards. We utilised Bio-Rad control materials, setting the warning limits at the mean ± 2SD.

FPG and HbA1c measurements

We used an automated biochemical analyser to measure FPG and HbA1c levels in serum. The instrument automatically completed the detection and output the results after loading the serum sample. Quality control: Bio-Rad Lyphochek controls (Levels 1 and 2) were used, with the CV% calculated monthly (intra-assay <2%, inter-assay <3%).

Neurological function testing

The motor conduction velocity (MCV) and sensory conduction velocity (SCV) of the median nerve (wrist-abductor pollicis brevis) and common peroneal nerve (capitulum fibulae-tibialis anterior muscle) were detected by a neuroelectrophysiological instrument. The vibration perception threshold (VPT) of the dorsum of both feet (the first metatarsal bone) was detected with a biothesiometer.

Statistical methods

The experimental data were imported into SPSS 34.0 for statistical analysis. The patient's sex and smoking history were recorded as [n(%)], with comparative analyses conducted with the chi-square test. Data such as adipsin and 25(OH)D test results were recorded as ($\bar{x}$+s) and the t-test was used for comparison. Diagnostic performance was determined using receiver operating characteristic (ROC) curves; areas under the curve (AUCs) closer to 1 indicated greater efficacy. The joint detection was modelled using Logistic regression. Correlation analysis employed Pearson's r. For multiple comparisons, Bonferroni correction was applied where appropriate, with significance set at $P<0.05/n$ (where n is the number of tests). Statistical significance was defined as two-tailed $P<0.05$.

Results

Selection bias analysis

By analysing patients' clinical data statistically, we found no notable inter-group differences in age, disease course, or sex ($P>0.05$), suggesting comparability. It is worth noting that the DM course was

Table I Comparison of baseline clinical characteristics between DPN and non-DPN groups in elderly T2DM patients.

	DM (n=57)	DPN (n=104)	Statistics	P
Age (years old)	72.82±4.73	72.72±4.71	t=0.133	0.895
Duration of DM (Years)	7.18±2.52	8.64±3.33	t=2.904	0.004
BMI (kg/m^2)	23.80±2.13	23.67±1.94	t=0.386	0.700
Sex			2=0.503	0.478
male	34 (59.65)	56 (53.85)		
female	23 (40.35)	48 (46.15)		
Smoking			2=1.088	0.297
yes	36 (63.16)	74 (71.15)		
no	21 (36.84)	30 (28.85)		
SBP (mmHg)	126.32±10.81	129.20±11.33	t=1.571	0.118
DBP (mmHg)	81.54±8.07	82.12±7.01	t=0.468	0.640
FPG (mmol/L)	7.90±0.94	8.58±1.05	t=4.112	<0.001
HbA1c (%)	10.91±2.29	13.71±3.46	t=5.466	
MCV (m/s)	47.33±3.72	43.01±3.85	t=6.886	
SVC (m/s)	42.39±4.81	38.41±4.96	t=4.914	
VPT (V)	23.02±4.44	27.75±4.36	t=6.541	

Table II Effects of adipsin and 25(OH)D on DPN.

	β	S.E.	Wals	OR	P
Adipsin	0.159	0.036	20.056	1.173	<0.001
25(OH)D	-0.168	0.050	11.128	0.845	0.001
Constant	-2.803	1.878	2.227	0.061	1.136

longer in DPN patients compared to non-DPN cases, while FPG and HbA1c were higher (P<0.05). Compared with non-DPN patients, NCV and SCV decreased in the DPN group, while VPT increased (P<0.05; *Table I*).

Value of adipsin and 25(OH)D in diagnosing DPN

The DPN group exhibited elevated adipsin and reduced 25(OH)D levels compared with the non-DPN group (P<0.05). ROC curve analysis was conducted using adipsin and 25(OH)D tests from the DPN and non-DPN groups. The results showed that the AUCs for adipsin and 25(OH)D in diagnosing DPN were 0.795 and 0.766, respectively. Subsequently, the combined detection model, based on Logistic regression analysis results (*Table II*), achieved an AUC of 0.831 for DPN diagnosis, with 64.42% sensitivity and 87.72% specificity, outperforming single-index testing (*Figure 1*).

Gender-stratified subgroup analysis

A subgroup analysis was conducted based on patient gender. Adipsin levels were significantly elevated in both sexes of the DPN group compared to their non-DPN counterparts; conversely, 25(OH)D levels were reduced (P<0.05). The logistic regression model showed a good fit (Hosmer-Lemeshow χ^2=5.342, P=0.622), indicating appropriate model specification. The combined detection of adipsin and

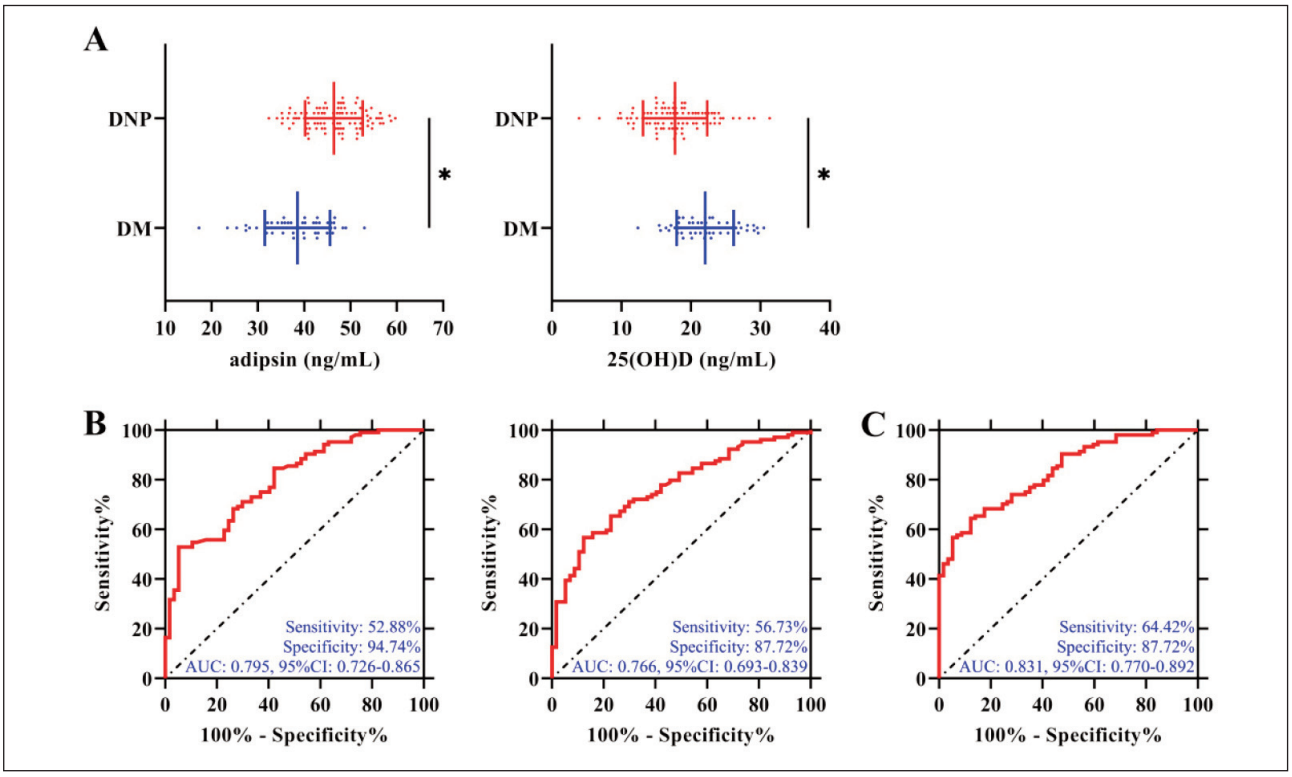

Figure 1 Analysis of adipsin and 25(OH)D status and diagnostic efficacy in DPN.

(A) Comparison of adipsin and 25(OH)D between DM patients and DPN patients. (B) Diagnostic efficacy of adipsin and 25(OH)D for DPN. (C) Diagnostic effect of combined detection of adipsin and 25(OH)D for DPN. * indicates P<0.05.

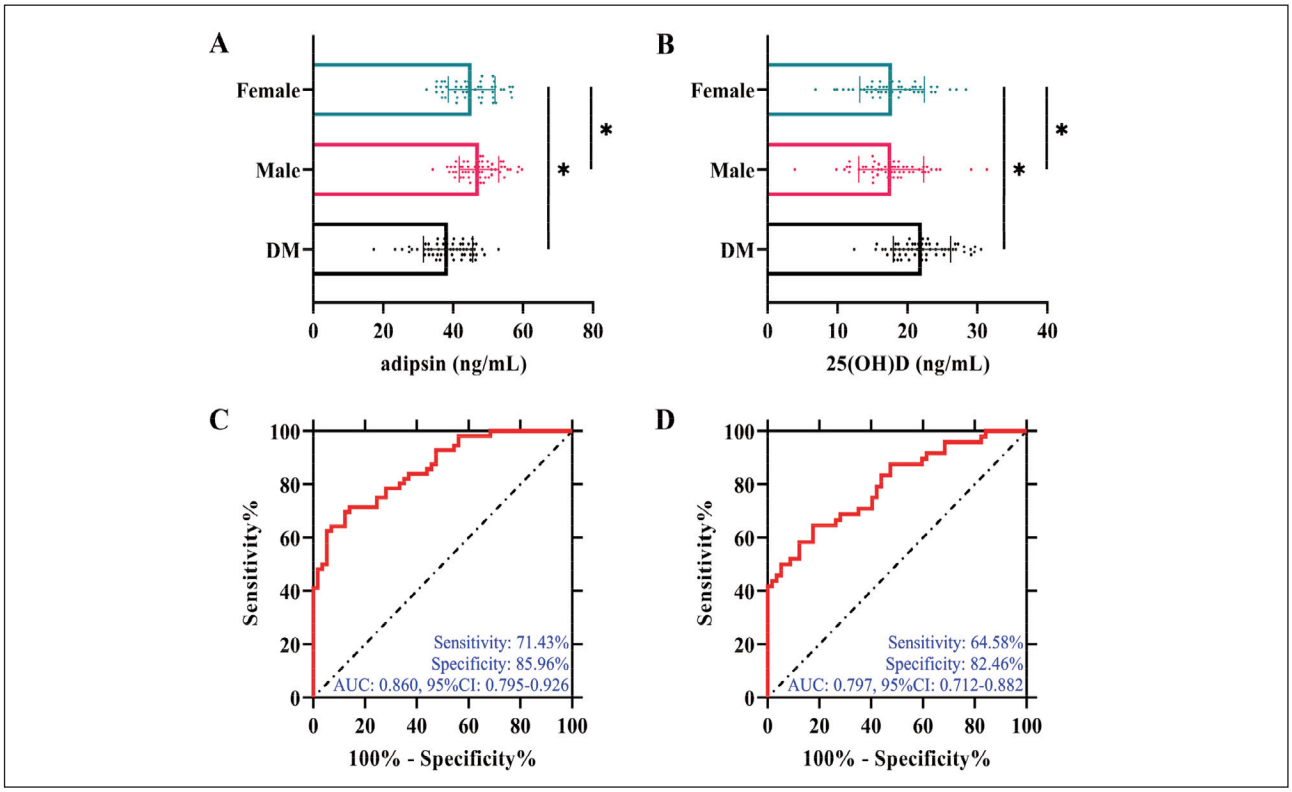

Figure 2 Status of adipsin and 25(OH)D in different genders.

(A) Comparison of adipsin in different genders. (B) Comparison of 25(OH)D in different genders. (C) Diagnostic efficacy of adipsin for DPN in female patients. (D) Diagnostic value of 25(OH)D for DPN in male patients. * indicates P<0.05.

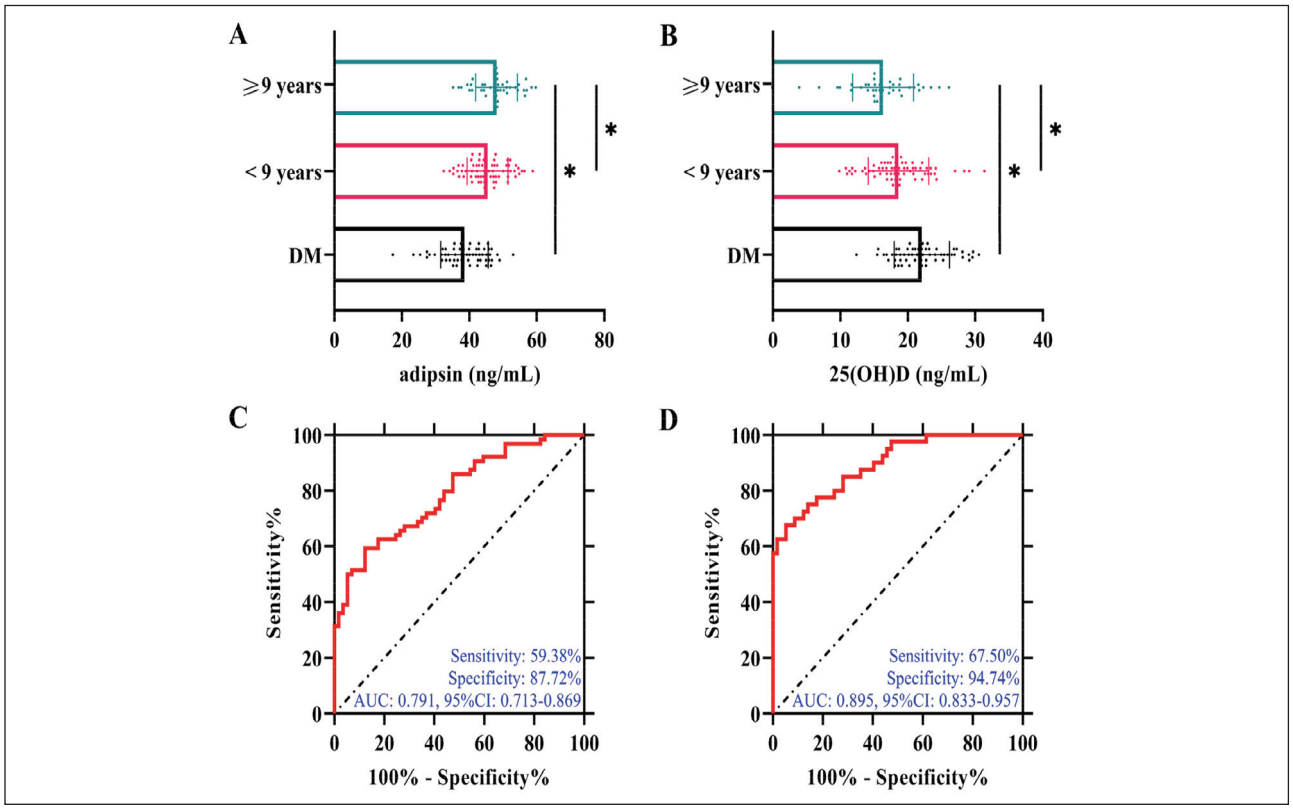

Figure 3 Status of adipsin and 25(OH)D in different DM courses.

(A) Comparison of adipsin in different DM courses. (B) Comparison of 25(OH)D in different DM courses. (C) diagnostic efficacy of adipsin for DPN in patients with DM duration <9 years. (D) diagnostic value of 25(OH)D for DPN in patients with DM duration 9 years. * indicates P<0.05.

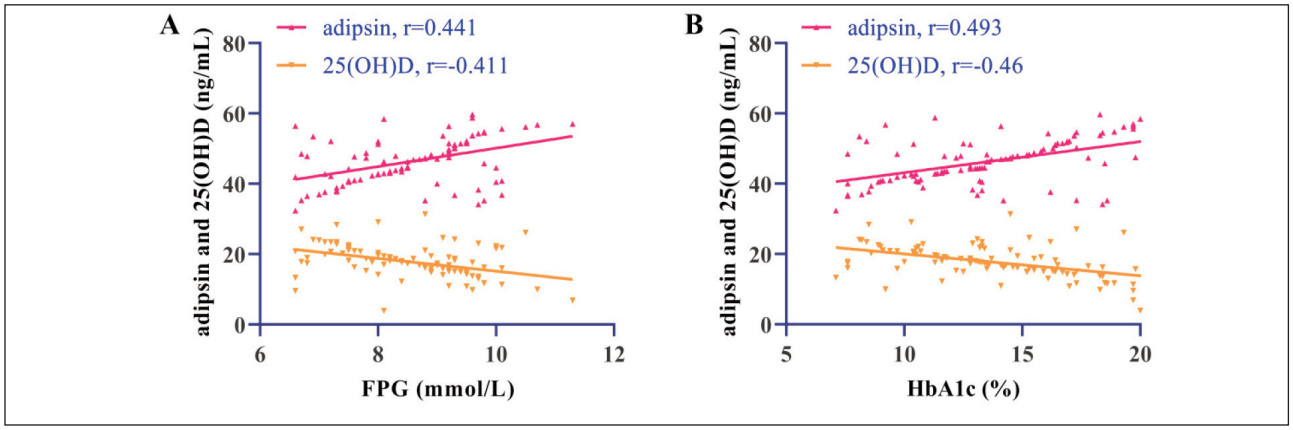

Figure 4 Relationship between adipsin, 25(OH)D, and glucose metabolism.

(A) Correlation analysis of adipsin, 25(OH)D and FPG. (B) Correlation analysis of adipsin, 25(OH)D and HbA1c.

25(OH)D had the same diagnostic effect in DPN cases of both sexes (AUC=0.860, 0.797, *Figure 2*).

Disease course-based subgroup analysis

The mean duration of DM in DPN patients was 8.64. Based on this, the patients were divided into ≥9 years group (n=40) and <9 years group (n=64). According to disease course-based subgroup analysis, patients with a DM course ≥9 years had higher adipsin and lower 25(OH)D levels (P<0.05). Similarly, ROC curve analysis showed that adipsin and 25(OH)D were more effective in diagnosing DPN in T2DM patients with disease duration of more than 9 years (P<0.05; *Figure 3*).

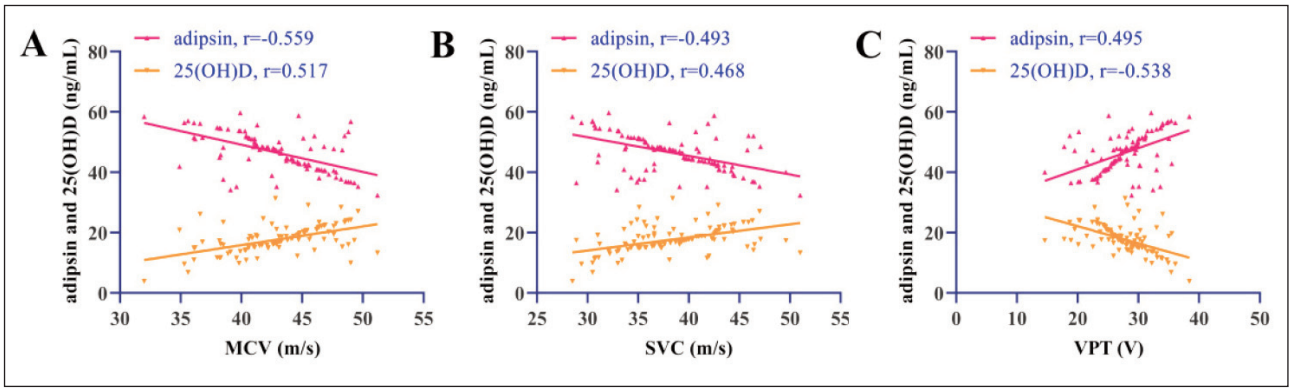

Figure 5 Relationship between adipsin, 25(OH)D, and neurological function.

(A) Correlation analysis of adipsin, 25(OH)D and NCV. (B) Correlation analysis of adipsin, 25(OH)D and SCV. (C) Correlation analysis of adipsin, 25(OH)D and VPT.

Association of adipsin and 25(OH)D with blood glucose in DPN patients

Correlation analysis revealed a positive association between FPG and HbA1c and adipsin, and a negative association between them and HbA1c in the DPN group ($P<0.05$). That is, the higher the blood sugar, the higher the adipsin and the lower the 25(OH)D (*Figure 4*).

Correlation of adipsin and 25(OH)D with neurological function in DPN patients

The correlation analysis showed that in the DPN group, NCV and SCV were negatively correlated with adipsin and positively correlated with 25(OH)D ($P<0.05$); VPT, on the contrary, showed a positive correlation with adipsin and an inverse link to 25(OH)D ($P<0.05$, *Figure 5*).

Discussion

As a common chronic complication of T2DM, DPN leads to adverse events such as foot ulcers and lower limb amputations, making it a significant global public health issue (16). Focusing on elderly T2DM patients for the first time, this study pioneers discussion of the predictive performance of adipsin and 25(OH)D for DPN in T2DM, aiming to provide a more convenient and sensitive tool for early screening and to assist in precise intervention for high-risk individuals.

First, we observed elevated serum adipsin levels and decreased 25(OH)D in DPN patients. The combined prediction yielded an AUC of 0.831, with a sensitivity of 64.42% and a specificity of 87.72%, which is better than single-index detection. This finding is supported by previous research. Multiple prior studies have confirmed, using univariate analysis, that adipsin is elevated and 25(OH)D is decreased in patients with DPN (17, 18). However, the synergistic effect of their combined detection had not been clearly validated in the elderly population before this study. From a mechanistic perspective, the interaction between adipsin and 25(OH)D may influence DPN progression through the following pathways: As an adipokine, adipsin can recruit macrophages to the vicinity of the nerve via activating the complement system (especially the C3a/C5a pathway), promoting the release of proinflammatory factors (such as IL-1β, TNF-α) and leading to Schwann cell damage and myelin loss (19).

Meanwhile, 25(OH)D can inhibit excessive inflammatory responses by inhibiting the NF-κB signalling pathway, reducing proinflammatory factor expression and enhancing regulatory T cell (Treg) functioning (20). In elderly T2DM patients, chronic adipose tissue inflammation and down-regulated vitamin D receptor (VDR) expression may form a vicious cycle, exacerbating the pathological process of neuroinflammation (21). 25(OH)D can increase the activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD), eliminating free radicals and reducing oxidative stress damage (22). Adipsin may promote the generation of reactive oxygen species (ROS) by activating NADPH oxidase (NOX), further damaging mitochondrial function and leading to neuronal apoptosis (23). Their synergy may impair the antioxidant defence system and accelerate neurodegeneration. In in vitro studies by Jiang X et al., (24), 25(OH)D deficiency upregulates DNA methyltransferase (DNMT) activity, leading to promoter hypermethylation of the nerve growth factor (NGF) gene and inhibiting its expression. The positive correlation between adipsin and HbA1c observed in our study provides indirect support for potential epigenetic mechanisms, though direct validation requires further investigation. In the DPN group, FPG and HbA1c were positively correlated with adipsin, but negatively correlated with 25(OH)D. This result further validates that poor glycemic control may amplify the pathologi-

cal effects of adipsin and 25(OH)D through the »glycotoxicity-inflammation-vitamin D deficiency« axis. For instance, hyperglycemia can induce adipose tissue to secrete adipsin, while inhibiting 1α-hydroxylase activity in the kidneys and reducing 25(OH)D synthesis, forming a vicious feedback loop.

Based on the excellent diagnostic efficacy of adipsin and 25(OH)D for DPN, it is recommended to incorporate both into the routine screening system for elderly patients with T2DM, especially for high-risk individuals with a disease duration of ≥ 9 years. In terms of treatment, patients with elevated adipsin levels and 25(OH)D deficiency should prioritise vitamin D3 supplementation and anti-infective therapy (such as statins) to synergistically alleviate neuroinflammation. However, since this study is based on single-centre electronic medical record data, there may be selection bias (e.g., due to the predominance of outpatients with relatively stable conditions). Future studies should verify the generalizability of the results using prospective cohorts. Furthermore, although the estimated sample size was 161 cases, the number of cases in some subgroups was relatively small, potentially affecting statistical power. In the future, it is necessary to increase the sample size to improve the reliability of the conclusions. Moreover, variations in measured adipsin levels can be caused by differences in the sensitivity and detection limits of ELISA kits. It is recommended that future research adopt an internationally standardised detection platform to enhance the comparability of the results.

Conclusion

The combination of serum adipsin and 25(OH)D demonstrates excellent predictive value for DPN in elderly T2DM patients, potentially offering a clinically valuable tool for early risk stratification. Future prospective multicenter studies are needed to validate these findings and explore clinical implementation pathways.

Consent to publish

All authors gave final approval of the version to be published.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

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Authors' contribution

S. X. conceived and designed the study, Y. W. and ML. L. wrote and revised the manuscript, Y. C. and XD. Q. collected and analysed data, LD. T. and H. Y. supervised the study, Y. W. and ML. L. made equal contributions in this work as co-first authors. All authors read and approved the final submitted manuscript.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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