Serum Albumin Was Negatively Associated With Diabetic Peripheral Neuropathy in Chinese Population: A Cross-sectional Study

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Abstract

Background: Studies that investigated the association between serum albumin and the risk of diabetic peripheral neuropathy (DPN) have reported inconsistent results. The objective of this study was to explore the relationship between serum albumin and DPN in Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: Serum albumin levels were measured in 1465 patients with T2DM aged 16–89 years. The relationships between serum albumin and the prevalence of DPN and other parameters were analyzed.

Results: Patients in the highest quartile of serum albumin had lower prevalence of DPN compared with subjects in the lowest quartile (P <0.01). Serum albumin was positively associated with DBP, total cholesterol, triglycerides, high-density lipoprotein cholesterol, uric acid, and negatively with glycated hemoglobin A1c, γ-glutamyltransferase, cystatin C, serum creatinine, albumin- to-creatinine ratio, neutrophil-to-lymphocyte ratio, vibration perception thresholds (VPT), and prevalence of DPN after adjustments for age, gender, body mass index, and diabetic duration (P<0.01 or P<0.05). There was an 50.1% decreased risk of DPN (95% confidence interval [CI] 0.404-0.544; P <0.01) per 1 SD increase of serum and 62.7% decreased risk of DPN in quartile 4 of serum albumin versus quartiles 1, 2, and 3 (95% CI 0.195-0.714; P=0.003) after multivariate adjustment. Serum albumin could predict DPN with 65.88% sensitivity and 66.7% specificity for the best cutoff value of 39.95 g/L.

Conclusions: These findings suggest that lower serum albumin might be associated with the presence of DPN via increased oxidative stress, inflammation, and vasculopathy. Further larger and prospective studies are needed to confirm our findings.

Background

Diabetic peripheral neuropathy (DPN), characterized by numbness, paraesthesia, and pain at an early stage, and sensory loss at advanced stages, is one of the most frequent diabetic microvascular complications, affecting up to 50% diabetic patients [1]. DPN is widely considered as a major risk factor for foot ulcers and even lower extremity amputation, resulting in considerable morbidity and mortality, and a high health care burden. To date, its underlying pathophysiological mechanisms are unknown, and there is a lack of targeted therapy. Therefore, it is clinically important to early detect novel modifiable risk factors that lead to DPN, with identification at an early stage likely providing an opportunity for effective intervention.

Albumin, an unglycosylated protein of 66.3 kD, is the most abundant soluble protein in plasma and extracellular compartments, and its levels are affected by several factors including rate of synthesis, catabolic state, inflammation, and distribution in the intra- and extravascular body compartments [2]. It has been reported that serum albumin can bind and transports endogenous and exogenous compounds such as bilirubin, fatty acids, hormones, metal ions, and most drugs [3]. There is considerable evidence indicated that serum albumin has a wide range of physiological functions, including antioxidant, anti- inflammatory, anticoagulant, antiplatelet aggregation activity, regulating immune response, preventing endothelial cell, Schwann cells and neuronal apoptosis, dilating blood vessel, protecting against neuronal injury from ischemia and reperfusion, and improving neuronal functional recovery [4-11], suggesting that albumin may

confer robust neuroprotection, and lower levels of serum albumin may be involved in the development of DPN. Although few observations have suggested presence of such a link [12-14], others have reported the lack of an independent association [15]. Such discrepancy in the literature may be due to differences in study population, diabetic duration, a limitation in the diversity of selected participants, diagnostic methods for DPN, variation in design, limitations in sample size, and a limited range in which serum albumin has been studied.

Therefore, the purpose of the present study was to examine the relationship between serum albumin concentrations and the presence of DPN in a Chinese population with T2DM. Moreover, the potential associations among serum albuminand metabolic parameters, oxidative stress and inflammatory markers, and vascular related indicators were evaluated.

Methods

Study population

A total of 1465 confirmed or newly diagnosed T2DM patients aged 16–89 years, long-term residence (≥5 years) in China's Sichuan province, in our inpatient department between August 2012 and September 2015, who completed the measurement of serum albumin and DPN screening, were finally enrolled in the cross-sectional study. The exclusion criteria were (1) presence of other endocrine disorders, acute complications of diabetes, neuropathy of a nondiabetic cause; (2) presence of severe respiratory and cerebrovascular disease, severe heart failure and renal failure, liver disease or abnormal liver function test; (3) presence of inflammatory and autoimmune diseases, acute infectious disease, cancer, alcoholism, pregnancy or lactation, and other diseases; (4) use of some drugs such as immunosuppressant, antioxidant, anti-inflammatory drugs, analgesics, systemic corticosteroids; (5) use of possible or known drugs affecting peripheral nerve function and sympathetic system.

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by the human research ethics committee of the Affiliated Hospital of Southwest Medical University, and informed consent was obtained from all T2DM patients prior to participation.

Clinical and biochemical measurements

Body weight, height, body mass index (BMI), and blood pressure [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] were determined, as described previously [16]. After an overnight fast of ≥8 h, venous blood samples were collected to measure blood glucose (FBG), glycated hemoglobin A1C (HbA1c), lipid profiles, including total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), uric acid (UA), cystatin C (CysC), serum creatinine (Cr), neutrophil and lymphocyte counts, neutrophil to lymphocyte ratio (NLR), red cell distribution width (RDW) and estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations modified by a Japanese coefficient [1], and urine specimens were also used to determine the urinary albumin-to-creatinine ratio (ACR). Ankle-brachial

index (ABI) measurements were measured by a continuous-wave Doppler ultrasound probe (Vista AVS, Summit Co.).

Diagnostic Criteria of DPN

Vibration perception threshold (VPT) was assessed at the metatarsophalangeal joint dig I using a neurothesiometer (Bio-Thesiometer; Bio-Medical Instrument Co., Newbury, OH, USA). Sensibility to touch was tested using 10-g Semmes-Weinstein monofilament (SWM) at four points on each foot. DPN was defined as VPT ≥25 V and/or inability to feel the monofilament [17].

Statistical analysis

All analyses were performed with the Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL). All data were first analyzed for normality of distribution using the Kolmogorov-Smirnov test of normality, and homogeneity of variance using the Levene homogeneity of variance test. Data are presented as mean ± standard deviation (SD) for continuous variables and absolute numbers (percentages) for categorical variables.

Serum albumin quartiles were categorized as follows: Q1 (21.70–37.60 g/L), Q2 (37.70–41.30 g/L), Q3 (41.40–44.40 g/L), and Q4 (44.50–57.60 g/L). Clinical and biochemical characteristics of the study population according to serum albumin quartiles were compared using one-way analysis of variance (ANOVA) for continuous variables with normally distribution and homogeneity of variance, the Kruskal-Wallis test for continuous covariates with nonparametric distribution and/or variance uneven and chi-square tests for categorical variables. Two-group comparisons were performed with χ^2 test for categorical variables or Student's *t* test or Mann–Whitney U test for distributed continuous variables. Associations between serum albumin and other variables were tested by the Spearman's correlation analysis and partial correlation analyses adjusted for age, gender, and BMI, and diabetic duration. Binary logistic regression analyses were conducted to investigate the association between serum albumin quartiles and DPN. Associations were first examined in model 1. Models were further adjusted for age, gender, and BMI, and diabetic duration. To determine if the association between serum albumin and DPN was independent of glucose and lipid metabolism, inflammation, oxidative stress, and angiopathy, models were then further adjusted for SBP, DBP, FBG, HbA1c, TC, TG , HDL-C, LDL-C, NLR, RDW, ALT, AST, GGT, UA, Cr, CysC, eGFR, ACR, and ABI. The Q1 served as the reference group, and Odds ratios (OR) and 95% confidence intervals (CI) were estimated. Possible dose-response relationships between albumin and DPN were examined by the trend χ^2 test. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff values for serum albumin as indicators of DPN.

In all statistical tests, a *P*-value of <0.05 was considered to be statistically significant (two sided).

Results

Clinical and biochemical characteristics of the studied population

Among the 1465 participants included in this study, 231 participants (15.77%) had DPN. The prevalence of DPN according to serum albumin quartiles was 31.25%, 16.76%, 9.81% and 5.19%, respectively. The subjects with higher serum albumin were more likely to be younger, and to have longer diabetic duration (all $P<0.01$). The subjects in the higher serum albumin quartiles exhibited higher levels of BMI, DBP, TG, TC, HDL-C, LDL-C, ALT, AST, UA, eGFR, ABI and lower FBG, HbA1c, GGT, Cr, CysC, ACR, NLR, VPT, and prevalence of DPN compared with subjects in the lowest quartile ($P<0.01$ or $P<0.05$). Gender, DBP, and RDW did not differ significantly across serum albumin categories (Table 1). When compared with subjects without DPN, the subjects with DPN had significantly older age, longer diabetic duration, higher levels of FBG, HbA1c, CysC, Cr, urinary ACR, NLR, and VPT, and lower levels of serum albumin, BMI, DBP, TC, TG, ALT, AST, GGT, eGFR, and ABI ($P<0.01$ or $P<0.05$) (Supplemental Table 1).

Association between serum albumin and risk factors related to DPN in study subjects

The Spearman correlation analysis revealed that serum albumin levels were positively associated with BMI, DBP, TC, TG , HDL-C, LDL-C, ALT, AST, GGT, UA, eGFR, and ABI, and negatively with age, diabetic duration, FBG, HbA1c, NLR, Cr, CysC, ACR, VPT, and prevalence of DPN ($P<0.01$ or $P<0.05$). After adjustments for age, gender, BMI, and diabetic duration, the associations among glucose and lipid metabolism parameters (DBP, TC, TG , HDL-C, HbA1c), inflammation marker (NLR), oxidative stress parameters (UA and GGT), and diabetic nephropathy related indicators (Cr, CysC, and ACR), and serum albumin remained statistically significant ($P<0.01$ or $P<0.05$) (Table 2).

Association between serum albumin quartiles and the risk of DPN in study subjects

The mean serum albumin in the study population was 40.93 g/L (range 21.70–57.60 g/L). There was an 18% decrease in non spine fracture risk per SD increase in serum albumin (OR = 0.469, 95% CI 0.404-0.544) in Model 1. Results remained significant after further adjustments for age, sex, BMI, diabetic duration, SBP, DBP, FBG, HbA1c, TC, TG , HDL-C, LDL-C, NLR, RDW, ALT, AST, GGT, UA, Cr, CysC, eGFR, ACR, and ABI in Model 3 (OR = 0.499, 95% CI 0.385-0.645). A graded association with prevalence of DPN and increase in serum albumin quartiles was observed (P for trend in Model 2 <0.01). The subjects in the highest quartile of serum albumin had a significantly lower risk of DPN compared with subjects in Q1 (OR = 0.174, 95% CI 0.102-0.297). Results were slightly attenuated but remained significant when models were further adjusted for SBP, DBP, FBG, HbA1c, TC, TG , HDL-C, LDL-C, NLR, RDW, ALT, AST, GGT, UA, Cr, CysC, eGFR, ACR, and ABI (OR for Q4 versus Q1 = 0.311, 95% CI 0.134-0.724, P for trend <0.01) (Table 3).

The predictive value of serum albumin in detecting DPN in T2DM individuals

The result from ROC curves of serum albumin revealed that the optimal cutoff point of serum albumin to indicate DPN was 39.95 g/L (sensitivity: 65.88%, specificity: 66.7%, and AUC 0.720) in T2DM individuals (Fig.1).

Discussion

In the present study, we found that patients in the highest quartile of serum albumin had lower prevalence of DPN compared with subjects in the lowest quartile ($P<0.01$). There was an 50.1% decreased risk of DPN

(95% confidence interval [CI] 0.404-0.544; *P* <0.01) per 1 SD increase of serum and 62.7% decreased risk of DPN in quartile 4 of serum albumin versus quartiles 1, 2, and 3 (95% CI 0.195-0.714; *P*=0.003) after multivariate adjustment. Serum albumin could predict DPN with 65.88% sensitivity and 66.7% specificity for the best cutoff value of 39.95 g/L. These findings suggest that lower serum albumin level may be associated with an increased risk of DPN.

Albumin, a multifunctional plasma protein, possesses an important antioxidant property by binding metal ions, and efficiently scavenging free oxygen and nitrogen radicals [3]. It has been reported that serum albumin has three to seven times the total antioxidant capacity compared to vitamin E, vitamin C, and bilirubin as a chain-breaking antioxidant in vitro [18]. Changes of plasma concentration and structural modification of albumin induced by high glucose or free radicals impair its antioxidant properties and aggravate oxidative stress [19]. Several previous studies have explored the association of serum albumin with the development of DPN, and provided inconsistent results [12-15]. Iwasaki et al. reported that serum albumin was independently related to the median motor nerve conduction velocity and minimum F-wave latency in 130 Japanese patients with T2DM, and was significantly inversely associated with the presence of DPN [12]. Data from a cross-sectional study of 409 Chinese patients with T2DM underwent measurement of nerve conduction (NC) showed that serum albumin was independently associated with peripheral nerve function as reflected by composite Z scores of all NC parametersin T2DM patients, especially in those with albuminuria [13]. Recently reported data from the Saudi study, which included 2,906 hospitalized adult diabetics, demonstrated that DPN cases had a significantly lower serum albumin levels compared with those without DPN [14]. However, no statistically significant association between serum albumin and DPN in US patients undergoing foot and ankle surgery with a history of Type 1 and 2 diabetes mellitus over a 13 month period [15]. In the present study, we observed that patients in the highest quartile of serum albumin had lower VPT, an useful and reliable method for early screening DPN and reflecting the clinical severity of DPN [16], and prevalence of DPN compared with subjects in the lowest quartile, and serum albumin was negatively associated with VPT and prevalence of DPN after adjustments for age, gender, BMI, and diabetic duration, demonstrating the potential neuroprotective actions of serum albumin in the pathogenesis of DPN. Moreover, there was an 50.1% decreased risk of DPN per 1 SD increase of serum and 62.7% decreased risk of DPN in quartile 4 of serum albumin versus quartiles 1, 2, and 3 after multivariate adjustment. Further analysis of ROC curves revealed that the serum albumin concentration of 39.95 g/L could predict DPN. Collectively, these data demonstrate that decreased serum albumin may play an important role in the development of DPN in a Chinese population with T2DM, which needed to be verified by further studies.

Numerous experimental and clinical studies have indicated that low-grade inflammation and oxidative stress induced by chronic hyperglycemia play a major role in the onset and development of DPN [13, 20]. Our study findings provided further evidence that patients with DPN had higher FBG, HbA1c, CysC, NLR, and lower GGT than those without DPN, mostly consistent with the findings of previous studies [20, 21, 22], supporting a role of inflammation and oxidative stress in the development of DPN. HbA1c represents blood glucose control conditions for recent 8-12 weeks [20]. UA, the end product of purine catabolism, has recently been regarded as an important endogenous antioxidant and anti-inflammatory [23]. GGT, the principal enzyme responsible for extracellular catabolism of the antioxidant glutathione, has been reported to be involved in oxidative stress and lipid peroxidation, and elevated under oxidative stress conditions [24]. CysC, a 13-kDa

endogenous cysteine proteinase inhibitor, has been found to be positively associated with proinflammatory cytokines c-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-α (TNF-α) and marker of oxidative stress homocysteine levels, and negatively with antioxidant paraoxonase 1 activity across a variety of populations [25, 26]. NLR, defined as the neutrophil count divided by lymphocyte count, has recently been increasingly recognized as a marker of systemic inflammation [21]. Our data suggest that the T2DM subjects in the higher serum albumin quartiles exhibited higher levels of UA, and lower FBG, HbA1c, GGT, NLR, and CysC compared with subjects in the lowest quartile, and serum albumin levels were positively associated with UA, and negatively with HbA1c, GGT, NLR and CysC after adjustments for age, gender, BMI, and diabetic duration, indicating that serum albumin as a negative acute phase protein may have anti-inflammatory and antioxidant activity. These findings are consistent with the published literature [27-29]. Yeh et al. found that serum albumin level was inversely correlated with CRP, white blood cell, and NLR., and change in serum albumin level was inversely correlated with change in NLR in adult surgical intensive care unit patients receiving enteral nutrition [27]. Cantin and co-workers demonstrated that albumin augments intracellular glutathione (GSH) levels in lymphocytes and modulates activation of nuclear factor-κB (NF-κB), whereas a thiol-mediated reduction in serum albumin decreases glutathione levels, thus allowing NF-κB activation, and stimulate the inflammatory response [28]. Zhang and collaborators demonstrated that physiological concentrations of albumin selectively inhibit TNF-α-induced upregulation of vascular cell adhesion molecule-1, expression and monocyte adhesion in human aortic endothelial cells, most likely by inhibiting NF-kB activation in a GSH- independent manner [29]. These findings, together with data from our study, suggest that albumin could modulate cellular GSH as well as transcription of inflammatory genes and apoptosis, and the inflammatory state and oxidative stress associated with low serum albumin may be the main mechanism of DPN in these individuals, although further studies are needed to clarify the underlying mechanism.

There is growing evidence that diabetic vasculopathy caused by low-grade inflammation and oxidative stress, which could affect the nutrition supply of neuronal and Schwann cells and contribute to adequate blood supply and nerve degeneration, is believed to play an important role in the pathogenesis of DPN [17, 21]. Our study provided further evidence that supported the potential role of diabetic vasculopathy in the development of DPN, since we found that patients with DPN had higher CysC, Cr, urinary ACR, and lower DBP, eGFR, ABI than those without DPN. Diabetic nephropathy (DN), a complication characterized by a decreased eGFR, increased urinary ACR, and high levels of Cr [30], is
one of the most feared diabetic chronic microvascular complications, and is independently associated with DPN [31]. The urinary ACR, a marker of DN, is used as a proxy for damage to the systemic microcirculation and predicts future progression of renal dysfunction and various cardiovascular events in several populations [32]. CysC, a new and more reliable surrogate marker than Cr and Scr-based eGFR for early detection of renal impairment in patients with diabetes, has been reported to be was significantly associated with DPN [22, 33]. ABI, a useful marker for detection of peripheral artery disease (PAD) or atherosclerosis at other vascular sites [34], has been demonstrated to be independently associated with DPN [35]. In the present study, we have revealed that the T2DM subjects in the higher serum albumin quartiles exhibited higher levels of DBP, eGFR, ABI, and lower Cr, CysC, and ACR compared with subjects in the lowest quartile, and serum albumin levels were positively associated with DBP, and negatively with Cr, CysC, and ACR after the adjustments, indicating that serum albumin may be associated with DN and PAD as diabetic

micro- and macrovascular complications, respectively, which are consistent with those of many previous reports [15, 36-38]. Zhang et al. conducted a study of 188 patients with T2DM and biopsy-proven DN followed up for at least one year, and found that serum albumin level was significantly associated with proteinuria, renal function, and glomerular lesions, and hypoalbuminemia was associated with a poorer renal prognosis [36]. Another cross-sectional study of Japanese reported that patients with DN had a decrease in serum albumin concentration compared with those with non-DN [37]. Recently, Greenhagen and collaborators showed that US subjects with PAD had lower levels of serum albumin [15]. More recently reported data from the cross-sectional study of 10,900 Chinese hypertensive patients aged ≥18 years demonstrated that serum albumin levels were significantly inversely associated with the prevalence of PAD in men [38]. Together, our results and those findings of above previous studies may provide evidence that a negative association between serum albumin and DPN appears to be due to the systemic circulation damage, mainly caused by DN and PAD and accordingly adequate nutrition and blood supply of neurons and nerves in these individuals. However, the mechanism may warrant further investigation in larger databases and interventional studies.

Our study has several limitations that must be acknowledged. First, the cross-sectional design of our study likely does not reflect cause and effect. Thus, prospective studies are needed to confirm our findings. Second, we only evaluated UA, GGT, and CysC as parameters of oxidative stress, and NLR as marker of inflammation. Data about TNF-α, IL-6, GSH and 8-iso-prostaglandin F2α as classical inflammatory and oxidative stress markers is lacking in our study, which makes it difficult to draw definite and consistent conclusion that inflammation and oxidative stress may mediate the association of serum albumin with DPN. Third, although many confounding factors were adjusted in our study, it is possible that there are still some residual confounding and unmeasured factors, which may affect the true association between serum albumin and DPN. In spite of some limitations, our study has some strength, including a relatively large sample size and a thorough clinical and laboratory assessment and appropriate adjustment, which can raise the reliability of our findings.

Conclusions

Our data suggests that serum albumin is independently negatively associated with the prevalence of DPN, and inflammatory state, oxidative stress and diabetic vasculopathy associated with low serum albumin may be the main mechanisms of DPN in Chinese T2DM patients. Further larger and prospective studies are needed to provide a more convincible conclusion.

Abbreviations

DPN: diabetic peripheral neuropathy; T2DM: type 2 diabetes mellitus; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HbA1c: glycated hemoglobin A1c; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyltransferase; UA: uric acid; CysC: cystatin C; Cr, creatinine; NLR: neutrophil to lymphocyte ratio; RDW: red cell distribution width; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease

Epidemiology Collaboration; ACR: albumin- to-creatinine ratio; ABI: Ankle-brachial index; VPT: vibration perception threshold; SWM: Semmes-Weinstein monofilament; SD: standard deviation; ANOVA: one-way analysis of variance; Q: quartile; CI: confidence intervals; ROC: Receiver operating characteristic; NC: nerve conduction; CRP: c-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; GSH: glutathione; NF-κB: nuclear factor-κB; DN: diabetic nephropathy; PAD: peripheral arterial disease.

Declarations

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Authors' contributions

All the authors contributed significantly to the manuscript. PJY designed and conducted the study, analyzed and interpreted the data, drafted and critically revised the manuscript. QT and YRW significantly revised the draft, interpreted the data, and involved in data analyses. QW and ZHZ conducted the study, collected the information and participated in data interpretation. YX, JHZ, YM involved in the sample test, data management and draft revision. All authors read and approved the final manuscript.

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Availability of data and materials

The data is available upon reasonable request to the corresponding author.

Ethics approval and consent to participate

The study was approved by the ethics committee of the Affiliated Hospital of Southwest Medical University. Written informed consent was obtained before the data collection and analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of study participants according to serum albumin quartiles

Characteristics	Q1	Q2	Q3	Q4	*P*
	21.70–37.60	37.70–41.30	41.40–44.40	44.50–57.60	
	(n=368)	(n=364)	(n=367)	(n=366)	
Albumin (g/L)	34.44±3.10	39.63±1.01**	42.77±0.91**##	46.90±1.93**##&&	0.000
Male/Female	185/183	177/187	179/188	183/183	0.958
Age (years)	62.75±11.13	60.63±11.25	58.89±11.23**	57.36±11.02**##	0.000
BMI (kg/m^2)	23.05±3.40	24.57±4.21**	24.59±3.60**	24.73±3.48**	0.000
Diabetic duration (years)	8.72±7.18	8.20±6.45	7.18±6.07	6.90±5.81**#	0.002
SBP (mmHg)	133.95±22.22	132.54±21.13	132.61±21.14	131.45±19.25	0.434
DBP (mmHg)	70.58±11.73	71.54±12.46	71.99±11.81	73.84±12.40**#	0.004
FBG (mmol/L)	11.51±5.69	10.60±5.37	10.62±4.99	10.27±4.59*	0.022
HbA1c (%)	10.33±2.76	9.57±2.32**	9.28±2.43**	8.71±2.03**##&	0.000
TC (mmol/L)	4.50±1.59	4.68±1.14*	4.97±1.28**#	5.12±1.23**##	0.000
TG (mmol/L)	1.72±1.57	2.23±1.99**	2.46±2.25**	2.82±3.12**##	0.000
HDL-C(mmol/L)	1.13±0.34	1.14±0.36	1.19±0.36*	1.23±0.38**##	0.000
LDL-C(mmol/L)	2.65±1.15	2.66±0.84	2.82±0.98**	2.90±1.01**#	0.000
ALT (U/L)	21.09±28.78	21.49±21.53*	24.89±18.67**##	28.55±22.53**##	0.000
AST (U/L)	21.95±25.80	20.39±19.12	22.84±12.91**##	24.72±14.17**##&	0.000
GGT (U/L)	52.57±9.41	41.34±3.69	41.32±3.32**	45.89±3.79**##	0.000
UA (μmol/L)	301.08±109.62	315.02±109.23	320.45±111.20	336.07±105.73**#	0.000
CysC (mg/L)	1.28±1.83	1.00±0.48**	0.96±0.44**	0.90±0.35**	0.000
Scr (μmol/L)	88.26±69.78	72.94±43.66**	70.55±36.28**	66.44±32.78**	0.000
eGFR (mL/min/1.73 m^2)	83.08±32.07	91.13±24.54**	93.55±23.94**	97.37±21.16**#	0.000
ACR (mg/g)	650.66±78.72	219.82±43.84**	85.46±14.04**	68.84±16.31**##	0.000
NLR	4.48±0.24	3.20±0.11**	3.01±0.13**	2.85±0.11**	0.000

RDW	13.27±1.49	13.11±1.22	13.10±1.13	13.23±1.31	0.501
ABI	1.00±0.20	1.01±0.16	1.03±0.14	1.04±0.11	0.033
VPT (V)	21.95±12.87	16.61±9.54**	14.65±7.74**	13.24±7.00**##	0.000
DPN (n, %)	115 (31.25)	61 (16.76)**	36 (9.81)**	19 (5.19)**##	0.000

Data are mean ±standard deviation for continuous variables or n (percentage) for categorical variables. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil to lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; UA, uric acid; CysC, cystatin C; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; ACR, albumin- to-creatinine ratio; NLR, neutrophil to lymphocyte ratio; RDW, red cell distribution width; ABI, Ankle-brachial index; VPT, vibration perception threshold; DPN, diabetic peripheral neuropathy. $^{*}P<0.05$, $^{**}P<0.01$ compared with Q1; $^{\#}P<0.05$, $^{\#\#}P<0.01$ compared with Q2; $^{\&}P<0.05$, $^{\&\&}P<0.01$ compared with Q3

Table 2 Linear correlation analysis of variables associated with serum albumin in the entire population studied

Variable	r	*P*-value	Adjusted r	Adjusted *P*-value
Age	-0.165	0.000	-	-
Gender	-0.009	0.742	-	-
BMI	0.179	0.000	-	-
Diabetic duration	-0.086	0.001		
SBP	-0.036	0.170	-0.025	0.563
DBP	0.101	0.000	0.107	0.013
FBG	-0.076	0.004	-0.042	0.336
HbA1c	-0.238	0.000	-0.217	0.000
TC	0.216	0.000	0.167	0.000
TG	0.230	0.000	0.223	0.000
HDL-C	0.129	0.000	0.203	0.000
LDL-C	0.127	0.000	0.077	0.077
ALT	0.283	0.000	0.006	0.898
AST	0.261	0.000	-0.045	0.298
GGT	0.148	0.000	-0.091	0.036
UA	0.139	0.000	0.159	0.000
CysC	-0.184	0.000	-0.123	0.004
Scr	-0.126	0.000	-0.120	0.005
eGFR	0.183	0.000	0.084	0.053
ACR	-0.284	0.000	-0.338	0.000
NLR	-0.196	0.000	-0.154	0.000
RDW	-0.001	0.963	0.020	0.647
ABI	0.066	0.012	0.009	0.829
VPT	-0.313	0.000	-0.314	0.000
DPN	-0.278	0.000	-0.241	0.000

Table 3 Odds ratios and 95% confidence intervals for the risk of DPN according to serum albumin quartiles in the entire T2DM population

		DPN	
Serum albumin (g/L)	Model 1	Model 2	Model 3
Per SD increase	0.469 (0.404-0.544)	0.505 (0.429-0.595)	0.499 (0.385-0.645)
Quartiles of albumin			
Q1 (21.70–37.60)	1	1	1
Q2 (37.70–41.30)	0.443 (0.311-0.630)	0.485 (0.329-0.714)	0.683 (0.416-1.122)
Q3 (41.40–44.40)	0.239 (0.159-0.360)	0.298 (0.192-0.463)	0.475 (0.251-0.900)
Q4 (44.50–57.60)	0.120 (0.072-0.201)	0.174 (0.102-0.297)	0.311 (0.134-0.724)
P for trend	0.000	0.000	0.000
Q4 versus Q1, Q2, Q3	0.000	0.000	0.003

Model 1: unadjusted;

Model 2: adjusted for age, gender, BMI, and diabetic duration;

Model 3: adjusted for age, sex, BMI, diabetic duration, SBP, DBP, FBG, HbA1c, TC, TG , HDL-C, LDL-C, NLR, RDW, ALT, AST, GGT, UA, Scr, CysC, eGFR, ACR, and ABI.

Figures

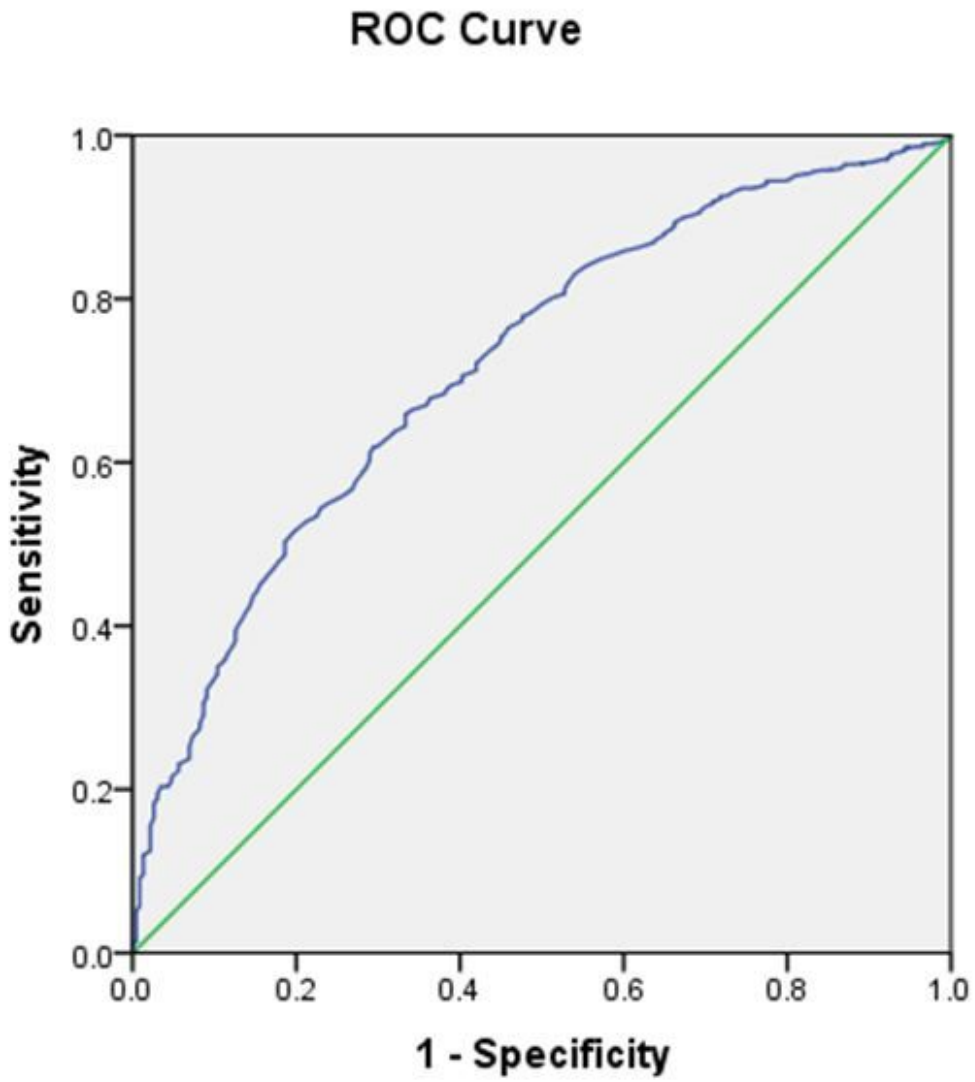

Figure 1

ROC analysis of serum albumin to indicate DPN for T2DM individuals. AUC = 0.720; 95% CI, 0.685–0.755; P <0.001; identified serum albumin cutoff value = 39.95 g/L; Youden index = 0.326; sensitivity: 65.88%; specificity: 66.7%.

Supplementary Files

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