# Elevated serum preptin concentrations in patients with diabetic nephropathy

Rui Wang,[1] Aili Xue,[2] Wenjian Zheng,[3] Linchuan Wang,[4] Fei Yan,[5] Wenchao Hu,[6] Jingna Lin,[7] Lanjie He[8]

For numbered affiliations see end of article.

**Correspondence to**
Dr Jingna Lin, Department of Endocrinology, Tianjin Union Medical Center, 190 Jieyuan Street, 300191, Tianjin, China; 13207628978@163.com and Dr Lanjie He, Department of Endocrinology, Qilu Hospital of Shandong University (Qingdao), 758 Hefei Road, Shibei District, 266035, Qingdao, China; helanjie@medmail.com.cn

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## ABSTRACT

Preptin is a peptide synthesized and secreted accompanied with insulin from pancreatic β cells. Here, we tested the hypothesis that serum preptin concentrations are correlated with diabetic nephropathy (DN). Our study was performed in a population of 234 patients with type 2 diabetes mellitus (T2DM) and 78 healthy subjects. Patients with T2DM were divided into three groups: normoalbuminuria group (DN0, n=106), microalbuminuria group (DN1, n=90), and macroalbuminuria group (DN2, n=38) according to urine albumin to creatinine ratio (ACR). Serum preptin concentrations were significantly increased in the three T2DM subgroups than those in the controls. DN2 group showed significantly higher serum preptin concentrations compared with DN0 and DN1 groups. Moreover, DN1 group had higher serum preptin concentrations than DN0 group. Serum preptin was correlated with a higher risk of T2DM and DN after logistic regression analysis. Simply linear regression analysis demonstrated a positive correlation between serum preptin and gender, body mass index (BMI), blood urea nitrogen, creatinine, ACR, and a negative correlation between serum preptin and glomerular filtration rate, metformin, acarbose treatment. Gender, BMI, and ACR were still positively correlated with serum preptin after multiple linear regression analysis. Our findings indicate that serum preptin concentrations are associated with renal function and DN.

## Significance of this study

**What is already known about this subject?**

- Preptin is a peptide synthesized and secreted accompanied with insulin from pancreatic β cells.
- Elevated preptin levels were observed in both patients with type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus.

**What are the new findings?**

- Macroalbuminuria group (DN2) showed significantly higher serum preptin concentrations compared with normoalbuminuria (DN0) and microalbuminuria (DN1) groups. Moreover, DN1 group had higher serum preptin concentrations than DN0 group.
- Serum preptin was correlated with a higher risk of T2DM and diabetic nephropathy (DN) after logistic regression analysis.
- Simply linear regression analysis demonstrated a positive correlation between serum preptin and gender, body mass index, blood urea nitrogen, creatinine, urine albumin to creatinine ratio, and a negative correlation between serum preptin and glomerular filtration rate, metformin, acarbose treatment.

**How might these results change the focus of research or clinical practice?**

- Serum preptin may be an indicator of DN in subjects with T2DM.

## INTRODUCTION

Diabetic nephropathy (DN), a chronic and progressive process leading to end-stage renal failure, has a prevalence of approximately 20%–40% in patients with diabetes.[1] Metabolic and hemodynamic alterations caused by hyperglycemia and hypertension are considered to be regulators in the pathogenesis of DN.[2] There are no effective treatments for DN except delaying the progression of DN or renal replacement therapies. Hence, it is essential to look for new biomarkers for early diagnosis and perform some reasonable treatments for patients at risk.

Preptin is a peptide of 34-amino acid synthesized and secreted accompanied with insulin from pancreatic β cells. Preptin is derived from its precursor called pro-insulin-like growth factor II.[3] Preptin acts as a physiological enhancer of glucose-mediated insulin release.[3] Elevated preptin levels were observed in both patients with type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM).[4 5]

Previous investigations have demonstrated the association of preptin with diabetes. However, no previous study focuses on the correlation between preptin with diabetic complication. Here, we tested the hypothesis that serum preptin concentrations are correlated with DN.

## MATERIALS AND METHODS

### Patients

The case group consisted of a consecutive population of 234 patients with T2DM. T2DM

**Table 1** Clinical characteristics of patients with T2DM and controls

| | | Patients with T2DM | | | |
|---|---|---|---|---|---|
| | Control | Normoalbuminuria | Microalbuminuria | Macroalbuminuria | P value |
| N | 78 | 106 | 90 | 38 | |
| Age (years) | 58.23±7.78 | 57.24±11.4 | 58.66±12.89 | 59.79±11.02 | 0.701 |
| Gender (M/F) | 46/35 | 58/521 | 49/46 | 21/19 | 0.911 |
| BMI (kg/m$^2$) | 25.71±2.87 | 26.09±4.03 | 26.37±3.56 | 26.22±3.06 | 0.512 |
| SBP (mm Hg) | 122.1±11.13 | 134.86±21.98* | 147.61±30.36*† | 157.13±23.43*†‡ | <0.001 |
| DBP (mm Hg) | 79.06±7.59 | 80.19±14.17 | 88±19.96*† | 86.13±13.03*† | 0.001 |
| HbA1c (%) | 4.76±0.31 | 7.82±1.44* | 8.07±1.19* | 7.88±1.66* | <0.001 |
| TG (mmol/L) | 2.08±1.61 | 1.9±1.11 | 2.07±1.6 | 2.07±1.13 | 0.626 |
| TC (mmol/L) | 5.24±0.91 | 5.11±1.08 | 5.44±1.19† | 5.37±1.02 | 0.115 |
| HDLC (mmol/L) | 1.49±0.25 | 1.12±0.24* | 1.13±0.21* | 1.17±0.33* | <0.001 |
| LDL-C (mmol/L) | 3.26±0.55 | 3.41±0.9 | 3.68±0.98* | 3.57±0.8 | 0.006 |
| BUN (nmol/L) | 5.4±1.18 | 5.33±1.6 | 5.95±1.99† | 8.75±4.01*†‡ | <0.001 |
| Cr (μmol/L) | 66.63±10.49 | 65.47±18.33 | 66.23±21.29 | 117.68±71.88*†‡ | <0.001 |
| ACR (mg/g) | – | 15.95±4.45 | 94.29±82.63† | >300†‡ | <0.001 |
| GFR (mL/min/1.73 m$^2$) | 101.82±11.96 | 110.17±39.56 | 108.59±33.16 | 69.44±35.74*†‡ | <0.001 |
| Preptin (ng/mL) | 177.68 (141.32–209.23) | 210.66 (163.51–246.38)* | 233.31 (186.57–260.41)*† | 266.84 (227.86–299.54)*†‡ | <0.001 |
| Treatment | – | 78 (73.6%) | 63 (70%) | 21 (55.3%) | |
| Metformin (n, %) | – | 53 (50%) | 48 (53.3%) | 15 (39.5%) | 0.108 |
| Acarbose (n, %) | – | 70 (66%) | 56 (62.2%) | 22 (57.9%) | 0.356 |
| Sulfonylureas (n, %) | – | 53 (50%) | 40 (44.4%) | 17 (44.7%) | 0.649 |
| DPP-IV (n, %) | – | 41 (38.7%) | 28 (31.1%) | 87 (47.4%) | 0.706 |
| Insulin (n, %) | | | | | 0.201 |

*Significant versus control subjects.
†Significant versus patients with T2DM with normoalbuminuria.
‡Significant versus patients with T2DM with microalbuminuria.
ACR, urine albumin to creatinine ratio; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; DPP-IV, dipeptidyl peptidase-IV; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

diagnosis was made based on the criteria recommended by the American Diabetic Association. Patients with T2DM were divided into three groups: normoalbuminuria group (DN0, urine albumin to creatinine ratio (ACR)<30 mg/g, n=106), microalbuminuria group (DN1, 30≤ACR≤300 mg/g, n=90), and macroalbuminuria group (DN2, ACR >300 mg/g, n=38) according to ACR. The exclusive criteria were as follows: severe cardiovascular diseases, malignant tumor, and acute infection. Seventy-eight healthy subjects who went to our hospital for health check-up were enrolled as the control group.

This study was approved by the Hospital ethics board and performed in compliance with the Declaration of Helsinki.

### Measurements

Blood specimen was drawn from all subjects after an overnight fast. Serum samples were assayed for preptin using an commercial ELISA kit (Phoenix Pharmaceuticals, USA).

### Statistical analysis

Data are expressed as means±SD or median (IQR). One-way analysis of variance , $\chi^2$ tests, or Kruskal-Wallis test were used to determine the group differences between the three T2DM subgroups and controls. Significant independent factors associated with T2DM and DN were identified by logistic regression analysis. Simple and multiple linear regression analysis were performed to indentify whether there was a correlation between serum preptin and other variables. Statistical significance was defined as $p<0.05$.

## RESULTS

### Patient variables

Systolic blood pressure (SBP) and HbA1c were higher, and high-density lipoprotein cholesterol was lower in T2DM groups compared with control subjects (table 1). In addition, DN2 group had significantly higher SBP, blood urea nitrogen (BUN) and creatinine (Cr), and lower glomerular filtration rate (GFR) than the other three groups (table 1).

### Serum preptin concentrations

As displayed in table 1, the three T2DM subgroups showed significantly elevated serum preptin concentrations compared with the control group. Serum preptin concentrations were significantly increased in DN2 group compared with those with DN0 and DN1 groups. Moreover, higher serum preptin concentrations were found in DN1 group than in DN0 group.

### The association of serum preptin concentrations with T2DM

Higher serum preptin concentrations were found in patients with T2DM than in the healthy controls (225.77

**Table 2** Logistic regression analysis for determining the risk factor of T2DM

| | Simple logistic regression | | Multiple logistic regression | |
|---|---|---|---|---|
| **Characteristics** | **OR (95% CI)** | **P value** | **OR (95% CI)** | **P value** |
| Age (years) | 1 (0.977 to 1.023) | 0.981 | – | – |
| Gender (M/F) | 1.252 (0.746 to 2.1) | 0.395 | – | – |
| BMI (kg/m$^2$) | 1.043 (0.968 to 1.124) | 0.272 | – | – |
| SBP (mm Hg) | 1.055 (1.036 to 1.073) | <0.001 | 1.081 (1.04 to 1.124) | <0.001 |
| DBP (mm Hg) | 1.028 (1.006 to 1.05) | 0.011 | 0.941 (0.892 to 0.993) | 0.027 |
| TG (mmol/L) | 0.957 (0.802 to 1.141) | 0.623 | – | – |
| TC (mmol/L) | 1.034 (0.812 to 1.315) | 0.788 | – | – |
| HDL-C (mmol/L) | 0.005 (0.001 to 0.019) | <0.001 | 0.001 (0.000 to 0.007) | <0.001 |
| LDL-C (mmol/L) | 1.54 (1.1 to 2.157) | 0.012 | 4.335 (2.128 to 8.829) | <0.001 |
| BUN (nmol/L) | 1.195 (1.031 to 1.384) | 0.018 | 1.188 (0.936 to 1.508) | 0.157 |
| Cr (μmol/L) | 1.009 (0.998 to 1.021) | 0.1 | – | – |
| GFR (mL/min/1.73 m$^2$) | 1.001 (0.993 to 1.009) | 0.802 | – | – |
| Preptin (ng/mL) | 1.018 (1.012 to 1.024) | <0.001 | 1.014 (1.005 to 1.022) | 0.001 |

BMI, body mass index ; BUN, blood urea nitrogen ; Cr, creatinine; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

(177.38 to 262.34) ng/mL vs 177.68 (141.32 to 209.23) ng/mL, p<0.001). Serum preptin was correlated with a higher risk of T2DM after simple and multivariate logistic regression analysis (table 2).

### The association of serum preptin concentrations with DN

Patients with T2DM with microalbuminuria and macroalbuminuria were considered to have DN. Patients with T2DM with DN showed higher serum preptin compared with those without DN (239.12 (198.69 to 275.09) ng/mL vs 196.88 (152.81 to 230.26) ng/mL, p<0.001). Serum preptin was correlated with a higher risk of DN after simple and multivariate logistic regression analysis (table 3).

### The correlation of serum preptin with other variables

As presented in table 4, serum preptin was correlated with gender (r=0.148, p=0.023), body mass index (BMI) (r=0.228, p<0.001), SBP (r=0.17, p=0.009), BUN (r=0.181, p=0.005), Cr (r=0.2, p=0.002), ACR (r=0.391, p<0.001), GFR (r=−0.176, p=0.007), metformin treatment (r=−0.169, p=0.01), and acarbose treatment (r=−0.15, p=0.022) after simple linear regression analysis. It showed that gender (β=0.195, p=0.003), BMI (β=0.252, p<0.001), and ACR (β=0.358, p<0.001) were still correlated with the serum preptin after a multiple linear regression analysis.

## DISCUSSION

Preptin is a peptide of 34-amino acid derived from its precursor called pro-insulin-like growth factor II.[3] Preptin is synthesized in pancreatic β cells and cosecreted together with insulin. Preptin enhanced glucose-mediated insulin secretion through the insulin-like growth factor 2 receptor. The infusion of antipreptin antibodies in isolated pancreas significantly inhibited glucose-mediated insulin secretion.[6] Furthermore, preptin regulated bone anabolism by

**Table 3** Logistic regression analysis for determining the risk factor of DN

| | Simple logistic regression | | Multiple logistic regression | |
|---|---|---|---|---|
| **Characteristics** | **OR (95% CI)** | **P value** | **OR (95% CI)** | **P value** |
| Age (years) | 1.013 (0.991 to 1.035) | 0.263 | – | – |
| Gender (M/F) | 1.127 (0.673 to 1.888) | 0.648 | – | – |
| BMI (kg/m$^2$) | 1.018 (0.949 to 1.091) | 0.625 | – | – |
| SBP (mm Hg) | 1.025 (1.013 to 1.036) | <0.001 | 1.019 (1.002 to 1.037) | 0.03 |
| DBP (mm Hg) | 1.03 (1.012 to 1.049) | 0.001 | 1.011 (0.984 to 1.04) | 0.416 |
| HbA1c (%) | 1.106 (0.917 to 1.335) | 0.292 | – | – |
| TG (mmol/L) | 1.111 (0.903 to 1.367) | 0.321 | – | – |
| TC (mmol/L) | 1.291 (1.012 to 1.647) | 0.04 | 1.22 (0.933 to 1.595) | 0.147 |
| HDL-C (mmol/L) | 1.348 (0.466 to 3.9) | 0.582 | | |
| LDL-C (mmol/L) | 1.329 (0.991 to 1.782) | 0.057 | | |
| BUN (nmol/L) | 1.349 (1.166 to 1.561) | <0.001 | 1.442 (1.161 to 1.791) | 0.001 |
| Cr (μmol/L) | 1.016 (1.005 to 1.027) | 0.005 | 1.002 (0.983 to 1.021) | 0.845 |
| GFR (mL/min/1.73 m$^2$) | 0.99 (0.983 to 0.998) | 0.014 | 1.009 (0.997 to 1.021) | 0.14 |
| Preptin (ng/mL) | 1.018 (1.012 to 1.025) | <0.001 | 1.014 (1.005 to 1.022) | 0.001 |

BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; DN, diabetic nephropathy; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

**Table 4** The correlation between serum preptin concentrations and various parameters

| | Simple regression analysis | | Multiple regression analysis | |
|---|---|---|---|---|
| **Parameters** | **r** | **P value** | **β** | **P value** |
| Age (years) | 0.053 | 0.419 | | |
| Gender (M/F) | 0.148 | 0.023 | 0.195 | 0.003 |
| BMI (kg/m$^2$) | 0.228 | <0.001 | 0.252 | <0.001 |
| SBP (mm Hg) | 0.17 | 0.009 | 0.052 | 0.394 |
| DBP (mm Hg) | 0.102 | 0.121 | | |
| HbA1c (%) | 0.086 | 0.19 | | |
| TG (mmol/L) | 0.127 | 0.052 | | |
| TC (mmol/L) | 0.101 | 0.124 | | |
| HDL-C (mmol/L) | 0.017 | 0.792 | | |
| LDL-C (mmol/L) | 0.075 | 0.253 | | |
| BUN (nmol/L) | 0.181 | 0.005 | −0.03 | 0.905 |
| Cr (μmol/L) | 0.2 | 0.002 | 0.079 | 0.501 |
| ACR (mg/g) | 0.391 | <0.001 | 0.358 | <0.001 |
| GFR (mL/min/1.73 m$^2$) | −0.176 | 0.007 | −0.05 | 0.559 |
| Treatment | | | | |
| Metformin | −0.169 | 0.01 | −0.098 | 0.171 |
| Acarbose | −0.15 | 0.022 | −0.027 | 0.701 |
| Sulfonylureas | −0.102 | 0.12 | | |
| DPP-IV | −0.104 | 0.114 | | |
| Insulin | −0.045 | 0.489 | | |

ACR, urine albumin to creatinine ratio; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; DBP, diastolic blood pressure; DPP-IV, dipeptidyl peptidase-IV; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

stimulating the proliferation of rat osteoblasts and osteoblast-like cell.[7]

Recent studies showed the correlation between preptin and diabetes. Elevated plasma preptin were found in T2DM subjects compared with impaired glucose tolerance (IGT) subjects and controls.[4] Our results also showed that higher serum preptin in patients with T2DM than in healthy controls. A investigation performed in patients with type 1 diabetes showed that patients with type 1 diabetes also had significantly increased preptin concentrations than in the controls.[8] In addition, GDM patients had elevated plasma, cord blood, and colostrum preptin than the control women.[4 9] However, another study demonstrated that there was no statistical difference in preptin between GDM patients and controls.[10] As for the status of prediabetes, IGT subjects had elevated serum preptin than subjects with normal glucose tolerance.[11] However, Yang *et al* reported that serum preptin concentrations showed no significant differences between IGT and healthy controls.[4] These conflicting results may be explained by different enrolled populations and different ELISA kits.

Preptin is shown to be correlated with cardiovascular disease. Plasma preptin levels of patients with carotid plaques were significantly lower than the patients without carotid plaques. This study also reported a significant correlation between plasma preptin and carotid intima-media thickness.[12] Li *et al* reported higher serum preptin level in the coronary artery calcification (CAC) patients when compared with the control group who had non-CAC.[13] In addition, preptin was positively correlated with CAC score.[13] These investigations focused on the macrovascular disease. This indicates that preptin may be correlated with diabetic macrovascular complication. Our results demonstrated that elevated serum preptin concentrations were correlated with DN and renal functional parameters. This is the first report about the correlation between serum preptin concentrations and diabetic microvascular complication.

Previous studies have showed the gender differences in preptin levels. There were higher serum preptin in female subjects compared with male subjects,[4 14] which is similar to our results. Moreover, serum preptin was correlated with metabolic syndrome characteristics including obesity,[15 16] hypertension,[4 11 12] and hyperlipidemia.[4 11] The present study also demonstrated that serum preptin concentrations were significantly associated with BMI and SBP. This confirms the important role of preptin in body metabolic mechanism.

Recent studies have demonstrated the significance of podocyte injury in the development and progression of DN. Podocyte hypertrophy, effacement, and apoptosis contribute to the podocyte injury and dysfunction.[17] Wnt signaling pathway plays an important role in podocyte dysfunction of DN.[18] Xiao *et al* reported that preptin promoted the proliferation and osteogenesis of osteoblast-like cells by activating Wnt/β-catenin signaling pathway.[19] Therefore, it is hypothesized that preptin may promote the odocyte dysfunction, the progression of albuminuria, and at last DN through Wnt/β-catenin pathway.

This study has several potential limitations. First, the conclusion is limited by relatively small sample size. Second, the cross-sectional nature of the data limited the strength of conclusion. We can only get the identification of association link.

In conclusion, serum preptin are correlated with renal function and DN.

**Author affiliations**
[1]Department of Blood Transfusion, Qilu Hospital of Shandong University (Qingdao), Qingdao, China
[2]Department of Infant Pediatrics, Women and Children Hospital of Qingdao, Qingdao, China
[3]Department of Geriatrics, Qingdao Haici Medical Treatment Group, Qingdao, China
[4]Department of General Dentistry, University of Rochester Eastman Institute for Oral Health Rochester, Rochester, New York, USA
[5]Department of Endocrinology, Shandong University Qilu Hospital, Jinan, China
[6]Department of Endocrinology, Qilu Hospital of Shandong University (Qingdao), Qingdao, China
[7]Department of Endocrinology, Tianjin Union Medical Center, Tianjin, China
[8]Department of Endocrinology, Qilu Hospital of Shandong University (Qingdao), Qingdao, China

**Contributors** JL and LH researched literature and conceived the study. RW, WZ, and WH were involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. FY collected and analyzed the data of the oral antidiabetes drug, and helped to answer the reviewer's question. RW wrote the first draft of the manuscript and LW revised the grammar of this manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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