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Serum levels of copeptin are associated with type 2 diabetes and diabetic complications in Chinese population

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ABSTRACT

Purpose: The aim of this study was to investigate copeptin levels in serum, and assess their associations with type 2 diabetes (T2DM) and diabetic complications.
Methods: In this post hoc analysis, serum levels of copeptin were tested in 306 patients with T2DM. Clinical information including diabetic retinopathy (DR) and diabetic nephropathy (DN) were collected. The relation of serum copeptin with DR and DN were investigated with the use of logistic regression models according to equal quartiles of the distributions of serum copeptin.
Results: We found that serum copeptin levels were significantly higher in diabetes as compared to normal controls [9.4(IQR, 7.4–12.5) pmol/L vs. 4.1(IQR, 2.5–6.2) pmol/L; $P < 0.0001$]. In multivariate analysis, there was an increased risk of T2DM associated with copeptin levels (OR 1.312, 95% CI: 1.204–1.403; $P < 0.0001$) after adjusting for possible confounders. After adjustment for possible confounders, serum copeptin levels were positively associated with the DR (odds ratio [OR], 1.117; 95% confidence interval [CI], 1.072–1.241; $P < 0.001$) and DN (OR, 1.259; 95% CI, 1.198–1.323; $P < 0.001$). Compared with the first quartile of serum copeptin levels, the ORs for DR and DN were as follows: second quartile, 1.19 (95% CI, 0.94–1.51, $P = 0.12$) and 1.37 (95% CI, 0.78–2.37, $P = 0.28$); third quartile, 1.61 (95% CI, 1.18–2.43, $P = 0.005$) and 2.12 (95% CI, 1.32–3.27, $P = 0.003$); fourth quartile, 2.83 (95% CI, 2.04–4.93; $P < 0.001$) and 3.48 (95% CI, 1.77–7.03; $P < 0.001$), respectively.
Conclusions: Using a post-hoc analysis our data show that elevated serum levels of copeptin are associated with type 2 diabetes and diabetic complications in Chinese population, suggesting a potential role of the AVP system (copeptin) in the pathophysiology of diabetes.

1. Introduction

Arginine vasopressin (AVP), which is also called antidiuretic hormone, is released from the neurohypophysis as a response to increased plasma osmolality and decreased blood volume (Enhörning, Bankir, Bouby, et al., 2013). However, investigation of the vasopressin system was limited so far due to the fact that vasopressin is unstable (half-life 5 to 15 minutes) and largely attached to platelets (Potocki, Breidthardt, Mueller, et al., 2010). An assay has been developed to measure plasma copeptin, the C-terminal portion of the precursor of AVP. Copeptin is considered to be a reliable and clinically useful surrogate marker for AVP (Morgenthaler, Struck, Alonso, & Bergmann, 2006). Due to the positive association of copeptin with the severity of illness and outcome, copeptin has been **shown to** relate with many acute illnesses, for instance, coronary artery disease (Tasevska, Enhörning, Persson, et al., 2016), recurrent cerebrovascular events (De Marchis, Weck, Audebert, et al., 2014), and acute stroke (Wendt, Ebinger, Kunz, et al., 2015).

Diabetes has become a major public health problem in China. In 2009, the age-standardized prevalences of total diabetes and prediabetes were 9.7% and 15.5%, respectively, accounting for 92.4 million adults with diabetes and 148.2 million adults with prediabetes (Liu, Du, Ma, et al., 2016). Previous studies in humans and animals have suggested a role for the copeptin in glucose homeostasis (Aoyagi, Birumachi, Hiroyama, et al., 2007), insulin resistance (Saleem, Khaleghi, Morgenthaler, et al., 2009), and diabetes mellitus (Enhörning, Wang, Nilsson, et al., 2010). In patients with poorly controlled diabetes mellitus, plasma AVP is markedly elevated (Zerbe, Vinicor, & Robertson, 1979), and in healthy subjects, AVP infusion leads to increased blood glucose levels (Spruce et al., 1985). Currently, no data are available on the role of copeptin in the Chinese patients with type 2 diabetes mellitus (T2DM). In this study, we aimed to investigate copeptin levels in serum, and to assess their associations with type 2 diabetes and diabetic complications.

Conflict of interest statement: The authors have no relevant potential conflicts of interest to declare.

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2. Method

We conducted a post-hoc cohort study at the First Hospital of Jiaxing, Jiaxing, China. From January 2015 to December 2015, three hundred and six patients with long-standing type 2 diabetes mellitus were recruited for this study. Diabetes was defined as self-report of a previous diagnosis of the disease by a clinician (excluding gestational diabetes mellitus) or hemoglobin A1c (HbA1C) of 6.5% or greater (AmericanDiabetes Association, 2010). We excluded patients with malignant tumor, cardiovascular and cerebrovascular diseases, a history of epilepsy or glaucoma, a history of recent surgery or trauma during the preceding 2 months, renal insufficiency (creatinine > 1.5 mg/dl), systemic infections at study enrollment, autoimmune diseases with or without immunosuppressive therapy. Participants who had no light perception or severe visual impairment in both eyes or had a severe infection in one or both eyes were excluded.

Two hundred age and gender-matched healthy volunteers were assigned as the healthy control group. The median age of controls included in this study was 64 (IQR, 55–70) years and 48% were women. The study followed the tenets of the Declaration of Helsinki and was approved by the Institute ethics committee of the First Hospital of Jiaxing, with written informed consent obtained from each participant.

We requested individual participant data regarding sex, age, ethnicity, waist, body mass index (BMI), diabetes duration, systolic and diastolic blood pressure, cigarette smoking status, daily insulin dose, and current drug use of diabetes, antihypertensive, and lipid-lowering medications. The information about diabetic retinopathy (DR, was defined as the presence of 1 or more retinal microaneurysms or retinal blot hemorrhages with or without more severe lesions using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading standards) (Man, Zhang, Yu, et al., 2015) and diabetic nephropathy (DN, was diagnosed clinically based on the following criteria: persistent albuminuria > 300 mg/24 h in at least two of three consecutive 24-h urine collections, presence of retinopathy, and no evidence of other kidney or renal tract disease) (Hansen, Tarnow, Thiel, Steffensen, et al., 2004) were also collected.

All investigations were performed in the morning after an overnight fast. Venous blood was drawn with minimal stasis from an antecubital vein. Clotted blood was centrifuged within 1 h and serum stored at −80 °C. HbA1c was measured by high-performance liquid chromatography (HLC-723 G7; TOSHO, Japan) with a normal range of 4–6%. Copeptin was measured in a single batch with a commercial sandwich immunoluminometric assay (B.R.A.H.M.S. LUMItest CT-proAVP, B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany). In our study, the lower detection limit was 0.5 pmol/L and the functional assay sensitivity (<20% inter assay CV) was <1 pmol/L. Median copeptin levels in 200 healthy individuals was 3.8 pmol/l and the 97.5th percentile was 16.0 pmol/L. The median in healthy individuals using this modification was similar as published in other studies (3.9 pmol/L in Zhang, Yin, Zhang, et al., 2013 and 3.7 pmol/L in Katan, Fluri, Morgenthaler, et al., 2009). Other biochemical parameters (triglyceride, cholesterol, low and high density lipoprotein, insulin, fasting blood-glucose [FBG] and C-reactive protein [CRP]) were assessed using ROCHE COBASC311 (ROCHE, Basel, Switzerland).

Results are expressed as percentages for categorical variables and as medians (interquartile ranges, IQRs) for the continuous variables. Proportions were compared using the $\chi 2$ test, and the Mann–Whitney test to compare continuous variables between groups. Spearman analysis was used for bivariate correlations. The relation of serum copeptin with DR and DN were investigated with the use of logistic regression models according to equal quartiles of the distributions of serum copeptin, after adjusting for the main baseline variables, such as, sex, age, ethnicity, waist, BMI, diabetes duration, systolic and diastolic blood pressure, cigarette smoking status, daily insulin dose, current drug use of diabetes, antihypertensive, and lipid-lowering medications, blood levels of triglyceride, cholesterol, low and high density lipoprotein, insulin, FBG, HbA1c and CRP. Results were expressed as adjusted OR (odds ratios) with the corresponding 95% CIs (Confidence interval). Receiver operating characteristic (ROC) curves were utilized to evaluate the accuracy of copeptin and other biomarkers to diagnose diabetes mellitus. Thereby the area under the receiver operating characteristic curve (AUC) is a summary measure over criteria and cut-point choices. All statistical analysis was performed with SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Table 1
Baseline Characteristics of Normal Controls and Subjects with DM.

Characteristics	Diabetes	Normal Controls	P[♯]
N	306	200	
Age at baseline (IQR, years)	64(54–70)	64(55–70)	NS
Ethnicity-Han, n(%)	284(92.8)	184(92.0)	NS
Male (%)	52.0	52.0	NS
Waist, (IQR, cm)	85(74–98)	80(69–88)	<0.05
BMI (IQR, kg/m2)	28.2(26.0–29.4)	26.0(24.8–27.5)	<0.05
Systolic blood pressure (IQR, mmHg)	148(127–168)	122(105–130)	<0.01
Diastolic blood pressure (IQR, mmHg)	95(84–103)	82(75–88)	<0.01
Smoking status, n (%)	85(27.8)	52(26.0)	NS
Family history of DM, n (%)	15(4.9)	10(5.0)	NS
Diabetes duration (IQR, years)	11(7–16)	–	–
Use of insulin treatment, n (%)	211(69.0)	–	–
Blood pressure treatment, n (%)	115(37.6)	–	–
Use of lipid-lowering medication, n (%)	117(38.2)	–	–
Laboratory findings(IQR)			
HbA1c (%)	7.2(6.3–8.3)	5.2(4.6–5.8)	<0.001
FBG(mmol/L)	8.2(6.3–9.9)	5.0(4.2–5.7)	<0.001
Total cholesterol (mmol/L)	4.88(4.16–5.75)	4.32(3.61–5.02)	<0.05
Triglycerides (mmol/L)	1.64(1.10–2.21)	1.18(0.85–1.75)	<0.01
LDL-cholesterol (mmol/l)	3.05(2.12–3.89)	3.12(2.06–3.76)	NS
HDL-cholesterol (mmol/l)	1.26(0.99–1.65)	1.52(1.33–1.78)	<0.01
CRP(mg/L)	2.12(1.25–4.03)	1.32(0.84–2.33)	<0.001
Insulin(mU/L)	13.2(7.2–18.5)	7.2(4.5–9.0)	<0.001
Copeptin(pmol/L)	9.4(7.4–12.5)	4.1(2.5–6.2)	<0.0001
Diabetic complications, n (%)			–
DR	71(23.2)	–	–
DN	80(26.1)	–	–

Results are expressed as percentages or as medians (IQR); DM, Diabetes Mellitus; BMI, body mass index; CRP, C-reactive protein; FBG, fasting blood-glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; DR, diabetic retinopathy; DN, diabetic nephropathy.
[♯] P values were compared by Mann–Whitney *U* test or chi-square test as appropriate.

3. Results

3.1. Main finding

In our study, a total of 306 patients with T2DM were included. The median age of patients included in this study was 64 (IQR, 54–70) years and 52.0% were men. In those patients, the median duration of diabetes on admission was 11 years (IQR, 7–16). A total of 15 patients (4.9%) had a family history of DM, and 211(69.0%) received insulin treatment. Clinical characteristics of the diabetic patients and controls were summarized in Table 1.

There was a modest positive correlation between levels of **copeptin** and HbA1c in patients with DM (*r[spearman]* = 0.396, $P < 0.0001$). Further, positive trends were also found between copeptin and FBG ($P = 0.001$), CRP ($P = 0.012$). In addition, there was a positive correlation between levels of **copeptin** and BMI in patients with DM ($r = 0.288$, $P < 0.0001$) or in the normal controls($r = 0.246$, $P < 0.001$). Statistical analysis here revealed no influence of sex, age, ethnicity, waist, diabetes duration, systolic and diastolic blood pressure, or daily insulin dose on copeptin levels($P > 0.05$, respectively).

3.2. Copeptin and DM risk

We found that serum copeptin levels were significantly higher in diabetes as compared to normal controls [9.4(IQR, 7.4–12.5) pmol/L