Molecular and Cellular Endocrinology 442 (2017) 106–112

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Elevated plasma levels of copeptin linked to diabetic retinopathy in type 2 diabetes

Qi Zhao*, Xiao-Xuan Wu, Jun Zhou, Xiao Wang

Department of Ophthalmology, The Second Hospital of Dalian Medical University, Dalian 116023, Liaoning Province, China

ARTICLE INFO

Article history:
Received 7 August 2016
Received in revised form
17 November 2016
Accepted 7 December 2016
Available online 8 December 2016

Keywords:
Copeptin
Diabetes mellitus
Diabetic retinopathy
Vision-threatening diabetic retinopathy

ABSTRACT

Background: The arginine vasopressin (AVP) system has been postulated to play a role in glucose homeostasis, insulin resistance, and diabetes mellitus in human and animal studies. The aim of this study was to evaluate the role of plasma copeptin in Chinese patients with type 2 diabetes mellitus (T2DM) with and without diabetic retinopathy (DR).

Method: Plasma copeptin concentrations were determined in 281 patients with T2DM. At baseline, demographic and clinical information including presence of DR and vision-threatening DR (VTDR) was collected. The relationship between copeptin and DR or VTDR was investigated using logistic regression.

Results: T2DM participants with DR or VTDR had significantly higher plasma copeptin concentrations on admission ($P < 0.0001$). Receiver operating characteristics to predict DR and VDTR demonstrated areas under the curve for copeptin of 0.784 (95% confidence interval [CI] 0.724–0.844) and 0.834 (95% CI 0.781–0.904), respectively, which were superior to those for the homeostasis model assessment of insulin resistance (DR AUC 0.736, 95% CI 0.676–0.797; VTDR AUC 0.754, 95% CI 0.703–0.828; $P < 0.01$). Multivariate logistic regression analysis adjusted for common DR risk factors showed plasma copeptin concentrations ≥28.6 pmol/L (>3rd quartile) to be an independent marker of DR (OR 3.68, 95% CI 2.04–6.79; $P < 0.0001$) and VTDR (OR 4.32, 95% CI 2.12–8.14; $P < 0.0001$).

Conclusions: We found that increased plasma copeptin concentrations were an independent marker of DR and VDTR in Chinese patients with T2DM, suggesting a possible role of copeptin in the pathogenesis of DR complications.

1. Introduction

One of the major complications in patients with diabetes mellitus (DM) is diabetic retinopathy (DR), a leading cause of blindness worldwide. DR causes visual impairment as a result of long-term accumulated damage to the small blood vessels in the retina (Ahsan, 2015). The prevalence of DR is expected to increase, and the number of people at risk of vision loss is predicted to double by the year 2030 with the progression of the DM epidemic (Wild et al., 2004). Liu et al. (2010). found that 14.8% of urban Chinese type 2 diabetes mellitus (T2DM) outpatients suffered from DR. The issue of DR has aroused public concern because nearly 100 million Chinese adults suffer from DM (Yang et al., 2010). It is now known that duration of DM and degree of hyperglycemia play a key role in DR, but maintenance of normoglycemia does not always completely prevent its development. Thus, additional factors related to the diabetic state are postulated to have a causal role in this disorder.

Cardiovascular disease (CVD) is the leading cause of death in patients with T2DM (Taylor et al., 2013). Arginine vasopressin (AVP) is released from the neurohypophysis to promote renal water conservation, and plays an important role in the regulation of the cardiovascular system, water-electrolyte balance and many functions of the central nervous system (Faraco et al., 2014). The AVP system has been postulated to play a role in glucose homeostasis, insulin resistance, lipid and fat metabolism, and T2DM in human and animal studies (Spruce et al., 1985; Hiroyama et al., 2009; Bankir et al., 2001).

Investigations into the AVP system are limited by the fact that AVP is unstable (half-life 5–15 min) and largely attached to platelets (Zhang et al., 2013). Plasma carboxy-terminal provasopressin (copeptin), a surrogate marker for AVP, is stable in serum and plasma, making it a more convenient biomarker. Copeptin

* Corresponding author. No. 467 Zhongshan Road, Dalian 116023, Liaoning Province, China.
E-mail address: pgrosexj91@126.com (Q. Zhao).

http://dx.doi.org/10.1016/j.mce.2016.12.003
0303-7207/

concentrations are elevated in T2DM (Enhörning et al., 2013) and have been associated with the development of DM (Wannamethee et al., 2015; Then et al., 2015). Elevated copeptin has been associated with CVD eventsandmortalityin patients with T2DM complicated by end stage renal disease (Fenske et al., 2011) or acute myocardial infarction (Mellbin et al., 2010) as well as those treated in primary care (Riphagen et al., 2013) and those in the general population (Enhörning et al., 2015). Interestingly, Wang et al. (2016). found that copeptin concentrations may reliably predict short-term stroke prognosis at its onset in Chinese patients with T2DM and stroke. In another study on Chinese patients, Zhu et al. (2016). report elevated serum copeptin concentrations to be associated with T2DM and diabetic complications. However, the role of copeptin in DR is not fully understood. In this study, we therefore evaluated the role of plasma copeptin concentrations in Chinese patients with T2DM, with and without DR.

2. Patients and methods

We conducted a cohort study at the Department of Endocrinology of the Second Hospital of Dalian Medical University, China. From January 2015 to March 2016, all patients with T2DM were recruited for the study. T2DM was defined according to the criteria of the American Diabetes Association for the diagnosis of DM (i.e. a glycated hemoglobin [HbA1c] level $\geq$ 6.5% or a fasting plasma glucose [FPG] $\geq$ 7.0 mmol/l). Fasting was defined as no calorie intakes for at least 8 h. Participants were carefully screened to identify metabolic conditions other than T2DM that are known to influence body composition and the immune system. We excluded patients with a malignant tumor, a history of recent surgery or trauma in the preceding 3 months, CVD in the past 3 months, renal insufficiency (creatinine>1.5 mg/dl), febrile disorders, recent or ongoing infection, or autoimmune diseases with or without immunosuppressive therapy. Patients who had no light perception or severe visual impairment in both eyes or had a severe infection in one or both eyes were also excluded.

One hundred participants without T2DM were recruited during the same period from the Physical Examination Center at our hospital, and matched with the T2DM participants for sex, age and body mass index (BMI). Any non-T2DM participants with fasting glucose >6.1 mmol/l at either of time points were excluded. The study followed the tenets of the Declaration of Helsinki and was approved by the institute ethics committee of the Second Hospital of Dalian Medical University, with written informed consent obtained from each participant.

At baseline, the following demographic and clinical data were taken: gender, age, BMI, systolic and diastolic blood pressure, diabetes duration, presence and severity of DR, diabetic macular edema (DME) status, history of conventional risk factors (hypertension, hyperlipoproteinemia, CVD events, smoking habits and alcohol abuse), and treatments (insulin, lipid-lowering and blood pressure-lowering).

We used the Canon CR6-45NM ophthalmic digital imaging system and a Canon EOS 10D digital camera (Canon, Tokyo, Japan) to take two digital images per eye through a nonpharmacologically dilated pupil. DR was defined as the presence of one or more retinal microaneurysms or retinal blot hemorrhages with or without more severe lesions, using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading standards (ETDRSRG, 1991). A DR severity score was assigned to each eye according to the modified Airlie House Classification system (Feman et al., 1995). DR severity was classified as non-proliferative diabetic retinopathy (NPDR; levels 20–53) or proliferative diabetic retinopathy (PDR; levels$\geq$60). DME was defined as present or absent and classified as with or without clinically significant DME and vision-threatening diabetic retinopathy (VTDR) was defined as the presence of PDR and/or DME.

All blood samples were collected on the first day of admission from participants in a fasting state, and copeptin was measured in accordance with standard detection methods in the biochemistry department of this hospital as follows. Blood was obtained from indwelling venous catheter and the plasma frozen at −70 °C. Measurements were taken in a single batch with a commercial sandwich immunoluminometric assay (B.R.A.H.M.S LUMI test CT-proAVP, B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany) as previously described (Morgenthaler et al., 2006). The lower detection limit was 0.5 pmol/l and the line range was 0.5–100 pmol/l. The intra- and inter-assay coefficients of variation were 2.4–4.5% and 3.2–6.0%, respectively. Results of routine blood analyses, includingHbA1c, high-sensitivity-C-reactive protein (Hs-CRP), insulin, fasting glucose, cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were obtained using routine laboratory methods. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated from fasting blood glucose and fasting serum insulin concentrations using the formula: HOMA-IR = fasting serum insulin (μU/ml) × fastingblood glucose (mmol/l)/22.5.

Results were expressed as percentages for categorical variables and as medians (interquartile ranges, IQRs) for the continuous variables. Univariate data on demographic and clinical features were compared by Mann-Whitney *U*-test or Chi-Square test as appropriate. Correlations among continuous variables were assessed by the Spearman rank-correlation coefficient. The relationship between copeptin levels and HOMA-IR was also analyzed by stepwise multiple regression analysis. To investigate whether copeptin allows predicting of both DR and VTDR in diabetes different statistical methods were used. First, the relation of copeptin with the two points was investigated with the use of logistic regression models. We used crude models and multivariate models adjusted for all significant predictors and report odds ratios (ORs). For multivariate analysis, we included confounders, known risk factors, and other predictors as assessed in univariate analysis. Second, receiver operating characteristic curves (ROC) was used to test the overall predict accuracy of copeptin and other markers, and results were reported as area under the curve (AUC). All statistical analysis was performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) and the ROCR package (version 1.0–2), which is available from CRAN repository (http://cran.r-project.org/). Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Patient characteristics

In this study, data from 281eligible patients with T2DM were analyzed. The median age of the patients was 61(IQR 55–69) years and 55.9% were men. The median diabetes duration was 12.0 (IQR 7.0–15.0) years. The median copeptin concentration in 100 non-T2DM individuals was 4.3 pmol/l and the 97.5th percentile was 17.5 pmol/l. Of the 281 T2DM participants, 124 were using insulin while 201 were taking oral hypoglycemic agents. Among the T2DM participants, DR was found in 79 cases (28.1%), with 37 classified as VTDR (13.2%). T2DM participants in the DR group had higher HbA1c, Hs-CRP, fasting glucose, BMI, CVD events, HOMA-IR and diabetes duration than those without DR ($P < 0.05$). Sex, age, smoking frequency, and blood pressure were comparable between the two groups ($P > 0.05$). Significantly more T2DM participants with DR than without DR received intensive glucose treatment ($P < 0.05$). Basal characteristics of the study participants are provided in Table 1.