Journal of Diabetes and Its Complications 29 (2015) 350–355

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Relationship between serum C-peptide level and diabetic retinopathy according to estimated glomerular filtration rate in patients with type 2 diabetes

Jin Ook Chung, Dong Hyeok Cho, Dong Jin Chung, Min Young Chung *

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chonnam National University Medical School, 8 Hak-Dong, Dong-Gu, Gwangju, 501-757, Republic of Korea

ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 22 December 2014
Accepted 23 December 2014
Available online 30 December 2014

Keywords:
C-peptide
Diabetic retinopathy
Glomerular filtration rate
Peptide hormones
Type 2 diabetes mellitus

ABSTRACT

Objective: To test the hypothesis that serum C-peptide level would relate to the risk of diabetic retinopathy (DR) in type 2 diabetic patients independently of estimated glomerular filtration rate (eGFR).
Design: A total of 2,062 patients with type 2 diabetes were investigated in this cross-sectional study. Fasting C-peptide, 2-hour postprandial C-peptide, and ΔC-peptide (postprandial C-peptide minus fasting C-peptide) levels were measured. The patients were divided into two groups according to eGFR ($ml \cdot min^{-1} 1.73\ m^{-2}$): patients without renal impairment (eGFR ≥60) and those with renal impairment (eGFR <60).
Results: In subjects both with and without renal impairment, patients with DR showed lower levels of fasting C-peptide, postprandial C-peptide and ΔC-peptide. In multivariate analysis, serum C-peptide levels were significantly associated with DR (odds ratio [OR] of each standard deviation increase in the logarithmic value, 0.85; 95% confidence interval [CI], 0.78–0.92 for fasting C-peptide, $P < 0.001$; OR, 0.87; 95% CI, 0.82–0.92 for postprandial C-peptide, $P < 0.001$; OR, 0.88; 95% CI, 0.82–0.94 for ΔC-peptide, $P < 0.001$) after adjustment for age, gender, and other confounding factors including eGFR.
Conclusions: Serum C-peptide levels are inversely associated with the prevalence of DR in type 2 diabetic patients independently of eGFR.

1. Introduction

Diabetic retinopathy is a common complication of diabetes and a leading cause of vision loss (Fong, Aiello, Ferris, & Klein, 2004). In addition to its adverse effects on vision, diabetic retinopathy might be associated with an increased risk of systemic vascular complications and mortality in patients with type 2 diabetes mellitus (DM) (Cheung, Mitchell, & Wong, 2010). Although hyperglycemia plays a central role in the development of diabetic retinopathy, intensive glycemic control cannot eliminate the risk of diabetic retinopathy, suggesting other mechanisms may also be at play (Cheung et al., 2010).

C-peptide, the 31 amino-acid residues formed during cleavage of insulin from proinsulin, is co-secreted from pancreatic beta cells in equimolar amounts with insulin and has long been considered an inactive by-product of insulin biosynthesis (Johansson et al., 2002; Wahren et al., 2004). However, recent evidence suggests that C-peptide may act as a hormonally active peptide with potentially important physiological effects (Johansson et al., 2002; Wahren et al., 2004). Several studies have reported that C-peptide might have beneficial effects on diabetic retinopathy in patients with type 2 DM (Inukai, Matsutomo, Tayama, Aso, & Takemura, 1999; Kim, Jung, Mok, Kang, & Kim, 2012; Yoon et al., 2012; Zheng, 2011). However, these studies have been limited to individuals with type 2 DM without renal impairment, and a relationship between C-peptide and retinopathy in association with renal function has not been fully understood.

Since C-peptide is extracted negligibly by the liver and the kidney is the major site for the catabolism and excretion of C-peptide, serum C-peptide level might be increased disproportionately despite reduced secretory beta cell function in patients with renal impairment (Brier et al., 1997; Regeur, Faber, & Binder, 1978). Thus it is important to examine whether altered serum C-peptide level according to renal function might have a physiologic impact on the retina in patients with type 2 DM. However, clinical utility of C-peptide is not often considered where there is renal impairment. For that reason, we sought to examine the relationships of serum C-peptide level with diabetic retinopathy according to estimated glomerular filtration rate (eGFR) in patients with type 2 DM. We tested the hypothesis that C-peptide would relate to the risk of diabetic retinopathy independently of renal function.

Conflicts of interest: The authors declare no conflict of interest.

* Corresponding author. Tel.: +82 62 220 6500; fax: +82 62 225 8578.
E-mail addresses: mychung@chonnam.ac.kr, jrjjo222@gmail.com (M.Y. Chung).

http://dx.doi.org/10.1016/j.jdiacomp.2014.12.013
1056-8727/

2. Patients and methods

2.1. Subjects

This study was conducted from January 2013 to June 2014. A total of 2,062 patients with type 2 DM were randomly selected from patients who visited the diabetes clinic of our hospital in this cross-sectional study. Type 2 DM was diagnosed according to the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Patients testing positive for autoantibody to glutamic acid decarboxylase, history of glucocorticoid use, alcoholism, chronic liver disease, acute kidney injury, pancreatitis, infection, or malignancy, with a continuous requirement of insulin within 1 year of diagnosis, and prior dialysis or renal transplantation were excluded. History and physical examinations including measurements of blood pressure, height, and body weight were conducted. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Hypertension was diagnosed if the patient had a blood pressure greater than 140/90 mmHg or used antihypertensive drugs. Hyperlipidemia was defined as serum concentrations of total cholesterol ≥ 6.5 mmol/l and/or triglycerides ≥ 2.3 mmol/l, or use of lipid lowering agents. Clinical data regarding diabetes duration, cigarette smoking, and other health-related variables were obtained using a standardized questionnaire. The study was approved by the local ethics committee. All participants gave informed consent.

2.2. Measurements

Venous blood samples were drawn from the antecubital vein without taking insulin or oral hypoglycemic agents (OHA) between 8:00 and 10:00 am after an overnight fast, but the antidiabetic drugs were continued until 1 day before the blood test to prevent hyperglycemia.

After an overnight fast, blood samples were taken, and patients were allowed to eat a standardized meal, calculated on the basis of the body weight (10 kcal/kg; carbohydrate 60%, protein 20%, and fat 20%) according to the Korean Diabetes Association recommendations (Ahn et al., 2010). Blood samples for the measurements of glucose and C-peptide level were taken 2 hours after a standardized meal. Delta C-peptide level was calculated as the postprandial serum C-peptide level minus the fasting C-peptide level. The plasma glucose was measured by the hexokinase method (Daiichi, Tokyo, Japan). Serum C-peptide level (Biosource Europe SA, Nivelles, Belgium) was measured by radioimmunoassay with an intra- and inter-assay coefficient of variation of 3.3% and 7.1%, respectively. The serum insulin level was measured using IRMA kit (Dainabot, Tokyo, Japan). The indices of insulin resistance were calculated as follows (Muniyappa, Lee, Chen, & Quon, 2008): the homeostasis model assessment of insulin resistance (HOMA-IR) = [insulin (μU/ml)xglucose (mmol/l)]/22.5. Glycated hemoglobin (HbA_{1c}) was measured using ion exchange liquid chromatography using an HLC-723-GHbV apparatus (Tosoh, Tokyo, Japan). Levels of total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), and triglycerides were measured using an AU5400 apparatus (Olympus, Tokyo, Japan). High-sensitivity C-reactive protein (hs-CRP) was measured (Dade-Behring, Marburg, Germany). Urinary albumin excretion was determined in random urine samples using urinary albumin: creatinine (Cr) ratio (UACR). Urinary albumin concentration was measured using an immunoturbidimetric commercial kit (Randox, Antrim, UK). Serum creatinine was measured by the Jaffe method, which was calibrated to isotope dilution mass spectrometry. The estimated glomerular filtration rate was calculated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009):

$$\mathrm{eGFR}\left(\mathrm{ml}\cdot\mathrm{min}^{-1}1.73\mathrm{m}^{-2}\right)_{\mathrm{male}} =$$
$$\mathrm{Sc_r}\le 80\ \mu\mathrm{mol/l} : 141\times(\mathrm{Sc_r}/80)^{-0.411}\times 0.993^{\mathrm{age}}$$
$$\mathrm{Sc_r}>80\ \mu\mathrm{mol/l} : 141\times(\mathrm{Sc_r}/80)^{-1.209}\times 0.993^{\mathrm{age}}$$
$$\mathrm{eGFR}\left(\mathrm{ml}\cdot\mathrm{min}^{-1}1.73\mathrm{m}^{-2}\right)_{\mathrm{female}} =$$
$$\mathrm{Sc_r}>62\ \mu\mathrm{mol/l} : 144\times(\mathrm{Sc_r}/62)^{-0.329}\times 0.993^{\mathrm{age}}$$
$$\mathrm{Sc_r}>62\ \mu\mathrm{mol/l} : 144\times(\mathrm{Sc_r}/62)^{-1.209}\times 0.993^{\mathrm{age}},$$

where Sc_r denotes serum creatinine level. The patients were divided into two groups according to eGFR ($ml{\cdot}min^{-1}1.73\ m^{-2}$): patients without renal impairment (eGFR ≥60) and those with renal impairment (eGFR <60). To evaluate retinopathy, an ophthalmologist performed fundoscopy following pupil dilation. The patients were classified into the following three categories: (1) no diabetic retinopathy (DR), (2) nonproliferative diabetic retinopathy (NPDR), and (3) proliferative diabetic retinopathy (PDR). In the present study, diabetic retinopathy was NPDR or PDR. A sample of retinal photographs in 210 randomly selected cases in this study was re-graded in a masked manner in order to assess the internal validity of the grading process. The intragrader repeatability kappa score was 0.94 (excellent).

2.3. Statistical analyses

Data were expressed as the mean ± standard deviation, unless otherwise stated. Variables with skewed distributions were log_{10}-transformed before analysis and are expressed as a geometric mean (95% CI). For statistical analysis, the chi-squared test was used for categorical variables, while a Student's t-test or Mann–Whitney U test was used for continuous variables. Analysis of covariance (ANCOVA) after adjustment for other covariates was performed to compare mean C-peptide levels according to the severity of diabetic retinopathy. Using the logistic regression model, multivariable analyses were performed to analyze the association of C-peptide with retinopathy with identified independent variables and factors previously reported to have independent associations. Because of skewed C-peptide distributions, the odds ratios were computed for a 1 standard deviation increase in the logarithmic value of C-peptide. Oral hypoglycemic agent (OHA) and insulin use were coded as dummy variables in the adjustment for anti-diabetic therapy. Age, BMI, HbA_{1c}, diabetes duration, hypertension, hyperlipidemia, anti-diabetic therapy, UACR, and eGFR were selected as covariates as they were significantly associated with diabetic retinopathy in the univariable analysis. hs-CRP, a chronic low-grade inflammation marker, was also included as a covariate, as this has previously been shown to relate to the risk of diabetic retinopathy (Cheung et al., 2010). Gender was also considered as a covariate. A test of interaction was conducted between C-peptide level and other covariates in the multivariable model. There was no significant interaction between C-peptide level and any of the covariates (P for interaction > 0.05). Model 1 was adjusted for age and gender. Model 2 included the model 1 variables plus BMI, hypertension, hyperlipidemia, HbA_{1c}, diabetes duration, hs-CRP and anti-diabetic therapy. Model 3 included all of the model 2 variables plus UACR and eGFR. Statistical analyses were performed using SPSS software version 17.0 (SPSS, Chicago, IL USA). A P-value < 0.05 was considered statistically significant.

3. Results

The clinical characteristics of the subjects with type 2 DM in this study are summarized in Table 1. Subjects with impaired renal function were older, had longer diabetes duration, higher systolic blood pressure, higher hs-CRP levels, and lower levels of total