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Original article

Variability of fasting plasma glucose and the risk of painful diabetic peripheral neuropathy in patients with type 2 diabetes

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ABSTRACT

Aim. – The relationship between glycaemic variability and painful diabetic peripheral neuropathy (PDPN) in patients with type 2 diabetes (T2D) is unclear. The aim of this study was to investigate whether variations in fasting plasma glucose (FPG), as represented by the coefficient of variation (CV), were associated with the risk of PDPN in patients with T2D.
Methods. – This case-control, retrospective study was conducted at a tertiary care hospital in Taiwan. We enrolled adults with T2D from January 1 through October 31, 2013. PDPN was diagnosed using the Michigan Neuropathy Screening Instrument (MNSI) and Douleur Neuropathique 4 (DN4) questionnaire. Variability in FPG was defined as a CV of visit-to-visit FPG for every 3-month interval during follow-up period before enrolment.
Results. – A total of 2,773 patients were enrolled. One hundred patients with PDPN were randomly selected and paired with 175 consecutive patients with non-painful diabetic peripheral neuropathy and 351 patients with T2D without diabetic peripheral neuropathy, matched for age, gender, and diabetic duration. After multivariate adjustment, the FPG-CV was significantly associated with a risk of PDPN with a corresponding odds ratio of 4.08 (95% confidence interval [CI] of 1.60-10.42) and 5.49 (95% CI of 2.14-14.06) for FPG-CV in the third and fourth versus first FPG-CV quartiles, respectively, after considering glycated haemoglobin (HbA1c).
Conclusion. – Long-term variability as evaluated by FPG-CV was associated to the risk of PDPN in adults with T2D. However, further studies are needed to know whether the FPG-CV is not simply a marker of the ambient hyperglycaemia.

Introduction

Diabetic peripheral neuropathy (DPN) is one of the most frequent complications of diabetes mellitus [1]. Painful diabetic peripheral neuropathy (PDPN) is generally considered a variant of DPN that affects 10%–20% of the entire population with diabetes and 40%–60% of people with documented DPN. Neuropathic pain is the most disabling symptom of PDPN causing substantial suffering and resulting in worse quality of life [2]. Though some treatments for neuropathic pain temporarily improve symptoms, the disease-modifying therapies are still lacking, which makes the discovery of modifiable risk factors essential for PDPN research.

Previous studies have indicated that age, gender, diabetes duration, and glycaemic control are associated with the risk of PDPN [3]. Glycaemic variability has emerged as a measure of glycaemic control and could be a predictor for diabetic complications in patients with T2D, independent of HbA1c levels [4]. Recent evidence has suggested that glycaemic variability is independently associated with the risk of developing DPN [5]. To date, no study has yet evaluated whether glycaemic variability is associated with the risk of PDPN in patients with type 2 diabetes (T2D). The objective of this study was to determine whether variations in fasting plasma glucose, as measured by the coefficient

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of variation (CV), were associated with an increased risk of PDPN in a large cohort of adult patients with T2D.

Methods

Study design and cohort

This was a retrospective study identifying patients with T2D aged over 20 years between January 2013 and October 2013, including prevalent and new cases. All patients were diagnosed by endocrinologists at the outpatient unit of a public tertiary care hospital in central Taiwan. The diagnosis of T2D was established based on the American Diabetes Association (ADA) criteria. We excluded patients with type 1 diabetes, gestational diabetes mellitus, < 1 year of follow-up, and fewer than two records of blood biochemical measurements 6 months before enrolment for calculation of glucose variability. Patient data were anonymized via the computer before analysis, and the study was approved by the Institutional Review Board of Taichung Veterans General Hospital (CE-17217B).

Anthropometric and biochemical measurements

All participants completed anthropometric measurements at the time of enrolment including height, weight (both recorded using a calibrated balance with a stadiometer) and resting blood pressure (measured in a sitting position in the right arm with an automatic sphygmomanometer) (BP203RV-II; Nippon Colin, Komaki, Japan). Body mass index was calculated from the weight in kilograms divided by the height in meters squared (kg/m^2).

Participants' laboratory tests and medications were taken from hospital records and were followed every three months. Blood samples were taken from the antecubital vein after an overnight fast, and levels of fasting plasma glucose (using standard enzymatic methods), glycated haemoglobin (HbA1c, using high-performance liquid chromatography), and lipid profiles (using standard enzymatic methods) including triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured. Variability in FPG was estimated from the CV of quarterly visit-to-visit FPG during the follow-up period before enrolment, namely the long-term glycaemic variability defined in recent studies [6,7].

Assessment of DPN

DPN was determined using the Michigan Neuropathy Screening Instrument (MNSI) – a validated screening tool for DPN. The MNSI includes two separate assessments: a 15-item self-administered questionnaire and a structured examination of feet (MNSIE) that is scored for abnormalities of appearance, presence of ulcers, vibration perception, and ankle reflexes. All MNSIE in our study were performed by a trained and certified health professional to reduce interobserver variability. The threshold for DPN was established via previous validation studies in adults. This used a score of > 2 on the MNSIE out of a total score of 8. The details of the examination have been described in the previous study [8].

Assessment of neuropathic pain

Neuropathic pain was diagnosed when the DN4 questionnaire gave a value more than or equal to 4. The DN4 questionnaire is a patient-reported symptom-based 10-item approach consisting of both sensory descriptors and signs related to bedside examination. It was developed and validated by the French Neuropathic Pain Group. The cut-off value of 4/10 represents the highest percentage of correctly diagnosing patients (86.0%), sensitivity (82.9%) and specificity (89.9%) [9]. Compared with the gold standards such as NeuPSIG grading system, DN4 questionnaire performed extremely well in identifying patients with neuropathic pain [10].

Comorbidities

Any of the following recorded during 2010–2012 in outpatient and inpatient claims were recognized as being comorbidities: a history of hypertension (ICD-9-CM codes 401-405), hyperlipidaemia (ICD-9-CM codes 272), cardiovascular disease (ICD-9-CM codes 390-438), ischemic heart disease (ICD-9-CM codes 410-414), chronic kidney disease (ICD-9-CM codes 582-583), chronic liver disease (ICD-9-CM codes 571-573), hypoglycaemia (ICD-9-CM codes 251.0, 251.1, 251.2), or hyperosmolar hyperglycaemic state (ICD-9-CM codes 250.20, 250.22).

Statistical analysis

Descriptive statistics were presented as the means with standard deviation (SD), numbers with percentages, or median values with interquartile range (IQR). Categorical variables were analysed using Fisher's exact test or the χ^2 test, and continuous variables were analysed using the Student *t* test or ANOVA. The CVs of FPG measurements from outpatient visits before entry for each patient were calculated for those with more than two FPG measurements within six months of enrolment. The mean number (SD) of measurements of FPG and HbA1c were 20.7 (15.1) and 32.3 (11), respectively.

When considering the effect of number of visits on CV, the CV of FPG was divided by square root of the ratio of total visits to total visits minus one [5]. Patients were grouped into quartiles according to FPG-CV. Multiple logistic regression analysis was performed with the identified independent variables, and the odds ratios (ORs) were obtained between the comparison groups with 95% confidence intervals (CIs). Multivariate models were:

- adjusted for demographics (age, gender, smoking, alcohol, body mass index);
- additionally adjusted for comorbidities (hypertension, hyperlipidaemia, cardiovascular disease, ischemic heart disease, chronic kidney disease, chronic liver disease) and drug-related variables (antihypertensive drug treatment, lipid-lowering agent treatment);
- additionally adjusted for diabetic-related factors (hypoglycaemia, hyperosmolar hyperglycaemic state, diabetes duration, type of hypoglycaemic drugs, HbA1c).

The interaction of FPG-CV and HbA1c was probed by adding their product terms into the full model using the likelihood ratio test for significance [11,12]. The strength between FPG-CV and HbA1c was quantified using Pearson's correlation coefficient test [13]. All tests were two-sided, and a *P* value of less than 0.05 was used to indicate statistical significance. All statistical analyses were conducted using SAS statistical software for Windows (version 9.4; SAS Institute Inc., Cary, NC).

Results

A total of 2,773 patients were included in this study. A hundred patients with PDPN were randomly selected and paired with 175 consecutive patients with non-painful DPN and 351 patients with T2D without DPN, who were matched for age, gender, and diabetes duration. The mean age of the patients was 72.9 ± 10.5 years at the time of the survey with a male-to-female

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