Journal of Diabetes and Its Complications 28 (2014) 185–190

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Visit-to-visit variability in systolic blood pressure predicts development and progression of diabetic nephropathy, but not retinopathy, in patients with type 2 diabetes ☆

Toshiko Takao [a,*], Yutaka Matsuyama [b], Hiroyuki Yanagisawa [c], Masatoshi Kikuchi [a], Shoji Kawazu [a]

[a] Division of Diabetes and Metabolic Diseases, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan
[b] Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan
[c] Department of Public Health and Environmental Medicine, the Jikei University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 15 July 2013
Received in revised form 15 October 2013
Accepted 6 November 2013
Available online 13 November 2013

Keywords:
Blood pressure variability
Systolic blood pressure
Nephropathy
Retinopathy
Type 2 diabetes

ABSTRACT

Objective: To investigate whether visit-to-visit variability in systolic blood pressure (SBP) can predict development and progression of diabetic nephropathy and retinopathy in patients with type 2 diabetes mellitus (T2DM).

Methods: From 1995 through 1996, 664 T2DM patients visited our hospital for the first time and were subsequently examined 4 times or more and at least once annually.

At first visit, 326 had normoalbuminuria, 644 had an estimated glomerular filtration rate (eGFR) of ≥45 ml/min/1.73 m^2, 526 had no diabetic retinopathy and 609 had no severe non-proliferative diabetic retinopathy (NPDR). They were followed through June 2012, at the latest.

Results: Ninety patients developed microalbuminuria, 76 showed decrease of eGFR to <45 ml/min/1.73 m^2, 113 developed mild–moderate NPDR and 50 progression to severe NPDR. The unadjusted, age- and sex-adjusted and multivariate-adjusted hazard ratios for development and progression of nephropathy, but not retinopathy, increased across tertiles of the standard deviation (SD) of SBP. Both the SD and coefficient of variation (CV) of SBP were significant predictors of development and progression of nephropathy, but not retinopathy, independently of mean SBP.

Conclusion: Visit-to-visit SBP variability is an independent predictor of development and progression of diabetic nephropathy, but not retinopathy, in T2DM patients.

1. Introduction

Hypertension is associated with the risk of macrovascular and microvascular complications in patients with type 2 diabetes mellitus (T2DM) (Adlar et al., 2000). Recent studies, mostly of treated hypertensive patients, found an increased visit-to-visit variability in blood pressure (BP) to be predictive of cerebrovascular events (Hata et al., 2000; Rothwell et al., 2010a, 2010b), acute myocardial infarction (Hata et al., 2002) and all-cause mortality (Muntner, Shimbo et al., 2011), independently of the mean BP. In patients with chronic kidney disease without diabetes, visit-to-visit BP variability was an independent determinant of deterioration of renal function (Yokota et al., 2013). In T2DM patients, visit-to-visit BP variability was a significant predictor of all-cause mortality, independent of the mean BP (Hsieh et al., 2012). It has been suggested that increased BP variability may reflect arterial stiffness and baroreceptor dysfunction, which have been associated with arteriosclerosis and result in vascular events (Floras et al., 1988; Hata et al., 2000, 2002; Rothwell, 2010; Shan, Dai, & Su, 2001).

Regarding diabetic microangiopathy, visit-to-visit BP variability was found to be an independent predictor of nephropathy, but not retinopathy, in patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) (Kilpatrick, Rigby, & Atkin, 2010). Visit-to-visit systolic BP (SBP) variability was also found to be a predictor of development of microalbuminuria (Okada et al., 2013) in T2DM patients, most of whom were taking antihypertensive agents. However, reports regarding the relationship between visit-to-visit BP variability and diabetic microangiopathy in T2DM patients remain limited. In particular, there has been no demonstration of a role of visit-to-visit SBP variability in advanced-stage diabetic microangiopathy. In addition, it is unknown whether visit-to-visit SBP variability has different effects on diabetic nephropathy and retinopathy in T2DM patients.

☆ Conflicts of interest: None.

* Corresponding author at: Division of Diabetes and Metabolic Diseases, The Institute for Adult Diseases, Asahi Life Foundation, 2-2-6, Nihonbashi Bakurocho, Chuo-ku, Tokyo 103-0002, Japan. Tel.: +81 3 36395501; fax: +81 3 36395520.
E-mail address: t-takao@asahi-life.or.jp (T. Takao).

1056-8727/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jdiacomp.2013.11.003

This study aimed to determine whether visit-to-visit SBP variability can predict development and progression of diabetic nephropathy and retinopathy, independently of the mean SBP, in T2DM patients.

2. Methods

2.1. Study subjects

A total of 1912 patients first visited our hospital between January 1995 and December 1996, and 664 T2DM patients who visited the hospital at least 4 times and at least once a year were enrolled in the study. Patients with impaired glucose tolerance had been excluded. At first visit, of the 664 patients, 326 had normoalbuminuria defined as urinary albumin excretion (UAE) of <30 mg/g Cr and 644 had an estimated glomerular filtration rate (eGFR) of ≥45 ml/min/1.73 m^2. These two cohorts were followed as nephropathy analysis groups through June 2012, at the latest. Similarly, 526 of the 664 patients had no diabetic retinopathy (DR), and 609 had no severe non-proliferative DR (NPDR) at first visit. These two cohorts were followed as retinopathy analysis groups, also through June 2012, at the latest.

The following patient's factors were investigated: age, sex, duration of diabetes, body mass index (BMI), HbA1c, BP, serum creatinine (SCr), serum lipids, funduscopic findings, treatment methods for diabetes, use of antihypertensive agents (angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, α-blockers and β-blockers), use of lipid-lowering agents (statins) and smoking habits. In 1995, when our study started, the only renin–angiotensin system inhibitors available in Japan were ACE inhibitors. Treatment started before the first visit, at the first visit or within 6 months thereafter was defined as the initial therapy. Patients who received a combination of oral antidiabetic drugs and insulin were handled as insulin-treated patients.

The study (retrospective cohort study) design was approved by the Ethics Committee of the Institute for Adult Diseases, Asahi Life Foundation. The study was performed in adherence with the principles of the Declaration of Helsinki and according to Good Clinical Practice standards.

2.2. Endpoint definitions

UAE was measured by a latex turbidimetric immunoassay through March 31, 2008, and by a turbidimetric immunoassay thereafter. Conversion of the earlier UAE data was not necessary due to the high correlation ($r = 0.999$) shown between duplicate assays using the two methods. SCr was measured by the Jaffe–Rate method through June 11, 1995, and by an enzymatic method thereafter. SCr data obtained by the Jaffe–Rate method were converted to enzymatic-method equivalents using a linear regression equation derived from duplicate assays. The estimated glomerular filtration rate (eGFR) was determined using the following equation, advocated by the Japanese Society of Nephrology: $eGFR\ (mL/min/1.73\ m^2) = 194 \times SCr^{-1.094} \times age^{-0.287}$ (×0.739 if female) (Matsuo et al., 2009). We used 2 endpoints for nephropathy: development and progression of nephropathy. Development of nephropathy was defined as development of microalbuminuria, i.e., UAE ≥30 mg/g Cr, and progression of nephropathy was defined as decrease of eGFR to <45 ml/min/1.73 m^2 (chronic kidney disease of at least stage 3b; Stevens, Levin, & for the Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members, 2013). Patients who did not have development or progression of nephropathy were regarded as censored cases on the final day of UAE or eGFR determination.

Funduscopy was performed at least once a year by an ophthalmologist specializing in diabetes. We used 2 endpoints for retinopathy: development and progression of retinopathy. Development of retinopathy was defined as development of mild–moderate NPDR, and progression of retinopathy was defined as progression to severe NPDR. When a microaneurysm, dot/blot hemorrhage or hard exudate was observed at one or more sites in at least one eye on two consecutive occasions, the first time point was defined as the time of development of mild–moderate NPDR. The time point of development of any one of multiple soft exudates, venous caliber abnormalities, intraretinal microvascular abnormalities or non-perfusion area on fluorescein angiograms was defined as the time of progression to severe NPDR. Patients who did not have development or progression of retinopathy were regarded as censored cases on the final day of funduscopy.

2.3. Data collection and determined variables

The SBP, diastolic BP (DBP), HbA1c and body weight were determined at each visit. The BP was, as a rule, measured one time in the sitting position by a trained medical technologist using an electronic sphygmomanometer (BP-10; OMRON, Kyoto, Japan). The standard deviation (SD) or coefficient of variation (CV) was used as a measure of intrapersonal visit-to-visit variability in the SBP. The recorded BP value was used irrespective of whether the patient was started on antihypertensive treatment during the follow-up period.

Beginning from November 1994, HbA1c was measured using the standard high-performance liquid chromatography (HPLC) method of the Japan Diabetes Society (JDS). Later, from June 2012, we used the National Glycohemoglobin Standardization Program (NGSP)-certified method. In June 2012, all the earlier HbA1c (%) values were converted to NGSP values (%) using the equation [HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) (%) + 0.25 (%)] (Kashiwagi et al., 2012).

The total cholesterol (TC) was measured by an enzymatic method. High-density lipoprotein cholesterol (HDLC) was measured by a dextran sulfate-Mg precipitation method through April 25, 1996, and by a direct enzymatic method thereafter. HDLC data obtained by the precipitation method were converted to direct enzymatic-method equivalents using a linear regression equation derived from duplicate assays. Lipids were measured irrespective of the fasting or postprandial status. The mean value of the ratio of TC to HDLC (TC/HDLC) was used as a covariate of analysis, because TC/HDLC was the best predictor of cardiovascular disease among men with T2DM (Jiang et al., 2004; Sone et al., 2012) and was a stronger predictor of cardiovascular risk than non-HDLC in the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine (Holman, Coleman, Shine, & Stevens, 2005).

2.4. Statistical analysis

Data were expressed as the mean ± SD for continuous variables, or as the number and percentage for categorical variables. Because the follow-up period and the number of SBP measurements showed skewed distributions, they were expressed as median values (interquartile range).

Hazard ratios for development and progression of nephropathy and retinopathy associated with tertiles of the SBP SD, with the lowest tertile serving as the reference group, were initially calculated without adjustment and then after age- and sex-adjustment using Cox proportional hazard models. A subsequent model included adjustment for age, sex, duration of diabetes, insulin therapy, use of ACE inhibitors, use of statins and current smoker at baseline, and for the intrapersonal means of SBP, HbA1c, TC/HDLC, BMI and number of SBP measurements (ln-transformed) during follow-up.

The values for the number of SBP measurements were ln-transformed for inclusion in the model in order to adjust for the possibility that the number of measurements might influence the SBP SD, such that a small number of measurements would result in a larger SD compared with in the case of many measurements.

The SD and CV of SBP, modeled as continuous variables, were evaluated for association with development and progression of nephropathy and retinopathy using multivariate Cox proportional hazard models. The covariates included the baseline characteristics and laboratory findings during follow-up, as described above.