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The usefulness of the revised classification for chronic kidney disease by the KDIGO for determining the frequency of diabetic micro- and macroangiopathies in Japanese patients with type 2 diabetes mellitus ☆

Hiroyuki Ito [a,*], Koshiro Oshikiri [a], Mizuo Mifune [a], Mariko Abe [a], Shinichi Antoku [a], Yuichiro Takeuchi [a], Michiko Togane [a], Chizuko Yukawa [b]

[a] Department of Diabetes, Metabolism and Kidney Disease, Edogawa Hospital, 2-24-18, Higashi-Koiwa, Edogawa, Tokyo 133-0052, Japan
[b] Laboratory Department, Edogawa Hospital, Tokyo, Japan

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ABSTRACT

Aims: A new classification of chronic kidney disease (CKD) was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2011. The major point of revision of this classification was the introduction of a two-dimensional staging of the CKD according to the level of albuminuria in addition to the GFR level. Furthermore, the previous CKD stage 3 was subdivided into two stages (G3a and G3b). We examined the prevalence of diabetic micro- and macroangiopathies in patients with type 2 diabetes mellitus based on the new classification.
Methods: A cross-sectional study was performed in 2018 patients with type 2 diabetes mellitus.
Results: All of the diabetic micro- and macroangiopathies significantly more common in the later stages of both the GFR and albuminuria. The proportion of subjects with diabetic retinopathy, neuropathy, cerebrovascular disease and coronary heart disease was significantly higher in the G3b group than in the G3a group. The brachial-ankle pulse wave velocity, which is one of the surrogate markers for atherosclerosis, was also significantly greater in the G3b group compared to the G3a group.
Conclusion: The subdivision of the G3 stage in the revised classification proposed by the KDIGO is useful to evaluate the risk for diabetic vascular complications.

1. Introduction

It is well-known that albuminuria is a major risk factor for atherosclerotic diseases, as well as end-stage renal disease (Gerstein et al., 2001; Sarnak et al., 2003). Type 2 diabetes mellitus is also an independent predictor of vascular events. We previously reported that the frequencies diabetic micro- and macroangiopathies were elevated with the progression of the chronic kidney disease (CKD) stage grading by the glomerular filtration rate (GFR) in 1197 Japanese patients with type 2 diabetes mellitus, even among the individuals without albuminuria (Ito, Takeuchi, Ishida, Antoku et al., 2010).

A new classification of CKD was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2011 (Levey et al., 2011). The major point in revising this classification was the introduction of a two-dimensional staging of the CKD according to the urinary albumin excretion rate (UAE), in addition to the GFR. Furthermore, the previous CKD stage 3 was divided into the two stages based on the GFR level (G3a; 60 mL/min/1.73 m^2 >GFR ≥45 mL/min/1.73 m^2 and G3b; 45 mL/min/1.73 m^2 >GFR ≥30 mL/min/1.73 m^2). Although the risk for mortality and progression of renal dysfunction were not substantially different between the groups, the stage with an albumin-to-creatinine ratio (ACR) <30 mg/g creatinine (A1 stage) equivalent to normoalbuminuria of diabetic nephropathy was also divided into two subgroups with ACR <10 mg/g creatinine and 10≤ACR<30 mg/g creatinine. The aim of this study was to examine the frequency of diabetic micro- and macroangiopathies in patients with type 2 diabetes using the new classification of the CKD in a cross-sectional design study.

2. Patients and Methods

2.1. Study population and methods

A population of 2018 patients diagnosed with type 2 diabetes mellitus who underwent consecutive evaluations, including blood pressure, urinalysis and determination of the serum creatinine levels, in the Department of Diabetes, Metabolism and Kidney Disease of Edogawa Hospital, Tokyo, Japan between April 2008 and March 2011 was recruited for the study.

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* Corresponding author. Tel.: +81 3 3673 1221; fax: +81 3 3673 1229.
E-mail address: ito@edogawa.or.jp (H. Ito).

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The obese individuals were defined as those having a BMI ≥25 kg/m^2 (Examination Committee of Criteria for 'Obesity Disease' in Japan and Japan Society for the Study of Obesity, 2002). The subjects' blood pressure was measured twice with the subjects in the sitting position after a 5 minute rest. The lower value of the two measurements was used for the study. Hypertension was defined as a SBP ≥140 mmHg and/or a DBP ≥90 mmHg. The participants currently using antihypertensive medications were also classified as positive for hypertension.

The serum total cholesterol, LDL-cholesterol and HDL-cholesterol concentrations were measured with a TBA-200 FR NEO device using the Determiner L TC II, Determiner L LDL-C, Determiner L HDL-C and Determiner L UA instruments (Kyowa Medex Co., Ltd., Tokyo, Japan). Hyperlipidemia was defined by serum concentrations of total cholesterol ≥5.7 mmol/L, a LDL-cholesterol level ≥3.6 mmol/L, or as patients who were already undergoing treatment with lipid-lowering agents. The triglyceride concentrations were not investigated in this study because fasting blood samples could not always be obtained for measurements.

The estimated GFR (eGFR) was calculated using the formula reported by Matsuo *et al* (Matsuo et al., 2009). This equation originated from the MDRD study group (Coresh, Astor, Greene, Eknoyan, & Levey, 2003) arranged for Japanese individuals, and it is recommended by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194 × Scr$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female).

The CKD stage was classified according to the levels of eGFR and ACR (Levey et al., 2011). The GFR stage was graded as: G1, eGFR ≥90 mL/min/1.73 m^2; G2, 90 mL/min/1.73 m^2 >eGFR ≥60 mL/min/1.73 m^2; G3a, 60 mL/min/1.73 m^2 >eGFR ≥45 mL/min/1.73 m^2; G3b, 45 mL/min/1.73 m^2 >eGFR ≥30 mL/min/1.73 m^2; G4, 30 mL/min/1.73 m^2 >eGFR ≥15 mL/min/1.73 m^2; or G5, 15 mL/min/1.73 m^2 >eGFR. The albuminuria stage was graded according to an analysis of a spot urine sample as: A1 (normoalbuminuria), ACR <30 mg/g creatinine; A2 (microalbuminuria), 30 ≤ACR <300 mg/g creatinine; or A3 (macroalbuminuria), ACR ≥300 mg/g creatinine (or when a dipstick urinalysis revealed 2+, 3+ or 4+). The A1 stage was subdivided according to the ACR as: A1a, ACR <10 mg/g creatinine and A1b, 10≤ACR <30 mg/g creatinine.

Diabetic retinopathy was graded as simple, pre-proliferative and proliferative retinopathy judged according to the results of a funduscopic examination performed by expert ophthalmologists. Diabetic neuropathy was diagnosed by the presence of two or more components among clinical symptoms (bilateral spontaneous pain, hypoesthesia, or paraesthesia of the legs), the absence of ankle tendon reflexes and decreased vibration sensations using a C128 tuning fork.

Cerebrovascular disease was diagnosed by the physicians as a history of an ischemic stroke using brain computed tomography or magnetic resonance imaging. Only the patients with symptoms were classified as having cerebrovascular disease, and cases of silent brain infarction, transient ischemic attack and brain hemorrhage were excluded from this study. Coronary heart disease was diagnosed based on a previous history of myocardial infarction, angina pectoris, electrocardiogram abnormalities suggesting myocardial ischemia or interventions after coronary angiographic examination. Peripheral arterial disease was diagnosed by the absence of a pulse in the legs, along with ischemic symptoms, obstructive findings on ultrasonographic or angiographic examinations of the lower extremities, or an ankle-brachial pressure index (ABI) <0.9.

The ABI and brachial-ankle pulse wave velocity (baPWV), as indicators of atherosclerosis, were measured using a Form PWV/ABI, BP-203PRE II instrument (Omron Colin Co., Ltd, Bunkyo, Tokyo, Japan). The intima-media thickness (IMT) of the carotid artery was measured via ultrasonographic examinations by skilled laboratory technicians using an Aplio XV ultrasound machine (Toshiba Medical Systems Corp., Ohtawara, Tochigi, Japan) as described previously (Ito, Komatsu et al., 2010).

The HbA1c levels were determined by a high performance liquid chromatography method using an automated HLC-723G7 analyzer (Tosoh Corporation, Tokyo, Japan) and calibrated by the Japan Diabetes Society (JDS) standard calibrators. The value for HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula: HbA1c = H-bA1c (JDS) + 0.4, considering the relational expression of HbA1c (JDS) measured by the previous Japanese standard substance and measurement methods and the HbA1c (NGSP) (Seino et al., 2010).

2.2. Ethics statement

This study was conducted according to the principles expressed in the Declaration of Helsinki. The Ethics Committees of Edogawa Hospital approved the protocol of this study and waived the need for written informed consent because the data were analyzed anonymously for this cross-sectional study based on the data stored in the hospital database.

2.3. Statistical methods

All data are shown as the means ± SD. An analysis of variance (ANOVA) was used to compare the continuous variables among the GFR (G1 + G2, G3a, G3b and G4 + G5) and stages of albuminuria (A1a, A1b, A2 and A3). An unpaired t-test was performed for comparisons of the continuous variables between two groups. The χ^2 test was used to determine the differences in the prevalence of diabetic complications between the A1a and A1b groups, as well as among the subjects with different stages of albuminuria (A1a, A1b, A2 and A3). In a similar fashion, the χ^2 test was also used to evaluate the differences between the G3a and G3b groups. Differences of $P<0.05$ (two-tailed) were considered to be statistically significant. The statistical software package JMP, version 8.0 (SAS Institute, Cary, NC, USA), was used to perform all of the analyses.

3. Results

Table 1 shows the clinical characteristics and laboratory parameters of the patients. Table 2 shows the distribution of the patients staged by the eGFR and ACR levels. As shown in Table 3, all of the diabetic micro- and macroangiopathies significantly more common in the later stages of both the eGFR and albuminuria ($P<0.01$). When the χ^2 test were performed among the A1 (A1a + A1b) stage patients, the number of subjects showing an eGFR<60 mL/min/1.73 m^2 (G3a + G3b + G4 + G5) was significantly lower in the A1b group than in the A1a group ($P=0.03$, Table 2), whereas the frequencies of diabetic retinopathy and macroangiopathies were not different (Table 3). However, diabetic neuropathy was significantly more common in the A1b group than in the A1a group ($P<0.01$). When the χ^2 test was performed among the G3 (G3a + G3b) stage patients, the proportion of subjects with diabetic retinopathy, neuropathy, cerebrovascular disease and coronary heart disease was significantly higher in the G3b group than in the G3a group ($P<0.01$, respectively). The subjects showing an ACR ≥30 mg/g creatinine (A2 + A3) were also more common in the G3b group than in G3a group ($P<0.01$). The odds ratios for diabetic angiopathies were higher in the patients with G3b than those with G3a status, even after adjusting for the ACR status and the other covariates using the logistic regression analyses (Table 4).

Fig. 1 shows the comparisons of the values of the ABI, baPWV and carotid IMT among the patients in the various CKD stages according to the ACR and eGFR levels. The value of the ABI significantly lower in the later stages with regard to both the ACR and eGFR ($P<0.01$, respectively). The values of baPWV and carotid IMT were also significantly higher in the later stages with regard to the ACR ($P<0.01$ and $P=0.04$, respectively) and eGFR ($P<0.01$, respectively). The baPWV