CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Risks of Diabetic Nephropathy with Variation in Hemoglobin A_{1c} and Fasting Plasma Glucose

Cheng-Chieh Lin, MD, PhD,[a,b,c*] Ching-Chu Chen, MD,[d,e*] Fei-Na Chen, PhD,[b*] Chia-Ing Li, MPH,[b,c] Chiu-Shong Liu, MPH, MD,[a,b,c] Wen-Yuan Lin, MD, PhD,[a,b] Sing-Yu Yang, BS,[f] Cheng-Chun Lee, MD,[b,g] Tsai-Chung Li, PhD[f,h]

[a]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan; [b]School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan; [c]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan; [d]Division of Endocrinology and Metabolism, Department of Medicine, China Medical University Hospital, Taichung, Taiwan; [e]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan; [f]Graduate Institute of Biostatistics, College of Management, China Medical University, Taichung, Taiwan; [g]Department of Neurology, China Medical University Hospital, Taichung, Taiwan; [h]Department of Healthcare Administration, College of Health Science, Asia University, Taichung, Taiwan.

ABSTRACT

BACKGROUND: This study examined whether annual variation in glycosylated hemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose (FPG), as represented by the coefficient of variation (CV), can predict diabetic nephropathy independently of mean FPG, mean HbA_{1c}, and other risk factors in patients with type 2 diabetes.
METHODS: A computerized database of patients with type 2 diabetes aged ≥30 years and free of diabetic nephropathy (n = 3220) who were enrolled in the Diabetes Care Management Program of China Medical University Hospital before 2007 was used in a time-dependent Cox proportional hazards regression model.
RESULTS: The incidence rates of diabetic nephropathy were 16.11, 22.95, and 28.86 per 1000 person-years in the first, second, and third tertiles of baseline HbA_{1c}-CV, respectively; the corresponding incidence rates for FPG-CV were 9.46, 21.23, and 37.51 per 1000 person-years, respectively. After multivariate adjustment, the corresponding hazard ratios for the second and third tertiles versus the first tertile of annual HbA_{1c}-CV were 1.18 (95% confidence interval [CI], 0.88-1.58) and 1.58 (95% CI, 1.19-2.11), respectively, and 1.55 (95% CI, 0.99-2.41) and 4.75 (95% CI, 3.22-7.01) for FPG-CV, respectively. The risks of diabetic nephropathy for HbA_{1c}-CV and FPG-CV stratified according to age, gender, renal function, and hypertension status were provided.
CONCLUSIONS: Annual FPG and HbA_{1c} variations have a strong association with diabetic nephropathy in patients with type 2 diabetes. Whether intervention for reducing glucose variation should be administered needs to be examined in a future study.
 • The American Journal of Medicine (2013) 126, 1017.e1-1017.e10

KEYWORDS: Diabetic nephropathy; Fasting plasma glucose; Hemoglobin A_{1c}; Type 2 diabetes

Diabetic nephropathy, the most common cause of end-stage renal disease worldwide, is the primary indication for renal replacement therapy in most developed countries.[1,2] The incidence and prevalence rates of end-stage renal disease have increased continuously in Taiwan since 2000.[3] The prevalence rate peaked in 2005 and 2007 at 435 and 2288 per 1,000,000 population, respectively.[4] The prevalence of chronic kidney disease and end-stage renal disease has become a heavier burden on the medical care in Taiwan because of the increasing aging population.

Funding: This study was supported primarily by National Science Council of Taiwan (NSC 98-2314-B-039-027-MY3 and NSC 101-2314-B-039-017-MY3), China Medical University (CMU97-176), and Taiwan Department of Health Clinical Trial and Research Center of Excellence (DOH102-TD-B-111-004).

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

[*]Drs C-C Lin, C-C Chen, and F-F Chen equally contributed as first author.

Requests for reprints should be addressed to Tsai-Chung Li, PhD, China Medical University, 91 Hsueh-Shih Road, Taichung, 40421, Taiwan

E-mail address: tcli@mail.cmu.edu.tw

0002-9343/$ -see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2013.04.015

Previous epidemiologic studies have demonstrated that diabetes is one of the major risk factors for the development and progression of chronic kidney disease and microalbuminuria.[5,6] The prevalence and incidence rates of type 2 diabetes have rapidly increased in Taiwan because of lifestyle westernization in the country. This disease has emerged as the fourth major leading cause of death in men and women in Taiwan since 2002.[7-9] Although type 2 diabetes is the leading cause of chronic kidney disease, only a few studies have examined other factors related to diabetic nephropathy expressed in terms of estimated glomerular filtration rate (eGFR) in patients with this type of diabetes.[5,6]

CLINICAL SIGNIFICANCE

- Higher hemoglobin A_{1c} and fasting plasma glucose variation assessed by coefficient of variation are associated with an increased risk of diabetic nephropathy in patients with type 2 diabetes.
- The increased risk persists after controlling for mean hemoglobin A_{1c}, mean fasting plasma glucose, and other risk factors.
- Whether intervention for reducing glucose variation should be administered needs to be examined in the future study.

Glucose stability is one of the many factors related to diabetes care and one of the goals in diabetes management for complication prevention.[10] However, glucose instability is not a routine measure for monitoring glucose in clinical practice. Many studies have examined the relation of hyperglycemia, classified according to the mean levels of glycosylated hemoglobin A_{1c} (HbA_{1c})[11-13] or fasting plasma glucose (FPG),[14-17] to diabetic complications. However, only one study has examined the relations of HbA_{1c} variation with diabetic microvascular complications in patients with type 1 diabetes.[18] A previous study reported that oscillating plasma glucose has more effects on endothelial function and oxidative-stress generation compared with constant high glucose.[19] Previous studies on the relation of the coefficient of variation (CV) of FPG to the outcomes in patients with diabetes focused on all-cause or cause-specific mortality.[20-22] However, whether annual glycemic variations determined by the CV of HbA_{1c} and FPG are independent predictors of diabetic nephropathy in patients with type 2 diabetes remains unclear.

The Taiwan Bureau of National Health Insurance established the Diabetes Care Management Program (DCMP) in 2002 to provide an intervention program aimed at meeting the treatment goals recommended by the American Diabetes Association through tight control of multiple factors. This program also provides financial incentives for physicians to increase exhaustive follow-up visits, educational programs for diet and lifestyle behaviors, annual examinations, and 4 annual laboratory tests (eg, HbA_{1c} and FPG). The Taichung Diabetes Study is a population-based cohort study of more than 5000 middle-aged and older Chinese patients with type 2 diabetes who were enrolled in the DCMP of a medical center in central Taiwan. This program facilitated the quantification of the overall effect of annual glucose variation on the incidence of diabetic nephropathy. Thus, the present study examined the association between annual HbA_{1c} and FPG variations as measured by CV and diabetic nephropathy as determined by eGFR in a large number of patients with type 2 diabetes monitored for an average of 4.13 years.

MATERIALS AND METHODS

Study Population

Subjects with type 2 diabetes were participants in the DCMP of the China Medical University Hospital (CMUH), Taichung, Taiwan. A total of 6964 patients with a clinically confirmed diagnosis of diabetes mellitus based on the criteria of the American Diabetes Association (International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 250) were invited to enroll in this program. Patients with type 1 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification Code of 250.x1/x3) and patients with an eGFR value of <60 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$ were excluded. Participants who were enrolled in the DCMP by the end of August 2006 were identified through an automated registry. All patients who were enrolled in the registry from August 2002 to August 2006 and had been continuously enrolled in the program until August 2007 were included. We included only patients who could provide records of at least 1 year of follow-up to estimate the variability for HbA_{1c} and FPG. The end point was August 2008 or the occurrence of diabetic nephropathy. Only the incidence of diabetic nephropathy that occurred 1 year after that interval was considered to rule out the possibility of effect-cause association. These criteria were met by 3455 continuously enrolled diabetic patients aged 30 to 89 years. After excluding those individuals with missing data, 3220 patients were included in the analysis. Among the patients with type 2 diabetes, 465, 669, 541, 353, and 1292 provided 1, 2, 3, 4, and 5 or more years of annual HbA_{1c}-CV and FPG measurements, respectively. The current study was approved by the ethical reviews board at CMUH.

Baseline and Follow-up Assessments

The subjects underwent a comprehensive assessment of the status of their disease and complications, as well as a series of blood tests, urine tests, and body measurements at the time of their enrollment into the DCMP. In addition, participants were required to complete a standard computerized questionnaire administered by a case management nurse to record the previous and current status of their disease, medication, and lifestyle behaviors. All patients were

Table 1 Comparisons of Baseline Sociodemographic Factors, Lifestyle Behaviors, Diabetes-related Variables, Drug-related Variables, Diabetes-related Diseases, and Blood Biochemical Indexes According to Tertiles of Coefficient of Variation of Baseline Glycosylated Hemoglobin A_{1C} and Fasting Plasma Glucose in Diabetic Patients Enrolled in Diabetes Care Management Program of a Medical Center (n = 3220)

	Baseline FPG-CV N (%)				Baseline HbA_{1c}-CV N (%)			
Variables	≤15.99 (N = 1063)	15.99～26.57 (N = 1063)	>26.57 (N = 1094)	*P* Value	≤6.68 (N = 1059)	6.68～13.44 (N = 1066)	>13.44 (N = 1095)	*P* Value
Sociodemographic factors								
Gender				.04				<.001
Female	498 (46.85)	550 (51.74)	517 (47.26)		541 (51.09)	546 (51.22)	478 (43.65)	
Male	565 (53.15)	513 (48.26)	577 (52.74)		518 (48.91)	520 (48.78)	617 (56.35)	
Age (y)*	56.82 (10.56)	57.44 (10.52)	57.30 (11.21)	.38	57.78 (10.40)	57.66 (10.49)	56.16 (11.32)	<.001
Lifestyle behaviors								
Smoking				.001				<.001
No	890 (83.73)	869 (81.75)	850 (77.70)		884 (83.47)	879 (82.46)	846 (77.26)	
Yes	173 (16.27)	194 (18.25)	244 (22.30)		175 (16.53)	187 (17.54)	249 (22.74)	
Alcohol drinking				.31				.12
No	937 (88.15)	942 (88.62)	947 (86.56)		939 (88.67)	944 (88.56)	943 (86.12)	
Yes	126 (11.85)	121 (11.38)	147 (13.44)		120 (11.33)	122 (11.44)	152 (13.88)	
Diabetes-related variables								
Diabetes duration (y)*	4.54 (5.43)	6.44 (6.22)	7.47 (7.20)	<.001	6.37 (6.26)	6.99 (6.75)	5.16 (6.20)	<.001
Type of DM treatment								
Oral hypoglycemic drug				<.001				<.001
Metformin	70 (6.59)	46 (4.33)	29 (2.65)		53 (5.00)	38 (3.56)	54 (4.93)	
SU	549 (51.65)	592 (55.69)	518 (47.35)		566 (53.45)	577 (54.13)	516 (47.12)	
Metformin/SU	116 (10.91)	198 (18.63)	160 (14.63)		125 (11.80)	149 (13.98)	200 (18.26)	
Other	190 (17.87)	120 (11.29)	119 (10.88)		159 (15.01)	134 (12.57)	136 (12.42)	
Inject insulin								
CT	5 (0.47)	17 (1.60)	50 (4.57)		26 (2.46)	29 (2.72)	17 (1.55)	
ICT	0 (0.00)	3 (0.28)	26 (2.38)		4 (0.38)	15 (1.41)	10 (0.91)	
Basal insulin	4 (0.38)	8 (0.75)	33 (3.02)		11 (1.04)	18 (1.69)	16 (1.46)	
Other	14 (1.32)	31 (2.92)	85 (7.77)		36 (3.40)	47 (4.41)	47 (4.29)	
Both								
Oral hypoglycemic drug + CT	0 (0.00)	1 (0.09)	7 (0.64)		2 (0.19)	4 (0.38)	2 (0.18)	
Oral hypoglycemic drug + ICT	0 (0.00)	1 (0.09)	6 (0.55)		1 (0.09)	3 (0.28)	3 (0.27)	
Oral hypoglycemic drug + basal insulin	0 (0.00)	0 (0.00)	1 (0.09)		1 (0.09)	0 (0.00)	0 (0.00)	
Oral hypoglycemic drug + other	3 (0.28)	2 (0.19)	8 (0.73)		5 (0.47)	2 (0.19)	6 (0.55)	
Diet or exercise	112 (10.54)	44 (4.14)	52 (4.75)		70 (6.61)	50 (4.69)	88 (8.04)	
Drug-related variables								
Hypertension drug treatment				.82				<.001
No	634 (59.64)	648 (60.96)	657 (60.05)		582 (54.96)	621 (58.26)	736 (67.21)	
Yes	429 (33.49)	415 (39.04)	437 (39.95)		477 (45.04)	445 (41.74)	359 (32.79)	

Table 1 Continued

Variables	Baseline FPG-CV N (%)				Baseline HbA_{1c}-CV N (%)			
	≤15.99 (N = 1063)	15.99∼26.57 (N = 1063)	>26.57 (N = 1094)	*P* Value	≤6.68 (N = 1059)	6.68∼13.44 (N = 1066)	>13.44 (N = 1095)	*P* Value
Heart disease drug treatment				.18				.28
No	922 (86.74)	904 (85.04)	918 (83.91)		888 (83.85)	912 (85.55)	944 (86.21)	
Yes	141 (13.26)	159 (14.96)	176 (16.09)		171 (16.15)	154 (14.45)	191 (13.79)	
Diabetes-related diseases								
Hypertension				.79				<.001
No	634 (59.64)	630 (59.27)	637 (58.23)		582 (54.96)	630 (59.10)	689 (62.92)	
Yes	429 (33.49)	433 (40.74)	457 (41.77)		477 (45.04)	436 (40.90)	406 (37.08)	
Hyperlipidemia				.83				.92
No	703 (66.13)	714 (67.17)	736 (67.28)		707 (66.76)	709 (66.51)	737 (7.31)	
Yes	360 (33.87)	349 (32.83)	358 (32.72)		352 (33.24)	357 (33.49)	358 (32.69)	
DKA				.003				.14
No	1057 (99.44)	1056 (99.34)	1073 (98.08)		1051 (99.24)	1057 (99.16)	1078 (98.45)	
Yes	6 (0.56)	7 (0.66)	21 (1.92)		8 (0.76)	9 (0.84)	17 (1.55)	
HHNK				.009				.47
No	1050 (98.78)	1052 (98.97)	1066 (97.44)		1046 (98.77)	1047 (98.22)	1075 (98.17)	
Yes	13 (1.22)	11 (1.03)	28 (2.56)		13 (1.23)	19 (1.78)	20 (1.83)	
Severe hypoglycemia				<.001				.83
No	1055 (99.25)	1050 (98.78)	1062 (97.07)		1041 (98.30)	1047 (98.22)	1079 (98.54)	
Yes	8 (0.75)	13 (1.22)	32 (2.93)		18 (1.70)	19 (1.78)	16 (1.46)	
Stroke				<.001				.27
No	1012 (95.20)	1010 (95.01)	1003 (91.68)		1005 (94.90)	998 (93.62)	1022 (93.33)	
Yes	51 (4.80)	53 (4.99)	91 (8.32)		54 (5.10)	68 (6.34)	73 (6.67)	
Coronary artery disease				.67				.78
No	1001 (94.17)	991 (93.23)	1024 (93.60)		993 (93.77)	994 (93.25)	1029 (93.97)	
Yes	62 (5.83)	72 (6.77)	70 (6.40)		66 (6.23)	72 (6.75)	66 (6.03)	
Myocardial infarction				.14				.05
No	994 (93.51)	972 (91.44)	1002 (91.59)		982 (92.73)	994 (93.25)	992 (90.59)	
Yes	69 (6.49)	91 (8.56)	92 (8.41)		77 (7.27)	72 (6.75)	103 (9.41)	
Peripheral neuropathy				<.001				.001
No	985 (92.66)	918 (86.36)	904 (82.63)		950 (89.71)	932 (87.43)	925 (84.47)	
Yes	78 (7.34)	145 (13.64)	190 (17.37)		109 (10.29)	134 (12.57)	170 (15.53)	
Intermittent claudication				.04				.11
No	1057 (99.44)	1054 (99.15)	1076 (98.35)		1053 (99.43)	1055 (98.97)	1079 (98.54)	
Yes	6 (0.56)	9 (0.85)	18 (1.65)		6 (0.57)	11 (1.03)	16 (1.46)	
Neuropathy				<.001				.01
No	1028 (96.71)	985 (92.66)	988 (91.22)		1009 (95.28)	993 (93.15)	1009 (92.15)	
Yes	35 (3.29)	78 (7.34)	96 (8.78)		50 (4.72)	73 (6.85)	86 (7.85)	

Table 1 Continued

Variables	Baseline FPG-CV N (%)				Baseline HbA_{1c}-CV N (%)			
	≤15.99 (N = 1063)	15.99～26.57 (N = 1063)	>26.57 (N = 1094)	*P* Value	≤6.68 (N = 1059)	6.68～13.44 (N = 1066)	>13.44 (N = 1095)	*P* Value
Blood biochemical indexes								
Triglyceride (mg/dL)*	145.79 (136.13)	157.57 (177.32)	181.54 (312.70)	<.001	137.86 (116.38)	165.86 (205.92)	181.07 (302.67)	<.001
HDL (mg/dL)*	41.38 (10.67)	41.20 (10.77)	41.47 (12.12)	.86	41.49 (10.43)	41.32 (11.32)	41.25 (11.83)	.88
LDL (mg/dL)*	122.10 (33.61)	121.55 (34.78)	124.79 (39.01)	.18	121.12 (30.65)	121.12 (37.19)	127.12 (38.89)	<.001
HDL/LDL ratio*	0.38 (0.27)	0.37 (0.22)	0.39 (0.50)	.37	0.37 (0.14)	0.40 (0.53)	0.37 (0.29)	.02
eGFR (mL/min/1.73 m^2)*	89.22 (14.80)	90.22 (15.19)	89.74 (15.84)	.32	88.08 (14.64)	89.58 (14.96)	91.46 (16.04)	<.001
Incidence of diabetic nephropathy (eGFR <60 mL/min/1.73 m^2)*	0.05 (0.21)	0.10 (0.29)	0.16 (0.37)	<.001	0.08 (0.26)	0.11 (0.31)	0.12 (0.33)	.002
Body mass index*	25.66 (3.74)	25.41 (3.74)	25.15 (3.87)	.007	25.46 (3.60)	25.49 (3.67)	25.27 (4.06)	.32

CT = conventional therapy; DKA = diabetic ketoacidosis; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FPG-CV = fasting plasma glucose coefficient of variation; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; HHNK = hyperglycemia hyperosmolar non-ketoacidosis; ICT = intensified conventional therapy; LDL = low-density lipoprotein; SU = sulfonylurea.

Chi-square test for categoric variables and analysis of variance for continuous variables were used to calculate *P* values.

*Mean (standard deviation).

followed up regularly every 3 to 6 months. Patients underwent the same tests as they had at baseline during each follow-up.

After a 12-hour overnight fast, blood was drawn with minimal trauma from an antecubital vein in the morning and sent for analysis within 4-hour post-collection. Serum FPG, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were analyzed using a biochemical autoanalyzer (Synchron System, LX20; Beckman Coulter, Fullerton, Calif) at the Clinical Laboratory Department of the CMUH. The inter- and intra-assay CVs for FPG were both 4%. HDL-C and low-density lipoprotein cholesterol levels were measured using a direct method. The inter- and intra-assay CVs for HDL-C were both 4.5%, whereas those for low-density lipoprotein cholesterol were 4.5% and 3%, respectively. Serum cholesterol and triglyceride levels were determined using an enzymatic colorimetric method. The inter- and intra-assay CVs for triglyceride were 6.8% and 5%, respectively. HbA_{1c} was measured using a boronate-affinity high-performance liquid chromatography assay (reference range, 4.6%-6.5%). The inter- and intra-assay CVs for HbA_{1c} were 2.91% for a normal level, 1.79% for an intermediate level, and 1.09% for a high level. We used the Chronic Kidney Disease Epidemiology Collaboration equation to obtain eGFR based on the serum creatinine level,[23] where eGFR in $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1} = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ ($\times$ 1.018 female), where SCr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1. Patients were stratified into renal function stages on the basis of the mean annual eGFR values according to the following Kidney Disease Outcome Quality Initiative guidelines: stage 1, eGFR $\geq$90 $mg \cdot min^{-1}$ $(1.73\ m^2)^{-1}$; stage 2, eGFR = 60 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$ to 89 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$; stage 3, eGFR = 30 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$ to 59 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$; stage 4, eGFR = 15 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$ to 29 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$; and stage 5, eGFR <15 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$. Diabetic nephropathy was defined as eGFR <60 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$,[24] which corresponds to stages 3 to 5.

Statistical Analyses

The annual CV of all HbA_{1c} and FPG measurements for each patient was calculated using a dataset of electronic laboratory records. HbA_{1c}-CV and FPG-CV were calculated only when more than 2 HbA_{1c} and FPG measurements were performed for each year. To adjust the possibility that the number of visits a patient had may influence the variation, the CV value was divided by the square root of the ratio of the number of visits divided by the number of visits minus 1.[18] Patients were grouped into tertiles according to the first year of HbA_{1c}-CV and FPG-CV.

Kaplan–Meier cumulative incidence plots were generated showing time-to-event for all end points. Time-dependent

Cox proportional hazards models were used to evaluate the association of annual HbA_{1c}-CV and FPG-CV with incident diabetic nephropathy by considering time-varying HbA_{1c}-CV and FPG-CV. We calculated hazard ratios (HRs) and their 95% confidence intervals (CIs) by adjusting for age and multiple variables. Two multivariate models were used. The first multivariate model was adjusted for age (continuous) only. The second model was adjusted for age (continuous), gender, hypertension (yes/no), antihypertensive treatment (yes/no), smoking (yes/no), alcohol consumption (yes/no), exercise (yes/no), hyperlipidemia (yes/no), type of hypoglycemic drug, body mass index, FPG, HbA_{1c}, and complications at baseline (diabetic ketoacidosis, hyperglycemia hyperosmolar nonketoacidosis, severe hypoglycemia, stroke, myocardial infarction, peripheral neuropathy, intermittent claudication, and neuropathy). The relations of FPG-CV and HbA_{1c}-CV with age, gender, and eGFR at baseline were further examined by adding their product terms into the full model, and the likelihood ratio test was used to test its significance. All P values were 2-tailed, and $P < .05$ was considered to indicate statistical significance. All analyses were performed with SAS for Windows version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

The average follow-up of 329 incidence cases of diabetic nephropathy with a crude rate of 22.46 per 1000 person-years (20.39 for men and 24.64 for women) was 4.40 years. The incidence rates of diabetic nephropathy were 16.11, 22.95, and 28.86 per 1000 person-years in the first, second, and third tertiles of baseline HbA_{1c}-CV, respectively; the corresponding incidence rates for FPG-CV were 9.46, 21.23, and 37.51 per 1000 person-years, respectively. Among these 329 incidence cases, 270, 38, and 21 patients were at stages 3, 4, and 5, respectively. **Table 1** shows the comparison of baseline variables according to tertiles of baseline HbA_{1c}-CV and FPG-CV. The correlation coefficients among the annual HbA_{1c}-CVs of years 1 to 5 were weak, ranging from 0.05 to 0.27, and moderate for FPG-CVs of years 1 to 5, ranging from 0.36 to 0.55.

Figure 1 presents the Kaplan–Meier curves for the cumulative incidence of diabetic nephropathy within subgroups defined by baseline HbA_{1c}-CV and FPG-CV. We found that patients with HbA_{1c}-CV $\geq$13.44% and patients with FPG-CV $\geq$26.57% were at increased risk for diabetic nephropathy (both log-rank $P < .001$; **Figure 1A** and **B**).

Table 2 shows the HRs of diabetic nephropathy according to tertiles of annual HbA_{1c}-CV. Compared with patients with the lowest tertile of annual HbA_{1c}-CV, those with the highest and second tertiles of annual HbA_{1c}-CV were associated with increased risk for diabetic nephropathy, with multivariate-adjusted HRs of 2.22 (95% CI, 1.67-2.93) and 1.36 (95% CI, 1.02-1.82), respectively. We found significant linear trends across annual HbA_{1c}-CV categories. Compared with patients with the lowest tertile of annual FPG-CV, the multivariate-adjusted HRs of diabetic nephropathy in patients with the highest and second tertiles of annual FPG-CV were 5.34 (95% CI, 3.64-7.83) and 1.63 (95% CI, 1.05-2.55), respectively. When FPG-CV and HbA_{1c}-CV were considered simultaneously, the multivariate-adjusted HR of HbA_{1c}-CV for the highest tertile was 1.58 (95% CI, 1.19-2.11) and that of FPG-CV for the highest tertile was 4.75 (95% CI, 3.22-7.01).

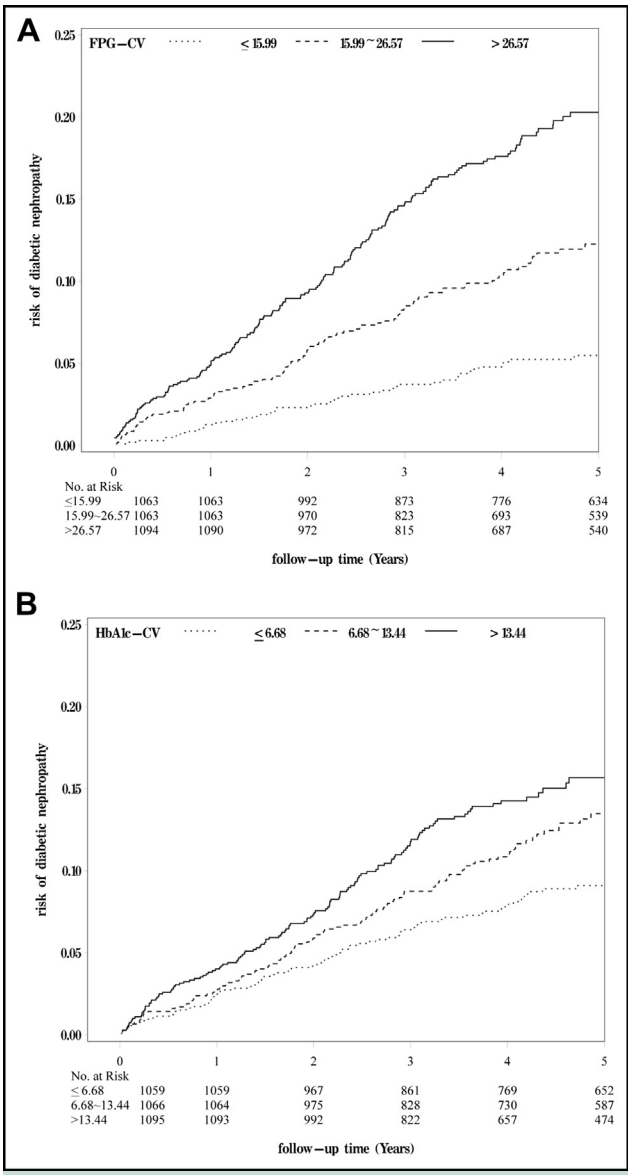

Figure 1 Risk of diabetic nephropathy for (**A**) baseline FPG–CV and (**B**) baseline HbA_{1c}–CV. FPG-CV = fasting plasma glucose coefficient of variation; HbA_{1c}-CV = hemoglobin A_{1c} coefficient of variation.

Two separate sensitivity analyses were conducted. One was to investigate the potential for bias caused by the existence of comorbidities by excluding patients with stroke, cardiovascular disease, diabetic ketoacidosis, and hyperglycemia hyperosmolar nonketoacidosis (n = 2570). Similar significant associations were found, and the HR for

Table 2 Hazard Ratios of Decreased Renal Function Incidence According to Tertiles of Annual Mean Fasting Plasma Glucose Coefficient of Variation and Hemoglobin A_{1c} Coefficient of Variation in Diabetic Patients Enrolled in Diabetes Care Management Program of a Medical Center (n = 3220)

				Decreased Renal Function (eGFR <60 mL/min/1.73 m^2)	
Variables	Person-years	No. of Diabetic Nephropathy Cases	IR	Age-Adjusted HR (95% CI)	Adjusted* HR (95% CI)
FPG-CV (%)					
≤15.99	5071.73	48	9.46	-	-
15.99～26.57	4804.08	102	21.23	1.74† (1.12-2.71)	1.63† (1.05-2.55)
>26.57	4772.00	179	37.51	6.25§ (4.32-9.03)	5.34§ (3.64-7.83)
P for trend				<.001	<.001
HbA_{1c}-CV (%)					
≤6.68	5090.71	82	16.11	-	-
6.68～13.44	4879.72	112	22.95	1.48‡ (1.11-1.98)	1.36† (1.02-1.82)
>13.44	4677.38	135	28.86	2.64§ (2.02-3.47)	2.22§ (1.67-2.93)
P for trend				<.001	<.001
FPG-CV (%)					
≤15.99	5071.73	48	9.46	-	-
15.99～26.57	4804.08	102	21.23	1.63† (1.05-2.54)	1.55 (0.99-2.41)
>26.57	4772.00	179	37.51	5.40§ (3.70-7.88)	4.75§ (3.22-7.01)
P for trend				<.001	<.001
HbA_{1c}-CV (%)					
≤6.68	5090.71	82	16.11	-	-
6.68～13.44	4879.72	112	22.95	1.22 (0.91-1.63)	1.18 (0.88-1.58)
>13.44	4677.38	135	28.86	1.64§ (1.24-2.17)	1.58‡ (1.19-2.11)
P for trend				<.001	.001

CI = confidence interval; eGFR = estimated glomerular filtration rate; FPG-CV = fasting plasma glucose coefficient of variation; HbA_{1c}-CV = hemoglobin A_{1c} coefficient of variation; HR = hazard ratio; IR = incidence rate (= number of incidence cases/person-years*1000).

*Multivariate adjustment for age, sex, lifestyle factors, hypertension, hypertension drug treatment, heart disease drug treatment, kidney disease drug treatment, hyperlipidemia, type of diabetes treatment, body mass index, mean FPG, mean HbA^{1c}, diabetic ketoacidosis, hyperglycemia hyperosmolar non-ketoacidosis, severe hypoglycemia, stroke, myocardial infarction, peripheral neuropathy, intermittent claudication, and neuropathy.

†$P < .05$.

‡$P < .01$.

§$P < .001$.

patients with the highest tertile of annual HbA_{1c}-CV was 1.44 (95% CI, 1.02-2.03). The HR for patients with the highest tertiles of annual FPG-CV was 5.08 (95% CI, 3.23-8.10). The second analysis was to consider eGFR and albuminuria for defining nephropathy. By defining urinary albumin-to-creatinine ratio >30 mg g^{-1}creatinine or eGFR <60 mL·min^{-1} (1.73 m^2)$^{-1}$ as diabetic nephropathy (n = 1164), the HRs for patients with the highest tertile of annual HbA_{1c}-CV and FPG-CV were 1.68 (95% CI, 1.07-2.65) and 2.44 (95% CI, 1.41-4.22), respectively.

The adjusted HRs of HbA_{1c}-CV and FPG-CV for diabetic nephropathy were further stratified according to age, gender, baseline eGFR, and hypertension status (**Figure 2**). The adjusted HRs of the highest tertile of HbA_{1c}-CV and FPG-CV for diabetic nephropathy were consistently significant across various strata. **Table 3** demonstrates the multiple linear regression models of baseline HbA_{1c}-CV and FPG-CV. Higher levels of FPG-CV were observed in patients with older age, smoking status, oral hypoglycemic drug use, both oral and insulin use, higher mean FPG and HbA_{1c}, severe hypoglycemia, and stroke. Higher variation in HbA_{1c} was observed in male patients with shorter diabetes duration, higher mean HbA_{1c}, stroke, myocardial infarction, peripheral neuropathy, triglyceride, and HDL-C, whereas lower variation in HbA_{1c} was observed in patients with hypertension drug treatment, oral hypoglycemic drug, and higher mean FPG.

DISCUSSION

The present study is the first to demonstrate that annual variation in HbA_{1c} and FPG measurements can predict diabetic nephropathy in 30- to 89-year-old patients with type 2 diabetes. An estimated HbA_{1c}-CV greater than 13.44% was associated with a 1.58-fold higher risk compared with HbA_{1c}-CV ≤6.68%, and an estimated FPG-CV >26.57% was associated with an approximately 4.75-fold higher risk compared with FPG-CV ≤15.99%. Our results demonstrated that FPG-CV is a new and good measure of glucose variation that can capture the association between oscillating plasma glucose and diabetic nephropathy in addition to HbA_{1c} variation. These findings are relevant to the clinical management of patients with type 2 diabetes. Managed care has facilitated routine collection of HbA_{1c} and FPG

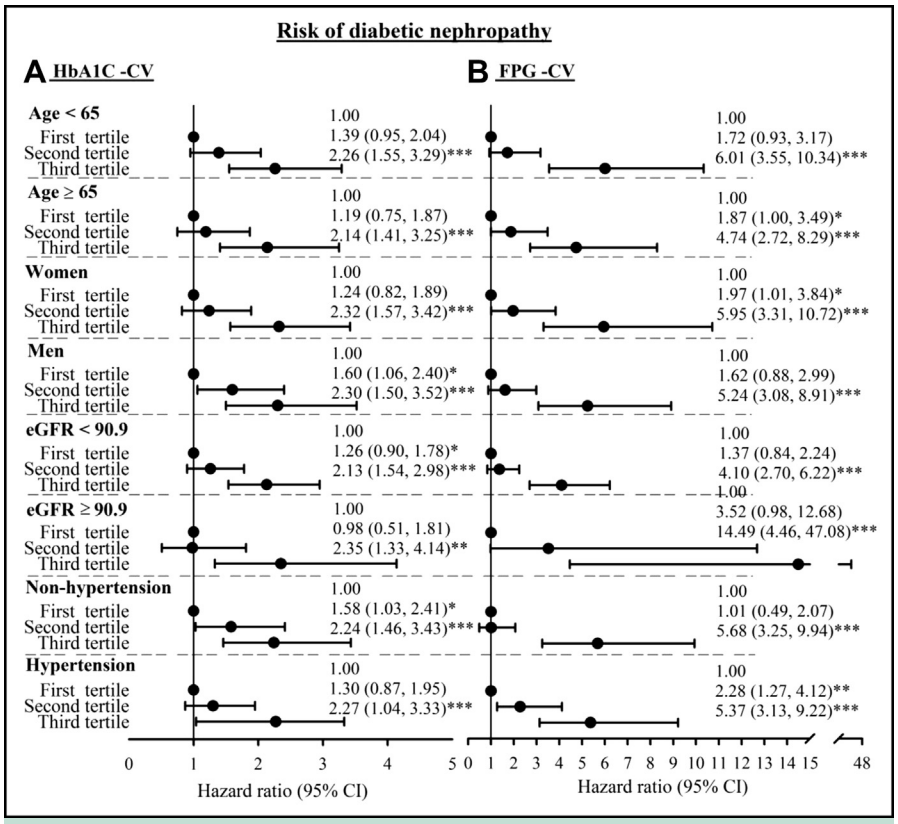

Figure 2 Adjusted HRs of diabetic nephropathy risk by (**A**) baseline FPG-CV and (**B**) baseline HbA_{1c}-CV according to age (<65 or ≥65 years), gender (female or male), and eGFR (<107.9 or ≥107.9 mL/min/1.73 m^2). The HRs were adjusted for age, sex, lifestyle factors, hypertension, hypertension drug treatment, heart disease drug treatment, kidney disease drug treatment, hyperlipidemia, type of diabetes treatment, body mass index, mean FPG, mean HbA_{1c}, diabetic ketoacidosis, hyperglycemia hyperosmolar non-ketoacidosis, severe hypoglycemia, stroke, myocardial infarction, peripheral neuropathy, intermittent claudication, and neuropathy. *$P < .05$. **$P < .01$. ***$P < .001$. CI = confidence interval; eGFR = estimated glomerular filtration rate; FPG-CV = fasting plasma glucose coefficient of variation; HbA_{1c}-CV = hemoglobin A_{1c} coefficient of variation.

measurements, which should be availed for glycemic assessment. Whether intervention for reducing glucose variation should be administered needs to be examined in a future study.

Several plausible mechanisms can be hypothesized to explain the association of HbA_{1c} and FPG variations with diabetic nephropathy. First, glucose variation may have an impact on some mechanisms that affect diabetic nephropathy. One possible mechanism involves glucose variation that may produce free radicals activating the pathways involved in the pathogenesis of diabetes complications.[19] Ceriello et al[19] reported that oscillating plasma glucose poses more deleterious effects than constant high glucose on endothelial function and oxidative-stress generation, which are 2 key factors that result in cardiovascular complications in diabetes.[19] The other possible mechanism is that oscillating plasma glucose may act directly on the kidney to interrupt renal function. Instead of focusing on functional and structural changes in the glomerulus, changes within the tubulointerstitium were reported, which contributed to progressive kidney diseases, including diabetic nephropathy. Such tubulointerstitial changes were found in approximately one third of type 2 diabetic patients in a biopsy study.[25] Cell growth, collagen synthesis, and cytokine secretion in cultured human tubulointerstitial cells were enhanced after intermittent exposure to high glucose rather than constant exposure to high glucose.[26] Second, glucose variation may be a sign and not a cause of incident diabetic nephropathy.

Finally, glucose variation might be an indication of poor health, comorbidity, or complication that can result in increased risk for diabetic nephropathy. The present study considered baseline comorbidity and complication in the regression models and excluded those who had comorbidity and complication in the analysis to mitigate this possibility. However, some residual confounding and uncontrolled confounding factors may exist, such as biochemical markers that were not considered in the study.

Table 3 Multiple Linear Regression Models of Baseline Fasting Plasma Glucose Coefficient of Variation and Hemoglobin A_{1c} Coefficient of Variation in Diabetic Patients Enrolled in Diabetes Care Management Program of a Medical Center (n = 3220)

	FPG-CV (%)			HbA_{1c}-CV (%)		
Variables	β (SE)	t Value	*P* Value	β (SE)	t Value	*P* Value
Age (y)	0.06 (0.03)	2.26	**.02**	0.01 (0.02)	0.31	.76
Gender (female as reference)	0.82 (0.55)	1.48	.14	2.33 (0.51)	4.56	**<.001**
Diabetes duration (y)	0.02 (0.04)	0.47	.64	−0.45 (0.04)	−11.45	**<.001**
Hypertension drug treatment	−0.69 (0.70)	−0.98	.33	−1.33 (0.65)	−2.05	**.04**
Hypertension	0.84 (0.71)	1.19	.23	−0.32 (0.65)	−0.49	.62
Heart disease drug treatment	−0.51 (0.76)	−0.67	.50	−0.66 (0.70)	−0.94	.35
Kidney disease drug treatment	−3.88 (13.59)	−0.29	.78	−11.31 (12.54)	−0.90	.37
Smoking	2.53 (0.69)	3.65	**<.001**	−0.06 (0.64)	−0.09	.93
Alcohol drinking	−0.27 (0.79)	−0.34	.74	0.27 (0.73)	0.37	.71
Type of DM treatment (diet or exercise as reference)						
Oral hypoglycemic drug	9.32 (1.35)	6.91	**<.001**	−2.95 (1.25)	−2.37	**.02**
Inject insulin	0.62 (1.00)	0.62	.53	−1.27 (0.92)	−1.38	.17
Both	17.90 (2.79)	6.42	**<.001**	−0.10 (2.58)	−0.04	.97
Mean FPG (mg/dL)	0.04 (0.01)	4.69	**<.001**	−0.05 (0.01)	−5.46	**<.001**
Mean HbA_{1c} (%)	3.24 (0.26)	12.64	**<.001**	4.25 (0.24)	17.97	**<.001**
Body mass index	−0.07 (0.07)	−0.98	.33	−0.05 (0.06)	−0.84	.40
DKA	3.73 (2.43)	1.54	.12	2.37 (2.24)	1.06	.29
HHNK	1.17 (1.91)	0.61	.54	0.45 (1.76)	0.25	.80
Severe hypoglycemia	6.05 (1.91)	3.16	**.001**	−1.42 (1.77)	−0.8	.42
Stroke	6.11 (1.07)	5.68	**<.001**	3.33 (0.99)	3.36	**<.001**
Coronary artery disease	−0.53 (1.07)	−0.49	.62	0.56 (0.99)	0.57	.57
Myocardial infarction	−0.24 (0.94)	−0.26	.79	2.00 (0.87)	2.31	**.02**
Peripheral neuropathy	1.18 (0.84)	1.40	.16	1.79 (0.78)	2.3	**.02**
Intermittent claudication	0.54 (2.42)	0.22	.82	3.14 (2.23)	1.41	.16
Neuropathy	0.21 (1.11)	0.19	.85	0.89 (1.02)	0.87	.39
Triglyceride (mg/dL)	0.001 (0.001)	0.91	.36	0.003 (0.001)	2.50	**.01**
HDL (mg/dL)	0.002 (0.01)	0.25	.81	0.02 (0.01)	3.59	**<.001**
LDL (mg/dL)	0.01 (0.02)	0.57	.57	−0.01 (0.02)	−0.54	.59
R^2	22.77%			17.18%		

Significant values in bold ($P < .05$).

β = regression coefficient of multiple linear regression model; DKA = diabetic ketoacidosis; DM = diabetes mellitus; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; HHNK = hyperglycemia hyperosmolar non-ketoacidosis; LDL = low-density lipoprotein; SE = standard error.

Our present study has several strengths, such as a standard procedure for data gathering, a large number of potential confounding factors, a large number of patients with type 2 diabetes, and a sufficiently long follow-up period. In addition, the current study is the first to use FPG-CV as a measure of glucose variation to explore its relation to diabetic nephropathy. It also is the first to use repeated measurements of annual glucose variation during the follow-up period.

Study Limitations

Our current study was limited by the potential residual and unrecognized confounding conditions that might be present because it was observational. In addition, measurement errors may have occurred because of the large amount of data gathered during clinical practice.

In addition to HbA_{1c}, the current study concluded that annual FPG-CV variation also can predict the risk for diabetic nephropathy.

CONCLUSIONS

The findings of the present study have implications for understanding nephropathy in diabetes. Moreover, annual HbA_{1c}-CV and FPG-CV may be included in the evaluation of glucose control in patients with type 2 diabetes for better prediction of diabetic nephropathy. Whether intervention for reducing glucose variation should be administered needs to be examined in a future study.

References

1. Levin A, Djurdjev O, Barrett B, et al. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. *Am J Kidney Dis*. 2001;38:1398-1407.
2. Colhoun HM, Lee ET, Bennett PH, et al. Risk factors for renal failure: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*. 2001;44(Suppl 2):S46-S53.
3. US Renal Data System. USRDS 2004 Annual Data Report. *Am J Kidney Dis*. 2005;45(Suppl 1):S8-S80.

4. US Renal Data System. USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2009.
5. Nelson RG, Bennett PH, Beck GJ, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus: diabetic renal disease study group. *N Engl J Med*. 1996;335:1636-1642.
6. Humphrey LL, Ballard DJ, Frohnert PP, Chu CP, O'Fallon WM, Palumbo PJ. Chronic renal failure in non-insulin-dependent diabetes mellitus. A population-based study in Rochester, Minnesota. *Ann Intern Med*. 1989;111:788-796.
7. Department of Health and Executive Yuan: Annual Statistics Report, Republic of China, 2002-2006. Available at: http://www.doh.gov.tw/CHT2006/DM/DM2_2.aspx?now_fod_list_no=10124&class_no=440&level_no=4. Accessed November 11, 2010.
8. Chang HY, Yeh WT, Chang YH, Tsai KS, Pan WH. Prevalence of dyslipidemia and mean blood lipid values in Taiwan: results from the Nutrition and Health Survey in Taiwan (NAHSIT, 1993-1996). *Chin J Physiol*. 2002;45:187-197.
9. Department of Health and Executive Yuan: The prevalence of type 2 diabetes mellitus. Department of Health, Taiwan 2009. Available at: http://www.doh.gov.tw/EN2006/index_EN.aspx. Accessed November 11, 2010.
10. Ceriello A, Ihnat MA. 'Glycemic variability': a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med*. 2010;27:862-867.
11. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of longer complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998;352:837-853.
13. Stettler C, Allemann S, Jüni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J*. 2006;152:27-38.
14. de Vegt F, Dekker JM, Ruhé HG, et al. Hyperglycaemia is associated with all cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia*. 1999;42:926-931.
15. DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001;161:397-405.
16. Sorkin JD, Muller DC, Fleg JL, Andres R. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care*. 2005;28:2626-2632.
17. Lawes CM, Parag V, Bennett DA, et al. Asia Pacific Cohort Studies Collaboration. Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care*. 2004;27:2836-2842.
18. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. *Diabetes Care*. 2008;31:2198-2202.
19. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57:1349-1354.
20. Muggeo M, Verlato G, Bonora E, et al. The Verona Diabetes Study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. *Diabetologia*. 1995;38:318-325.
21. Muggeo M, Verlato G, Bonora E, et al. Long-term instability of fasting plasma glucose predicts mortality in elderly NIDDM patients: the Verona Diabetes Study. *Diabetologia*. 1995;38:672-679.
22. Muggeo M, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: the Verona Diabetes Study. *Diabetes Care*. 2000;23:45-50.
23. Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.
24. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(Suppl 1):S1-S266.
25. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia*. 1996;39:1569-1576.
26. Jones SC, Saunders HJ, Qi W, Pollock CA. Intermittent high glucose enhances cell growth and collagen synthesis in cultured human tubulointerstitial cells. *Diabetologia*. 1999;42:1113-1119.