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Reduced Glomerular Filtration Rate in Asymptomatic Diabetic Patients

Predictor of Increased Risk for Cardiac Events Independent of Albuminuria

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OBJECTIVES This study aimed to investigate the prevalence of a reduced glomerular filtration rate (GFR) with and without albuminuria and its ability to predict cardiac events in asymptomatic diabetic patients undergoing stress-rest thallium-201 myocardial perfusion single-photon emission computed tomography.

BACKGROUND Diabetic patients have a higher prevalence of asymptomatic coronary heart disease. Therefore, identifying predictors of cardiac events in asymptomatic diabetic patients is needed.

METHODS In 269 asymptomatic patients, baseline evaluation included diabetes-related complications, including creatinine clearance (CrCl) and albuminuria. During follow-up (mean 2.3 ± 1.0 years), all cardiac events were recorded.

RESULTS Seventy-seven patients (29%) had a reduced GFR defined by CrCl <60 ml/min/1.73 m^2. Compared with the 177 patients with CrCl ≥60 ml/min/1.73 m^2, the reduced GFR group was older ($p < 0.0001$), had a longer duration of diabetes ($p = 0.002$), and had a higher prevalence of albuminuria ($p = 0.04$). Nevertheless, 35% of the reduced GFR group had normoalbuminuria. Patients with reduced GFR had a significant two-fold increase in total cardiac events (unstable angina, nonfatal myocardial infarction, and cardiac procedures) (25% vs. 13%, $p = 0.019$), and multivariate analysis found that reduced GFR was an independent predictor of cardiac events (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.1 to 4.46). Other independent predictors of cardiac events included stress-induced abnormal myocardial perfusion imaging (OR 3.1, 95% CI 1.3 to 7.5), an electrocardiographic ischemic response (OR 2.7, 95% CI 1.01 to 7.14), and peripheral artery disease (OR 2.1, 95% CI 1.05 to 4.23); however, albuminuria was not.

CONCLUSIONS A reduced GFR was common in our group of asymptomatic diabetic patients and was associated with a two-fold increase in cardiac events. Multivariate analysis found that reduced GFR independent of albuminuria was a significant predictor of cardiac events. (J Am Coll Cardiol 2004;44:2142–8) © 2004 by the American College of Cardiology Foundation

Diabetes mellitus (DM) is associated with a more than three-fold increase of coronary artery disease (CAD) (1). Patients with diabetes are often asymptomatic, and the prevalence of silent ischemia diagnosed by noninvasive techniques ranges from 10% to 30% (2). The American Diabetes Association recommended noninvasive testing in diabetics with evidence of peripheral artery disease, resting electrocardiographic (ECG) abnormalities, or the presence of additional risk factors (3). However, others have argued that there is not enough evidence to perform routine noninvasive testing in asymptomatic diabetic patients (4), and there is a need for further characterization of a high-risk subgroup in whom early diagnosis and treatment can reduce subsequent cardiac events and improve prognosis.

Several studies in the past have suggested that both microalbuminuria and macroalbuminuria are risk factors for cardiovascular morbidity and mortality (5,6). These entities are clinically defined by the urinary albumin excretion rate or albumin/creatinine ratio (6). In "classic" diabetic nephropathy, after the phase of microalbuminuria, there is a continued increase in urinary albumin excretion with a declining glomerular filtration rate (GFR). This phase, characterized by macroalbuminuria, relates to the histologic findings of glomerulosclerosis and is often accompanied by diabetic retinopathy. However, the entity of non-albuminuric chronic kidney disease, defined by reduced GFR, previously described in the general population, has recently emerged as a common and distinct form also in diabetes (7,8). The pathogenesis of this entity is still undetermined; however, atherosclerosis has been suggested as one possible mechanism (7). Diffuse atherosclerosis may be the link between chronic kidney disease and cardiovascular mortality and morbidity, as shown by several recent studies (9–11). Diabetic patients were included in these studies but were not analyzed separately. Moreover, the predictive value of non-albuminuric chronic kidney disease for cardiac events in asymptomatic diabetic patients is

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
CrCl = creatinine clearance
CVD = cardiovascular disease
DM = diabetes mellitus
ECG = electrocardiogram/electrocardiographic
GFR = glomerular filtration rate
OR = odds ratio
PVD = peripheral vascular disease
SPECT = single-photon emission computed tomography

unknown. The aims of the present study were to determine in a group of asymptomatic diabetic patients undergoing stress-rest thallium (Tl)-201 myocardial perfusion single-photon emission computed tomography (SPECT), the prevalence of reduced GFR with and without albuminuria, as well as the association between baseline reduced GFR and subsequent cardiac events.

METHODS

Study population and study design. Between January 1999 and February 2003, a total of 1,587 diabetic patients underwent a stress Tl-201 myocardial perfusion SPECT study in our laboratory at Kaplan Medical Center, a university hospital serving an area of 450,000 people in the center of Israel. Among them there were 324 patients who met the following inclusion criteria: 1) asymptomatic, defined by a lack of chest pain or anginal equivalent, according to a standard questionnaire administrated on the day of cardiac testing by the physician performing the test; 2) a minimum of one-year follow-up. Twenty-two patients were excluded due to equivocal perfusion tests, and 33 patients were excluded due to a lack of complete clinical or laboratory data; 269 patients were included in the final analysis. This group of 269 patients were referred for perfusion study according to the treating physician's clinical judgment for one or more of the following reasons: risk assessment before general surgery (21%), history of CAD, myocardial infarction (MI), or angiography demonstrating ≥50% occlusion of a coronary artery (47%), abnormal resting ECG (44%), including MI (14%), and ST-segment changes (30%). Patients were followed for a mean period of 2.3 ± 1.0 years for occurrence of cardiac events. The follow-up was based on computerized charts available in our hospital since 1997. In order to ascertain cardiac outcomes, patients or treating physicians were contacted by telephone calls by staff personnel blinded to baseline kidney function. Two patients were lost to follow-up. We defined as major cardiac events: non-fatal MI documented by appropriate cardiac enzyme level changes and ECG evidence of acute MI and cardiac death determined by a death certificate or hospital record. Minor cardiac events included unstable angina (documented by in-hospital diagnosis of resting ischemia without evidence of acute MI) and coronary re-vascularization (either coronary artery bypass graft surgery or percutaneous coronary intervention). Only the first event was used for analysis, and in patients who had major and minor events, the major cardiac event was considered. Total events included major and minor cardiac events.

Stress and imaging protocol. EXERCISE TEST. Patients performed a symptom-limited exercise treadmill test using the standard Bruce protocol. At near-maximal exercise, Tl-201 (3.0 to 3.5 mCi) was injected intravenously with the dose adjusted for the patient's weight, and exercise was continued at maximal workload for 1 min.

Pharmacologic test. Dipyridamole stress was performed in patients who were unable to perform an exercise stress test. Patients were tested after an overnight fast and discontinuation of xanthine-containing products for 24 h before the test. Intravenous dipyridamole was infused at rate 0.14 mg/kg/min during 4 min, up to total dose 0.56 mg/kg, under ECG and blood pressure monitoring. Thallium was injected 4 min later, and scintigraphy was performed after stress completion.

Imaging. The SPECT imaging was performed <6 min after stress Tl-201. The Tl-201 redistribution imaging was performed 3 h after stress imaging. Re-injection of Tl-201 (1 mCi) was performed in the presence of a significant stress perfusion defect immediately after stress SPECT acquisition. All SPECT studies were acquired on a single-head gamma camera (Elscint Ltd., Haifa, Israel) equipped with a low-energy, all-purpose collimator. Images were acquired using a continuous mode on a circular orbit over 180° arc, starting at the 45° right anterior oblique projection and ending at the 45° left anterior oblique projection, for a total of 60 projections at 20 to 25 s per projection. One energy window was used, consisting of a 20% windowed centered on the 70-keV peak. All projections were acquired into a 64 × 64 image matrix, corrected for non-uniformity, center of rotation, and patient or organ movement.

Clinical and ECG responses to stress. During both types of stress, the 12-lead ECG was recorded each minute and continuously monitored for leads aVF, V_1, and V_5. Significant ST-segment depression during the stress test was defined as 1 mm of horizontal or downsloping or 1.5 mm of upsloping ST-segment depression occurring 80 ms after the J point. The ECG response to stress was categorized as ischemic in the presence of a significant stress-induced ST-segment depression in the absence of ST-T segment changes on the baseline ECG. The clinical response to stress was categorized as ischemic when exercise-induced typical angina pectoris or anginal equivalent symptoms occurred.

Image interpretation. For each study, a semi-quantitative visual interpretation of SPECT was performed by dividing short-axis and vertical long-axis tomograms into 17 segments. Each segment was graded with a 5-point scoring system (0 = normal, 4 = absent uptake). These segments were assigned to four evenly spaced regions in distal ventricular, six mid-ventricular, and basal slices of the

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short-axis views and one apical segment on the mid-ventricular long-axis slice. A summed stress score (SSS) was obtained by adding the scores of the 17 segments of the stress images. A summed redistribution score (SRS) was obtained by adding the scores of the 17 segments at-rest images. The sum of the differences between the stress and redistribution scores of each of the 17 segments was defined as the summed difference score (SDS) or reversibility score, an index of jeopardized myocardium. Image interpretation was done by physicians blinded to the creatinine clearance (CrCl) and albumin stratification.

Clinical evaluation. Patients were classified as having diabetes based on a treating physician's previous diagnosis ascertained by either treatment for diabetes or fasting glucose levels ≥126 mg/dl on two occasions. Baseline CrCl was calculated by the use of the Cockroft-Gault formula: 140 − age (years) × weight (kg)/72 × serum creatinine concentration (mg/dl) × 0.85 if female (12). The formula was expressed per 1.73 m^2 body surface area. Reduced GFR was defined as CrCl <60 ml/min/1.73 m^2. Albumin excretion was based on spot collection and determination of μg albumin/mg creatinine: normal = <30; microalbuminuria = 30 to 299; macroalbuminuria = ≥300 (13). Microalbumin was determined by immunoturbidimetric assay (Roche Diagnostic GmbH, Mannheim, Germany). In five patients (one in the CrCl <60 ml/min/1.73 m^2 group and four in the CrCl ≥60 ml/min/1.73 m^2 group), urine albumin measurements were not available. Albuminuria was confirmed in 85% of the patients by at least one more urine specimen. Urine testing was done 5 to 92 days before or after stress test. Clinical data on diabetic complications were taken from hospital or HMO clinic charts.

Statistical analysis. Data were analyzed with SAS statistical software, version 8 (SAS Institute, Cary, North Carolina), and $p < 0.05$ was considered significant. Continuous variables were reported as the mean value ± SD, and comparisons between groups were performed using the *t* test. Categorical data were compared by the chi-square test or Fisher exact test whenever the asymptomatic chi-square test was not appropriate (i.e., the excepted value of a cell count was <5). The Kaplan-Meier method was used for the survival curves, and curves were compared by the log-rank test. The variables included in the analysis of predictors for reduced GFR and cardiac events were chosen based on previous data and included smoking, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, microalbuminuria and macroalbuminuria, usage of beta-blockers, aspirin, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and statins (14). To determine the predictors of cardiac events, logistic regression analysis was performed by the model selection procedure (15). Potential variables to be included in the model were identified as the variables that were statistically significant ($p < 0.05$). Akaike's information criteria were used for choosing the best model (16).

RESULTS

Baseline characteristics. The study group included 269 patients (173 males and 96 females). The mean age was 66.1 ± 9.6 years, and the mean duration of diabetes was 11.4 ± 8.2 years. There were 77 patients (29%) with at least moderately reduced GFR (CrCl <60 ml/min/1.73 m^2) and 192 patients (71%) without reduced GFR (CrCl ≥60 ml/min/1.73 m^2). Baseline characteristics of both groups are shown in Table 1. Patients with reduced GFR were significantly older, more of them were women, and their body mass index was lower. Patients with reduced GFR had a longer duration of diabetes, but the glycemic control based on glycosylated hemoglobin (HbA_{1C}) measurements was similar. There were no significant differences between the two groups in the prevalence of CAD history, hypertension, smoking, and hyperlipidemia.

More patients in the reduced GFR group received insulin ($p = 0.04$). There were no significant differences in the usage of sulfonylurea and acarbose (54% vs. 53% and 8% vs. 5.3%, respectively) and less received metformin (42% vs. 59%, $p = 0.012$), probably due to avoidance of metformin in patients with impaired renal function. There were no significant differences in the usage of the following medications between patients with and without reduced GFR: beta-blockers (62% vs. 67%), aspirin (73% vs. 82%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (70% in both groups), calcium channel blockers (32% vs. 28%), and statins (66% vs. 65%).

Retinopathy, non-proliferative and proliferative, was more common in the reduced GFR group ($p = 0.034$). The distribution of albumin excretion categories was significantly different ($p = 0.04$) in patients with and without baseline reduced GFR. Normoalbuminuria was found in almost one-half of the patients without reduced GFR; however, normoalbuminuria was also found in a substantial number of patients with reduced GFR (35.5%). More patients in the reduced GFR group had macroalbuminuria, as compared with the group without reduced GFR (35.5% vs. 21%). Microalbuminuria was found in 29% of the group with reduced GFR and 33% of the group without reduced GFR. There were no significant differences in the prevalence of peripheral vascular disease (PVD), and peripheral neuropathy, defined by the presence of symptoms, occurred in 55% in the reduced GFR group compared with 47% in the group without reduced GFR.

Abnormal myocardial perfusion images were similarly common findings in both groups: 65% in the reduced GFR and 62% in the group without reduced GFR. There were no significant differences between the two groups in the SSS, SRS, and SDS.

Clinical outcomes. Patients were followed for a mean period of 2.3 ± 1.0 years. During this period, 44 events (16%) occurred in the study group, including 32 minor events and 12 major events. Patients with CrCl

Table 1. Baseline and Laboratory Characteristics Stratified by Baseline Creatinine Clearance

	CrCl		
	<60 ml/min/1.73 m^2 (n = 77)	≥60 ml/min/1.73 m^2 (n = 192)	p Value
Age (yrs)	71.6 ± 8.5	63.9 ± 9.1	< 0.0001
Female (%)	45	32	0.034
BMI (kg/m^2)	26.9 ± 4.2	29.8 ± 4.3	< 0.0001
Duration of diabetes (yrs)	14.3 ± 9.6	10.3 ± 7.3	0.002
Insulin treatment (%)	30	14	0.004
Reasons for referral			
History of CAD (%)	49	46	NS
Abnormal ECG (%)	48	42	NS
Assessment before surgery (%)	18	22	NS
Hypertension (%)	88	83	NS
Smoking (%)	13	20	NS
PVD (%)	53	44	NS
Stroke (%)	14	13	NS
Retinopathy (%)	49	35	0.034
LDL cholesterol (mg/dl)	112 ± 34	110.5 ± 32	NS
HDL cholesterol (mg/dl)	44.2 ± 12	43.3 ± 11	NS
Triglycerides (mg/dl)	186 ± 116	192 ± 120	NS
HbA_{1c} (%)	7.7 ± 1.6	7.9 ± 1.9	NS
Microalbuminuria* (%)	22 (29)	62 (33)	0.04
Macroalbuminuria (%)	27 (35.5)	39 (21)	
Normoalbuminuria (%)	27 (35.5)	87 (46)	
AMPI (%)	65	62	NS
SSS	9.9 ± 11.4	10.4 ± 12.0	NS
SRS	5.6 ± 8.0	4.9 ± 8.7	NS
SDS	4.3 ± 6.1	5.4 ± 7.4	NS

*In five patients (one in the group of CrCl <60 ml/min/1.73 m^2 and four in the group of CrCl ≥60 ml/min/1.73 m^2), urine albumin measurements data were missing. Data are expressed as the mean value ± SD or number (%). Categorical data were compared by the chi-square test.

AMPI = abnormal myocardial perfusion imaging; BMI = body mass index; CAD = cornary artery disease; CrCl = creatinine clearance; ECG = electrocardiogram; HbA_{1c} = glycosylated hemoglobin; HDL and LDL = high- and low-density lipoprotein, respectively; NS = not significant; PVD = peripheral vascular disease; SSS = summed stress score; SRS = summed redistribution score; SDS = summed differences score.

<60 ml/min/1.73 m^2 had about two-fold more total events than did patients with CrCl ≥60 ml/min/1.73 m^2: 25% vs. 13%, p = 0.019 (Table 2). Nonfatal MI, unstable angina, and percutaneous coronary intervention occurred more often in the reduced GFR group, as compared with the group without reduced GFR; however, these differences did not reach statistical significance. Patients with reduced GFR had significantly reduced event-free survival compared with patients without reduced GFR (p = 0.012), demonstrated by the Kaplan-Meier curve (Fig. 1). There was no statistically significant difference in the Kaplan-Meier event-free survival curves stratified by normoalbuminuria and albuminuria (data not shown).

Multivariate logistic analysis of predictors of cardiac event is shown in Table 3. The following parameters were found to be independent predictors of cardiac events: abnormal myocardial perfusion imaging (OR [odds ratio] 3.1, 95% confidence interval [CI] 1.3 to 7.5), stress-induced ECG ischemic response (OR 2.7, 95% CI 1.01 to 7.14), reduced GFR (OR 2.2, 95% CI 1.1 to 4.46), and PVD (OR 2.1, 95% CI 1.05 to 4.2). Age, history of CAD, smoking, left ventricular function, and microalbuminuria and macroalbu-

Table 2. Cardiac Events in Patients Stratified by Baseline Creatinine Clearance

	CrCl		
Events	<60 ml/min/1.73 m^2 (n = 77)	≥60 ml/min/1.73 m^2 (n = 192)	p Value
Total events (%)	19 (25)	25 (13)	0.019*
Nonfatal MI (%)	6 (9.4)	6 (3.4)	0.09†
Unstable angina (%)	6 (9.4)	8 (4.5)	NS†
PCI (%)	6 (9.4)	7 (4.0)	NS†
CABG (%)	1 (1.7)	4 (2.3)	NS†

*Compared by the chi-square test. †Comparisons by the Fisher exact test. Data are expressed as the number (%) of subjects.

CABG = coronary artery bypass graft surgery; CrCl = creatinine clearance; MI = myocardial infarction; PCI = percutaneous coronary intervention.

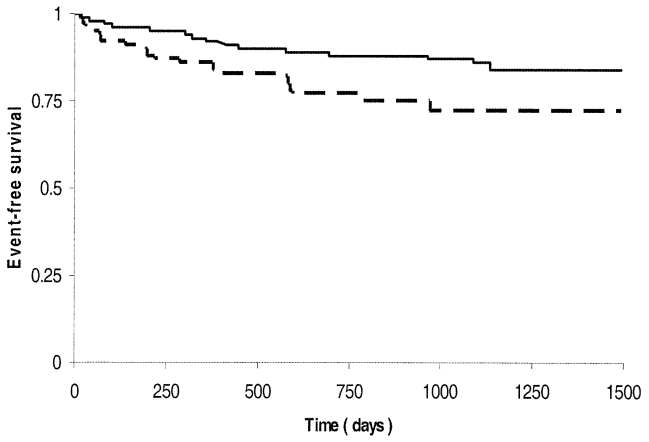

Figure 1. Kaplan-Meier event-free survival curves in patients with and without baseline reduced glomerular filtration rate (p = 0.019). **Broken line** = creatinine clearance (CrCl) <60 ml/min/1.73 m^2; **solid line** = CrCl ≥60 ml/min/1.73 m^2.

minuria were not found to be independent predictors of cardiac events.

DISCUSSION

In the current study of asymptomatic diabetic patients who underwent stress-rest Tl-201 myocardial perfusion SPECT, we found that 29% had at least moderately reduced GFR, defined by CrCl <60 ml/min per 1.73 m^2. Among patients with reduced GFR, 64% had no macroalbuminuria and 35% had no albuminuria (microalbuminuria or macroalbuminuria). These findings are consistent with the results of recent studies showing that normoalbuminuria is a common finding in patients with type II DM and at least moderately reduced GFR (7,8). Analysis of data from the National Health and Nutrition Examination Survey (NHANES III) showed that 13% of diabetics had moderate reduced GFR and 30% of them had no albuminuria or retinopathy (8). Moreover, previous data from the NHANES III showed that 20% of diabetics with even more severe chronic kidney disease (GFR <30 ml/min/1.73 m^2) had no albuminuria (17). In another study of 301 outpatients with type II DM, 36% had moderate reduced GFR, and 39% of them were normoalbuminuric (9). All these data imply that chronic kidney disease with normoalbuminuria is a common entity in type II DM.

Table 3. Multivariate Analysis of Predictors for Developing Cardiac Events

	OR	95% CI	p Value
Abnormal myocardial perfusion imaging	3.1	1.3–7.52	0.013
Stress ECG ischemic response	2.7	1.01–7.14	0.048
CrCl <60 ml/min/1.73 m^2	2.2	1.1–4.46	0.026
Peripheral vascular disease	2.1	1.05–4.23	0.034
Micralbuminuria	0.68	0.35–1.3	NS
Macroalbuminuria	0.82	0.41–1.7	NS

Logistic regression analysis of cardiac event predictors. Variables included age, history of coronary artery disease, smoking, left ventricular function, abnormal stress-induced electrocardiographic (ECG), abnormal myocardial perfusion imaging, peripheral vascular disease, creatinine clearance (CrCl) <60 ml/min/1.73 m^2, micro- and macroalbuminuria.

CI = confidence interval; OR = odds ratio.

The major finding of this study is that reduced GFR was a significant predictor of cardiac events. We found that diabetics with at least moderately reduced GFR at baseline, compared with diabetics without reduced GFR, had an OR of 2.2 for developing subsequent cardiac events. It was shown that PVD was an additional significant independent predictor of cardiac events, whereas albuminuria and retinopathy were not. These data provide supportive evidence that chronic kidney disease, defined by reduced GFR, independent of albuminuria, is a distinct entity, and the pathogenesis may be different from the classic diabetic glomerulosclerosis characterized clinically by progressive albuminuria and retinopathy (6). Furthermore, the association between reduced GFR and increased risk of cardiac events suggests that the underlying pathogenesis is related to atherosclerosis. Studies of diabetic patients with reduced GFR and normoalbuminuria lack data on kidney histology; however, atherosclerosis involving renal arteries or smaller-caliber arteries has been suggested as a possible underlying process (7). In a study of diabetic patients, half of them with normoalbuminuria, the GFR correlated with carotid intimal-medial thickness and resistance index of renal intralobar arteries, as determined by pulsed Doppler sonography (18). The association between cardiovascular disease (CVD) morbidity and mortality and moderate reduction of GFR, in the general population, has been reported recently (9,10,19). In addition, in patients with known cardiac disease undergoing percutaneous coronary interventions, even a moderate reduction of GFR was associated with increased one-year mortality (11,20). These studies included diabetics but did not analyze them separately nor addressed the issue of non-albuminuric chronic kidney disease. Our findings confirm and extend these findings in the diabetic population. Furthermore, the present study shows that reduced GFR predicted cardiac events, independent of the presence and severity of albuminuria.

An association between microalbuminuria and macroalbuminuria and CVD morbidity and mortality has been shown by several studies (5,19,21,22). The difference between our results and previous data can be related to differences in study populations and design. Our patients were relatively old and many of them had evidence of CVD at baseline. Interestingly, in a study that evaluated long-term mortality of diabetic patients, the value of urinary albumin excretion disappeared, suggesting that albuminuria may be a stronger risk factor for CVD in the short term (23). In addition, most previous studies did not analyze the GFR, a more accurate measurement of renal function than serum creatinine. Further studies that will include both urine albumin measurements and renal function estimation (by simple measures, such as the Cockroft-Gault formula), may be useful in dissecting the prognostic contribution of

albuminuric and non-albuminuric chronic kidney disease in different subgroups of diabetic patients.

In the current study, despite the fact that patients with reduced GFR had a similar baseline prevalence of CAD and PVD, as the group without reduced GFR, they developed significantly more cardiac events. Moreover, this increased risk was not explained by the traditional risk factors. These intriguing findings are in accordance with recent data suggesting that patients with chronic kidney disease have other nontraditional risk factors contributing to the excess risk of cardiac events (14). These factors include endothelial dysfunction, oxidative stress, inflammation, and increased coagulation, which can lead to increased risk of plaque rapture and increased risk of arrhythmias (14,19). All of these data are consistent with the current recommendation of the National Kidney Foundation that patients with chronic kidney disease should be considered in the highest risk group for cardiovascular diseases (24). Further intervention studies are needed to determine whether different therapeutic modalities, including intensive control of both traditional and nontraditional risk factors for CAD, alter the unfavorable clinical course of diabetic patients with reduced GFR.

Our study included asymptomatic diabetic patients who underwent Tl-201 myocardial perfusion SPECT. Previous studies using noninvasive tests found that the prevalence of silent ischemia was between 10% and 30% (2). In our study, the prevalence of abnormal myocardial perfusion imaging abnormalities was even higher. This high prevalence can be due to the baseline characteristics of our study group, which included a substantial number of patients with a history of CAD and PVD. During follow-up, 16% developed cardiac events, and both stress-induced ECG ischemic response and abnormal myocardial perfusion imaging were independent predictors of events. Most previous studies of asymptomatic diabetic patients also showed that abnormal myocardial scintigraphy is a strong independent predictor of cardiac events (25–27). However, one study of 120 asymptomatic diabetic patients found that silent ischemia diagnosed by noninvasive testing was only weakly associated with cardiac events, whereas cardiac autonomic neuropathy was a significant independent predictor (28). Nevertheless, 50% of patients in this study who had both silent ischemia and cardiac autonomic neuropathy developed events. The contribution of cardiac autonomic neuropathy could not be assessed in the current study due to the lack of standard testing, but there was no difference in the prevalence of peripheral neuropathy, which was high in both groups, and often accompanies autonomic neuropathy. Other predictors found in previous studies included coronary stenosis, peripheral or carotid occlusive arterial disease, diabetes duration, and retinopathy (25–27). Based on our data and previous studies, noninvasive testing (i.e., stress-induced ECG and myocardial perfusion test) has an important role in assessing cardiac risk in asymptomatic diabetic patients. However, routine usage of these noninvasive tests in all diabetic patients is still a controversial issue due to uncertainties regarding the clinical benefit of early intervention and cost-effectiveness (4). Additional markers that identify high-risk patients can lead to better selection of patients who would benefit from noninvasive testing. Our data suggest that reduced GFR, independent of albuminuria, is an important predictor of cardiac events and should be searched for in the routine assessment of diabetic patients.

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REFERENCES

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–44.
2. Navare SM, Heller GV. Role of stress single-photon emission computed tomography imaging in asymptomatic patients with diabetes. Am Heart J 2004;147:753–5.
3. American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes. Diabetes Care 1998;21:1551–9.
4. Grundy SM, Garber A, Goldberg R, et al. Prevention Conference VI: diabetes and cardiovascular disease. Writing Group IV: lifestyle and medical management of risk factors. Circulation 2002;105:153–8.
5. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non–insulin-dependent diabetes mellitus: a systematic overview of the literature. Arch Intern Med 1997;157:1413–8.
6. Cooper ME. Pathogenesis, prevention and treatment of diabetic nephropathy. Lancet 1998;352:213–9.
7. Kramer HJ, Nguyen QD, Curhan G, Hsu C. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–7.
8. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 2004;27:195–200.
9. Henry RMA, Kostense PJ, Bos G, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. Kidney Int 2002;62:1402–7.
10. Rahman M, Brown CD, Coresh J, et al. The prevalence of reduced glomerular filtration rate in older hypertensive patients and its association with cardiovascular disease. Arch Intern Med 2004;164:969–76.
11. Sadeghi HM, Stone GW, Grines CL, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. Circulation 2003;108:2769–75.
12. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
13. American Diabetes Association. Position statements: nephropathy in diabetes. Diabetes Care 2004;27:S79–83.
14. McCullough PA. Cardiorenal risk: an important clinical intersection. Rev Cardiovasc Med 2002;3:71–6.
15. Collett D. Modeling Binary Data. London: Chapman and Hall, 1991.
16. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Statist Med 1997;16:2349–80.
17. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. Kidney Int 2002;61:2165–75.
18. Taniwaki H, Nishizawa Y, Kawagishi T, et al. Decrease in glomerular filtration rate in Japanese patients with type 2 diabetes is linked to atherosclerosis. Diabetes Care 1998;21:1848–55.
19. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease. A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108:2154–69.

20. Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol 2002;39:1113–9.
21. Stiegler H, Standl E, Schulz K, Roth R, Lehmacher W. Morbidity, mortality, and albuminuria in type 2 diabetic patients: a three-year prospective study of random cohort in general practice. Diabet Med 1992;9:646–53.
22. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G. Prospective study of microalbuminuria as predictor of mortality in NIDDM. Diabetes 1992;41:736–41.
23. Damsgaard EM, Froland A, Jorgensen OD, Morgensen CE. Prognostic value of urinary albumin excretion rate and other risk factors in elderly diabetic patients and non-diabetic control subjects surviving the first 5 years after assessment. Diabetologia 1993;36:1030–6.
24. Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with chronic kidney disease. Am J Kidney Dis 2003;41 Suppl 3:S1–91.
25. De Lorenzo A, Lima RSL, Siqueira-Filho AG, Pantoja MR. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. Am J Cardiol 2002; 90:827–32.
26. Cosson E, Paycha F, Paries J, et al. Detecting silent coronary stenosis and stratifying cardiac risk in patients with diabetes: ECG stress test or exercise myocardial scintigraphy? Diabet Med 2004; 21:342–8.
27. Faglia E, Favales F, Calia P, et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary artery disease: 5-years follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). Diabetes Care 2002;25: 2032–6.
28. Valensi P, Regis-Nessim S, Harfouche B, et al. Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. Diabetes Care 2001;24:339–43.