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Prevalence of Albuminuria and Cardiovascular Risk Profile in a Referred Cohort of Patients with Type 2 Diabetes: An Asian Perspective

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Abstract

Background: Microalbuminuria (MA) is a risk marker for diabetic nephropathy and cardiovascular (CV) disease (CVD) in patients with diabetes. This study aimed to describe the prevalence of albuminuria, CV risk factors, and treatments for renal and CV protection in an Asian population with type 2 diabetes.
Methods: This cross-sectional study conducted in eight Asian countries enrolled normotensive/hypertensive adults with type 2 diabetes without known proteinuria and/or non-diabetic kidney disease. Exclusion criteria were type 1 diabetes, menstruation, pregnancy, and acute fever. A single random urinary albumin/creatinine test was carried out in all patients.
Results: Of 8,561 patients, 14% had diabetic retinopathy, and 17% and 21% had history of CV disease and smoking, respectively. Normoalbuminuria was seen in 44%, MA in 44%, and macroalbuminuria in 12%. Target glycosylated hemoglobin (HbA1c) (<7%) was reached in only 37% of 3,834 patients with available values. Diabetes was managed by diet alone in 6%, while others received oral hypoglycemic drugs and/or insulin. In total, 75% did not reach target blood pressure (BP) of ≤130/80 mm Hg. Antihypertensive drugs were prescribed to 52%, with the number of drugs increasing as the level of systolic BP increased. Drugs blocking the renin–angiotensin system were most commonly prescribed, followed by calcium channel blockers. Lipid-lowering drugs and anticoagulant/antiplatelet agents were used in about 30% and 25% of patients, respectively.
Conclusions: Asian patients with type 2 diabetes had a high prevalence of MA and reduced kidney function. Furthermore, BP and HbA1c control was only achieved in a minority of patients. Aggressive risk management by administration of reno- and cardioprotective treatments is urgently needed.

Introduction

MICROALBUMINURIA (MA), which is defined as an abnormal increase in the rate of urinary excretion of albumin to between 30 and 300 mg/24 h, was first described in patients with diabetes mellitus in 1969.[1] It is the earliest manifestation of diabetic kidney disease in both type 1 and type 2 diabetes and a strong risk marker for the progression of nephropathy.[2] Several prospective epidemiologic studies have also demonstrated that MA is an important risk factor for cardiovascular (CV) disease (CVD) in patients with type 2 diabetes. A meta-analysis of these studies showed that the

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presence of MA doubled the risk of CV morbidity or mortality.[3]

Besides its role in diabetic nephropathy, MA is also associated with essential hypertension,[4] ischemic heart disease,[5] atherosclerosis,[6] acute stroke,[7] and diastolic dysfunction[8] and is an independent powerful risk factor for fatal and nonfatal vascular events and all-cause mortality in subjects without diabetes.[9,10] In fact, Ibsen et al.[11] showed that a reduction in urinary albumin excretion was associated with a reduction in CV events in hypertensive patients treated with blockade of the renin-angiotensin system (RAS).

In the last 4 decades, the knowledge about MA and its implications has grown significantly. Guidelines such as the ones produced by the American Diabetes Association (ADA) recommend annual screening for MA in patients with diabetes.[12] However, since MA is not associated with clinical symptoms, it is often underdiagnosed, and the awareness of its importance as renal and CV risk marker is still poor. Several interventional studies aiming at improved glycemic control and blockade of the RAS have shown that the onset of diabetic nephropathy can be postponed in patients with type 2 diabetes with normoalbuminuria and/or MA.[13–15] Despite the knowledge about early identification and intervention in high-risk patients with type 2 diabetes, diabetic nephropathy is still the leading cause of end-stage renal disease in most countries of the world.[16] Thus, it is critically important to identify incident kidney disease in patients with diabetes at the earliest stage by screening for MA in order to best prevent evolution to overt nephropathy and subsequent end-stage renal disease.

In 2003, the International Diabetes Federation and the International Society of Nephrology developed the theme "Diabetes could cost you your kidneys: act now!" In collaboration with these organizations, a study was created on Developing Education on Microalbuminuria for Awareness of Renal and CV risk in Diabetes (DEMAND). This cross-sectional, global, clinic/medical center-based study described the prevalence and risk factors for MA and implementation of CV protective treatment in normotensive and hypertensive patients with type 2 diabetes without known proteinuria and/or kidney disease not due to diabetes.[17] We present here data from Asia, including the People's Republic of China, Hong Kong, Indonesia, the Republic of Korea, Malaysia, Singapore, the Republic of China, and Thailand.

Materials and Methods

Study design

The DEMAND study was a multinational, cross-sectional, clinic/medical center-based study designed to evaluate the prevalence and determinants of MA and macroalbuminuria in patients with type 2 diabetes by random screening at each participating center during the interval from June to September 2003. The goal was to enroll 10 patients with type 2 diabetes per center. The study was mainly performed in primary care settings. The study was endorsed and the centers selected by local diabetes associations in collaboration with Bristol-Myers Squibb (New York, NY) and sanofi-aventis (Paris, France). A total of eight different countries in Asia, including the People's Republic of China (50 sites), Hong Kong (74 sites), Indonesia (30 sites), the Republic of Korea (20 sites), Malaysia (50 sites), Singapore (97 sites), Republic of China (14 sites), and Thailand (nine sites) participated. The study protocol was approved by the Ethics Committee of each participating clinic, and all patients gave written informed consent.

Patients

Eligible patients were normotensive or hypertensive women and men between 18 and 80 years with type 2 diabetes mellitus (World Health Organization criteria) without prior known proteinuria and/or kidney disease due to diabetes. Exclusion criteria included type 1 diabetes mellitus, menstruation, pregnancy, and acute fever.

Concomitant medications such as cimetidine (which may falsely elevate creatinine levels) and drugs containing azo dyes, nitrofurantoin, and riboflavin (which affect the readability of the reagent strips) were prohibited. Contamination of the urine specimen with soaps, detergents, antiseptics, or skin cleansers or the use of urine preservatives other than boric acid (1.0 g/L) was also restricted.

Investigations

All participating general practitioners, physicians, and nurses received the study protocol and were instructed in performing the urinary albumin/creatinine test (single determination) and blood pressure (BP) measurement with an appropriate cuff after approximately 10 min of rest in the sitting position (single recording).

Furthermore, demographic profile (age, gender, ethnicity, and region), clinical characteristics (height, body mass index [BMI], known duration of diabetes, glycosylated hemoglobin [HbA1c], and serum creatinine), medical history (retinopathy, diabetic foot lesion, CVD, smoking, hyperlipidemia, and family history of diabetes/hypertension/CVD), and simultaneous treatments (glucose-lowering treatment, antihypertensive agents, lipid-lowering drugs, and antiplatelet/anticoagulant agents) for each patient were recorded on a single-page clinical report form.

Presence of CVDs such as coronary artery disease, myocardial infarction, left ventricular hypertrophy, congestive heart failure, stroke, transient ischemic attack, or peripheral vascular disease was based on medical records and information obtained during the interview. Standardized definitions of the different CVDs were not applied. Presence of hyperlipidemia was based on objective measurements as stated in the medical records. Presence of arterial hypertension was based on medical history of patients receiving BP-lowering therapy.

A single random urine albumin/creatinine ratio was measured using Bayer reagent strip Multistix® 10SG (Siemens Medical Solutions Diagnostics, Tarrytown, NY and Los Angeles, CA). According to this semiquantitative strip test, normoalbuminuria is defined as albumin-to-creatinine ratio <30 mg/g, MA as 30–299 mg/g, and macroalbuminuria as ≥ 300 mg/g. According to the manufacturer, the Multistix 10SG test has a sensitivity of 84% and specificity of 91% for the albumin-to-creatinine ratio. Urine samples with concentrations of creatinine of ≤ 10 mg/dL were discarded as too dilute, as prespecified in the protocol.

We used the Modification of Diet in Renal Disease 2 formula to calculate the estimated glomerular filtration rate (eGFR) (in mL/min/1.73 m^2).[18] The stages of chronic kidney

disease were defined according to the American National Kidney Foundation: stage 1, eGFR ≥90; stage 2, eGFR 60–89; stage 3, eGFR 30–59; stage 4, 15–29; and stage 5, eGFR <15 or dialysis.[19] Patients in stage 1 and 2 needed to have structural or functional abnormalities of the kidney, for example, MA/macroalbuminuria, to be classified as having chronic kidney disease. An eGFR of <60 mL/min/1.73 m^2 is defined as renal insufficiency.

Statistical analysis

Univariate comparisons of the impact of independent variables on the average levels of continuous and categorical dependent variables were made using one-way analysis of variance and the χ^2 statistic, respectively. A minimal multivariate model predicting the level of albuminuria (normal albuminuria, MA, or macroalbuminuria) was constructed using "proportional odds" ordinal logistic models as realized by the function lrm for S.[19] Parallel models predicting the albumin/creatinine ratio (log transformed) as a continuous variable were built using ordinary linear regression models and gave comparable results. To build these models, independent variables were added to the model in the order in which they increased the total likelihood of the model, taken as a measure of explanatory power, until no further additions significantly ($P < 0.05$) improved the likelihood, using the likelihood ratio test. All data management was performed using SAS for Windows version 9.0 (SAS Institute, Cary, NC), and all analyses were performed using S-Plus version 6.2 for Windows (Insightful Corp., Seattle, WA).

Table 1. Characteristics of Patients with Type 2 Diabetes

Characteristics (n = *8,561)*	n	%
Demographic		
Countries and regions		
People's Republic of China	4,238	50
Hong Kong	403	5
Indonesia	770	9
Republic of Korea	184	2
Malaysia	181	2
Singapore	499	6
Republic of China	1,648	19
Thailand	638	7
Gender		
Male	4,208	49
Female	4,314	50
Missing	39	<1
Age (years) (mean ± SD)	60.2 ± 11.6	
20s	63	1
30s	323	4
40s	1,279	15
50s	2,333	27
60s	2,579	30
70s	1,688	20
80s	178	2
Missing	118	1
Ethnicity		
White	2	<1
Black	1	<1
Asian	7,842	92
Hispanic	0	0
Other	0	0
Missing	716	8
Clinical (*n* = 8,561)		
BMI (kg/m^2)	24.7 ± 3.9	
Missing	116	1
Duration of diabetes (years)	7.3 ± 6.2	
Missing	642	8
HbA1c (%)	7.8 ± 1.8	
Missing	4,727	55
Medical history (*n* = 8,561)		
Family history of diabetes	3,234	38
Family history of CVD	1,490	17
Smoking history	1,794	21
History of hyperlipidemia	3,276	38
History of CVD	1,461	17
History of retinopathy	1,217	14
History of diabetic foot	314	4

Table 2. Medical Treatment in Patients with Type 2 Diabetes

Treatment	n	%
Glucose-lowering		
Diet-alone	514	6
Oral hypoglycemic agent	6,577	77
Insulin	637	7
Both oral hypoglycemic agent and insulin	774	9
Missing	59	1
Antihypertensive treatment		
On no antihypertensive medications	4,110	48
Diuretics	891	10
ACEI	1,905	22
ARB	735	9
Calcium channel blockers	1,902	22
Alpha blockers	190	2
Other antihypertensive agents	367	4
Lipid-lowering agents		
Statin	1,521	18
Other lipid-lowering agents	1,016	12
On anticoagulant/antiplatelet agents		
Aspirin	1,809	21
Warfarin	28	<1
On other anticoagulant/antiplatelet agents	273	3

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Results

A total of 8,561 patients were included in the study. Their characteristics are shown in Table 1. Overall, the mean age was 60 years, the gender distribution was 50/50, and the mean duration of diabetes was 7.3 years. Diabetic retinopathy was present in 14%, while 17% had history of CVD, and 21% had history of smoking. The mean HbA1c was 7.8% (data missing for 55% of patients), and HbA1c was at target level (<7%) in only 37% of 3,834 patients for whom the values were available.

Medical treatments received by patients are presented in Table 2. Only 6% of patients with type 2 diabetes were managed with diet alone, whereas the remaining received oral hypoglycemic drugs and/or insulin. Among the 8,561 patients, 250 (3%) had missing data with regard to antihypertensive drug use. Antihypertensive drugs were prescribed to

4,451 (52%) patients. Drugs blocking the RAS, followed by calcium channel blockers and diuretics, were most commonly used. The number of BP-lowering drugs prescribed increased with the level of systolic BP (SBP). The percentage of patients not receiving antihypertensive medication dropped from approximately 36% at a SBP of 140 mm Hg to approximately 14% at a SBP of 200 mm Hg. Only 30% of patients received lipid-lowering drugs, and anticoagulant/antiplatelet agents were given to about 25% of patients.

Normoalbuminuria was demonstrated in 44% and MA in 44%, and the remaining 12% had macroalbuminuria (Table 3). Overall, eGFR averaged 78 ± 127 mL/min/1.73 m^2 (data missing in 67% of patients). In the subset of patients with data permitting estimation of glomerular filtration rate (n = 2,841), 23% had renal insufficiency, that is, eGFR <60 mL/min/1.73 m^2. While 61% of patients did not achieve target SBP (<130 mm Hg), 62% did not achieve target diastolic BP (DBP) <80 mm Hg. In total, 6,250 (75%) had SBP ≥130 mm Hg and/or DBP ≥80 mm Hg.

Discussion

In this Asian cross-sectional study of patients with type 2 diabetes without previously known proteinuria or kidney disease, approximately 56% had MA or macroalbuminuria. Although serum creatinine data were missing in two-third of our patients, renal insufficiency was detected in 23% of those with available data. This large clinic/medical center-based study confirms and extends previous observations suggesting a high prevalence of MA in several Asian countries.[20–22] Our results highlight the need for more regular and earlier testing of MA to detect the presence of kidney disease due to diabetes. In fact, based on abundant evidence showing that MA predicts both renal and CV outcomes in patients with diabetes and in the general population, the latest European guidelines now include MA in routine testing because it is simple and cheap and has good predictive value.[23]

The main strength of our study was that it included a large, multinational referred cohort of subjects with type 2 diabetes in Asia with validated identification of predefined primary and secondary end points. Although there are other single-country studies assessing kidney function,[20–22] there are very few large multinational studies on MA in Asian subjects with diabetes and hypertension.[24] Moreover, our study enrolled a higher number of Asian patients and was part of a much larger global study to establish worldwide prevalence and risk factors of MA in patients with diabetes. Our study also had some limitations. First, we carried out only a single measurement of urinary albumin/creatinine ratio and arterial BP. However, the large sample size and the high frequency of diagnostic abnormality detected with a single urine collection minimize the uncertainty associated with day-to-day differences in urinary albumin excretion, and single measurement has been shown to be a useful tool for assessing MA in large epidemiological studies. A second limitation was that since we only looked at patients' historical data on lipids and HbA1c values, there was no standardized method for determining these values. Although cigarette smoking is a strong and modifiable risk factor for macrovascular disease in patients with diabetes,[25] we did not collect data on current smoking history. An additional limitation that may potentially confound the results of this regional analysis is the fact that almost 50% of patients were contributed by the Republic of China alone. Hence, because of unequal representation from different countries, the results may not be uniformly applicable to the eight participating Asian countries. Since our study was not population-based, there is a possibility of selection bias in relation to the participating centers. However, the prevalence of MA or macroalbuminuria in our study (56%) is comparable with 58.6% observed in a cross-sectional study of consecutively screened 5,549 patients with type 2 diabetes from 10 Asian countries.[24]

Table 3. Albuminuria, Kidney Function, and Arterial BP in Patients with Type 2 Diabetes

Variable	*Value*	*%*
Albuminuria		
None	3,794	44
MA	3,753	44
Macroalbuminuria	1,014	12
Log 2 (albumin/creatinine ratio) (mg of albumin/g of creatinine)	37 (2.9–467)[a]	
Serum creatinine (mg/dL)	1.01 ± 0.40	
Missing	5,700	67
MDRD GFR (mL/min)	78 ± 127	
Missing	5,720	67
SBP (mm Hg)	133 ± 18	
Missing	250	3
DBP (mm Hg)	79 ± 10	
Missing	258	3

MDRD GFR, modification of diet in renal disease glomerular filtration rate.

[a]The 95% confidence interval is given in parentheses.

Our study revealed an increased prevalence of several vascular risk factors. Patients with type 2 diabetes have a two to six times higher risk of fatal and non-fatal CV events than subjects without diabetes.[3,26,27] Patients with MA and macroalbuminuria suffer the highest risk, possibly because of several modifiable risk factors such as hypertension, dyslipoproteinemia, and increased platelet aggregability. Randomized double-blind trials in patients with type 2 diabetes demonstrated benefits of intensified intervention involving a single vascular risk factor on macro- and microvascular disease.[27–30] The Steno-2 study revealed that an intensified, targeted, multifactorial intervention aimed at several modifiable risk factors in patients with type 2 diabetes and MA reduced the risk of CV and microvascular events by about half.[31,32] The latest scientific statement from the American Heart Association (AHA) and the ADA for the primary prevention of CVD in people with diabetes also recommends comprehensive risk assessment and broad-based treatment of risk factors.[32]

The average HbA1c in our study was lower than that reported in the intensive treatment arm of the Steno-2 study.[31] However, values were missing in 63% of our patients. Only 37% patients (of 3,834 with HbA1c values) achieved target HbA1c (<7%), attesting the fact that in some cases the management of glycemia was less aggressive than desired. Among those with the highest HbA1c levels, many patients were not started on insulin therapy.

A target BP of <130/80 mm Hg is recommended in patients with type 2 diabetes.[34] In our study, the majority of

patients had uncontrolled BP, and yet almost half of these patients did not receive BP-lowering therapy, despite the well-documented benefit on large and small vessel disease.[35] A study by Ramirez et al.[36] suggested that the association between SBP or DBP and proteinuria did not seem to have a minimal threshold level because a trend for an increase in odds for proteinuria was observed even with BP measurements within the recommended range. The fact that even mild BP elevations were associated with proteinuria in a multi-ethnic population from Singapore might suggest that normal BP values for Asians are not equivalent to those established for Caucasians and indicates the need to establish BP nomograms specific to the Asian population.[36] The most frequently used antihypertensive drugs were agents blocking the RAS, followed by calcium channel blockers. The AHA-ADA guidelines recommend an antihypertensive regimen containing an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker.[32] Nonetheless, even these drugs were utilized in only 30% of our patients. A combination of drugs is often needed for adequate BP control in patients with diabetes—although angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are the preferred first-line agents, a low-dose thiazide diuretic generally should be one of the first two drugs used.[32] However, diuretics were underused (only 10%) in our study. While the emphasis is on tight BP control to reduce morbidity, the actual choice of drug should be individually decided by the physician.[37] Since most patients in our study were only on one or two classes of antihypertensive agents even at the highest SBP, the treatment of hypertension needs to be more aggressive.

Several statin trials have demonstrated a beneficial effect on CV events, including ischemic stroke, in patients with type 2 diabetes.[28,29,38] Furthermore, since these drugs are safe, there is a strong argument that type 2 diabetes patients warrant statin treatment.[39] Although 38% patients had history of hyperlipidemia, lipid-lowering therapy was only recorded in 30% of patients, despite these patients having a high frequency of several conventional CV risk factors including MA and macroalbuminuria. Even among patients with a history of hyperlipidemia, only 38% received statins.

A large meta-analysis of the use of antiplatelet agents clearly indicates a CV benefit in diabetes.[40] Low-dose therapy with aspirin (or another antiplatelet agent) is recommended as a primary prevention strategy in those with diabetes at increased CV risk, including those who are <40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).[33] While a large proportion of patients in our study had one or more of these risk factors, only one-fourth of the patients received antiplatelet agents.

To summarize, there is a high prevalence of MA and macroalbuminuria and reduced kidney function, conditions associated with adverse renal and CV events, in Asian patients with type 2 diabetes without prior known nephropathy. MA is known to be more prevalent in South Asian individuals than in white Europeans, which is consistent with the observation that they are at greater risk for CV complications compared to white Europeans.[41,42] A study by Dixon et al.[42] showed that almost one-third of South Asian patients with diabetes having untreated normal BP had MA. This increased prevalence of MA, even in normotensive subjects, suggests that the threshold for intervention and the target for therapy of CV risk factors in South Asian patients with type 2 diabetes should be lower than for white Europeans.[42] In conclusion, early detection of MA, monitoring of vascular complications, and more aggressive multifactorial treatment aiming at renal and vascular protection are urgently needed.

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