Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore

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ABSTRACT

Introduction: Microalbuminuria is a marker of increased cardiovascular morbidity and mortality. It represents the earliest clinical evidence of diabetic nephropathy. Its early detection allows for implementation of individually-tailored cardiovascular risk reduction management programmes. Despite this, information on the prevalence of microalbuminuria in hypertensive patients with type 2 diabetes mellitus in Singapore is limited.

Methods: The Microalbuminuria Prevalence Study (MAPS) assessed the prevalence of macroalbuminuria and microalbuminuria in consecutively-screened hypertensive adult patients with type 2 diabetes mellitus in ten Asian countries. This paper presents the results of a sub-analysis of data from patients in Singapore.

Results: Singapore contributed seven percent of the overall enrolment into MAPS; a total of 499 patients were enrolled and 388 constituted the per-protocol population (patients with bacteriuria and haematuria were excluded). Overall, the prevalence of diabetic kidney disease was high. In our study population, 23.5 percent of patients had macroalbuminuria (95 percent confidence interval [CI] 21.3-25.6), and 48.5 percent of patients had microalbuminuria (95 percent CI 45.9-51.0). Only 28.1 percent (95 percent CI 25.8-30.4) of patients were normoalbuminuric. Associated factors were poor glycaemic control and poor blood pressure control.

Conclusion: The high prevalence (72 percent) of microalbuminuria and macroalbuminuria found in hypertensive patients with type 2 diabetes mellitus in Singapore is a cause for concern. These findings highlight the need to screen for microalbuminuria and better manage hypertensive patients with type 2 diabetes mellitus, if we are to avoid a major increase in end-stage renal disease.

Keywords: diabetic nephropathy, diabetes mellitus, hypertension, macroalbuminuria, microalbuminuria

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INTRODUCTION

Patients with type 2 diabetes mellitus are approximately twice as likely to have hypertension as the non-diabetic population[1]. The prevalence of hypertension is further increased in patients with type 2 diabetes mellitus and renal disease, as manifested by elevated urinary albumin excretion (UAE) rates, compared with patients with type 2 diabetes mellitus and no evidence of renal involvement. The higher the systolic blood pressure (SBP), the greater the absolute excess cardiovascular (CV) risk for patients with diabetes mellitus. This indicates a greater potential for prevention of CV death among patients with diabetes mellitus by controlling elevated blood pressure[2]. Because of the ageing population and an increase in obesity and sedentary lifestyle, the prevalence of diabetes mellitus is growing, particularly in Asia[3]. According to the 1998 National Health Survey, the prevalence of diabetes mellitus is approximately 9% among Singaporeans aged 18-69 years[4].

Diabetes mellitus is the major cause of end-stage renal disease (ESRD) in Singapore[5]. Because of the adverse impact of microalbuminuria and proteinuria on survival in patients with type 2 diabetes mellitus[6-8], screening and intervention programmes should be implemented early, at the stage of microalbuminuria. Annual screening for microalbuminuria is recommended by the American Diabetes Association[9]; the use of a semi-quantitative dipstick test is easy, and provides immediate and accurate results[10].

There have been few studies in Asian populations on the prevalence of microalbuminuria[11-14]. These studies have only explored the percentage of microalbuminuria

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in either patients with diabetes mellitus or patients with hypertension. MAPS is the first study to evaluate the prevalence of microalbuminuria and macroalbuminuria in patients with type 2 diabetes mellitus and hypertension[15]. The primary study objective was to assess the prevalence rate of macroalbuminuria and microalbuminuria in Singapore. Secondary objectives aimed to assess levels of glycaemic and blood pressure control.

METHODS

MAPS was a large study involving 6,801 patients in the Asia Pacific Region[15]. This analysis was for a subgroup of patients recruited at five diabetes clinics and 15 general practices in Singapore. Outpatients of different Asian ethnic subgroups, older than 18 years of age, with previously diagnosed hypertension (treated or untreated) and type 2 diabetes mellitus (treated or untreated) were consecutively screened at each participating centre. Previously-diagnosed hypertension and diabetes mellitus were historically defined as mentioned in the patient medical record and verified during monitoring visits. Patients with known (previously-diagnosed) macroalbuminuria were excluded. Patient data included demographical information, past medical history, dates of onset of hypertension and diabetes mellitus, current diabetes status (complications such as retinopathy, peripheral neuropathy, as well as CV disease, glycaemic control and current therapy), current hypertensive status (mean of two consecutive measurements of office supine SBP and diastolic blood pressure (DBP), current treatment), and dyslipidaemic status (known or previously-diagnosed dyslipidaemia, use of lipid-lowering agents).

A single urine specimen was collected in disposable plastic vessels on the same day as the screening visit. The urine sample collected were preferably the first morning urine specimen. If collection of the first morning specimen was not possible, a morning random urine sample was collected. The date and time of the urine collection was reported in the case report form. The primary study objective was to assess the prevalence rate of macroalbuminuria and microalbuminuria. Informed consent was obtained from all participants. The study was designed and supervised by a multidisciplinary steering committee.

As recommended by the American Diabetes Association guidelines[9], a two-step MAU screening process was conducted. First, the detection of macroalbuminuria was carried out on the fresh urine (first morning void or random morning specimen) using a visual colourimetric semi-quantitative urine test strip (Nephur7Test®, Roche Diagnostics GmbH, Mannheim, Germany). The Nephur7test® strip also allowed quantification of pH5-9, urine glucose (0-55 mmol/L), ketones bodies (0 to +++), leukocytes (0-500/microL), nitrites (negative or positive), and blood (erythrocytes and haemoglobin, 0-250 microL). Then, if negative for albumin, detection of microalbuminuria was performed on the same urine with a second specific semi-quantitative urine test strip (Micral-test®, Roche Diagnostics GmbH, Mannheim, Germany). The intensity of the colour produced, proportional to the albumin concentration, was visually compared with the reference chart on the Micral-test® bottle (0, 20, 50, 100 mg/L, >100 mg/L). A measurement of 20 mg/L or above was considered positive.

Specificity, sensitivity, positive and negative predictive values of the Micral-test® were determined according to the manufacturer's evaluation report and with a cut-off point set at 20 mg/L: sensitivity of 90.1%, specificity of 87.2%, positive predictive value 0.82, and negative predictive value of 0.93. In addition, a within-trial validation of the Micral-test® was performed by one of the authors (PC). Micral-test® results of 119 consecutive Chinese patients were compared to those obtained by immunochemical assay (DCA 2000+ commercial kit, Bayer Diagnostics, Germany) and 56 samples were compared with immunoturbidimetric determination (Beckman Array 360 system, USA). In comparison with DCA 2000+ (albumin/creatinine ratio), Micral-test® had an overall sensitivity of 91.9% and specificity of 63.4%. In comparison with immunoturbidimetric assay, the overall sensitivity and specificity of Micral-test® was 95% and 80%, respectively.

For the current analysis, we restricted data to include only those patients recruited from study centres in Singapore. All patients with confirmed onset dates of hypertension and type 2 diabetes mellitus constituted the analysed population. Patients with positive leukocytes and nitrites, indicative of significant bacteriuria, and patients with erythrocytes or haemoglobin equal or above 25/microL, indicative of significant haematuria, were excluded from the analysed population to constitute the per-protocol population.

Quantitative variables were described by their mean, standard deviation, count and number of missing values. Qualitative variables were described by the counts and percentages of each response choice, missing data were included in the calculation

Table I. Patient demographics.*

	Mean	Standard deviation	STDM
Age (in years)	58.26	11.48	0.58
Body mass index (kg/m^2)†	26.27	4.35	0.22
Systolic blood pressure§/ diastolic blood pressure° (mmHg)	144/84	19/9	1.0/0.5
Blood glucose (mmol/L)‡	8.7	3.0	0.2
Duration of hypertension (years)	7.54	7.67	0.39
Duration of diabetes mellitus (years)	8.64	7.61	0.39

*per-protocol population; †n: 381; ‡n: 327; §n: 386; °n: 386.

of percentages. No statistical tests were performed on the albuminuric subgroups. Prevalence rates were calculated with a two-sided 95% confidence interval (CI). Association between two qualitative variables were assessed by a chi-square test or a Fisher's exact test if the assumptions of the chi-square test were not met. The best global model of prediction was assessed by a two-step logistic regression.

Univariate analyses were performed to determine links between the variable microalbuminuria and the following variables: ethnic subgroup, gender, age subgroup, duration of diabetes mellitus in classes, SBP levels, DBP levels, cardiovascular complications and diabetic complications. A link between two variables was judged significant if the t-test p-value was ≤0.25 (this was done to minimise the probability of missing a potentially predictive factor). In the second step, these variables were analysed through logistic regression (using p-value <0.05 to determine which factors were predictive for microalbuminuria. All analyses were performed using Statistical Analysis System (SAS) version 8.02 (Lyon, France).

RESULTS

Singapore constituted 7% of the overall enrolments in MAPS. A total of 499 patients were recruited from 20 medical centres in Singapore, from May 2002 to December 2002. Patients with bacteriuria, and/or haematuria, on the Nephur7Test® were excluded from the per-protocol analysis (Fig. 1). Patient demographics of the per-protocol population (n=388) are described in Table I. 50.0% had a family history of hypertension and 57.7% had a family history of diabetes mellitus.

The mean duration of diabetes mellitus was 8.6 (±3.0) years. Measures of glycaemic control revealed a mean HbA1c level of 7.9% and a mean creatinine level of 81.8 mmol/L. Overall, 16.8% of patients had known CV complications, namely: previous TIA (1.5%), previous stroke (4.6%), angina pectoris (6.7%), myocardial infarction (2.3%), heart failure (0.8%), and symptomatic peripheral arterial disease (0.8%).

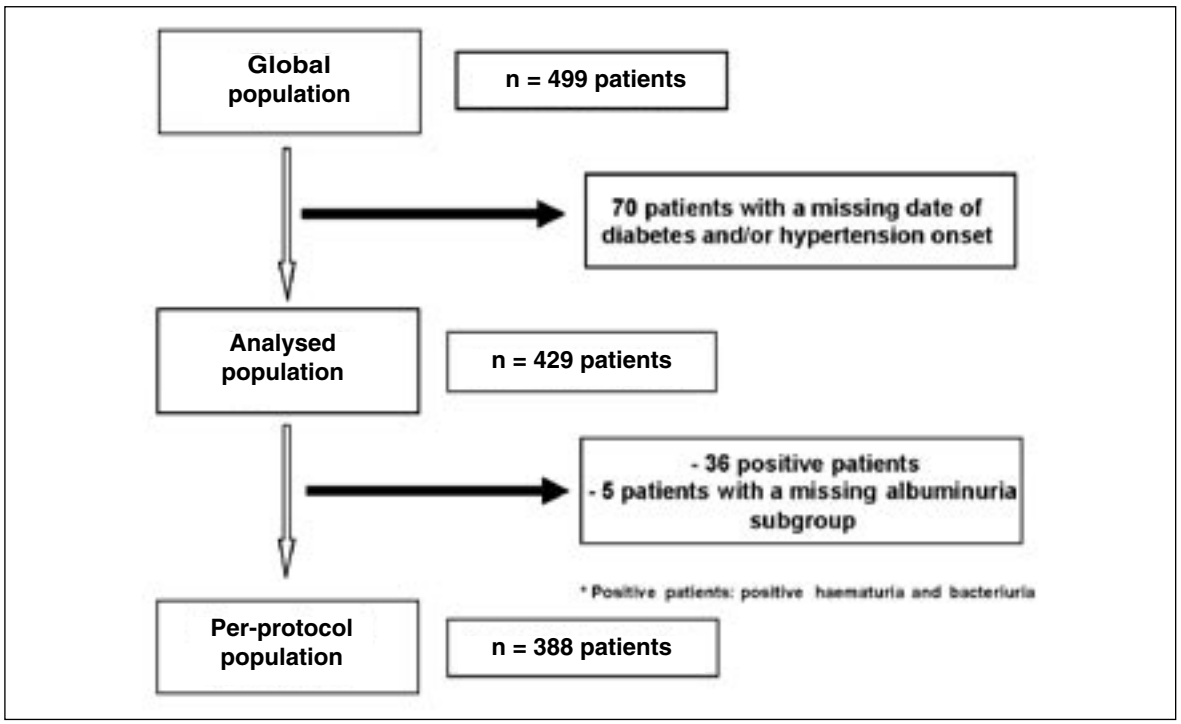

Fig. 1 Patient classification.

Table II. Detection of macroalbuminuria and microalbuminuria.*

	Count	%	95% CI
Macroalbuminuria	91	23.5	21.3-25.6
Microalbuminuria	188	48.5	45.9-51.0
Normal	109	28.1	25.8-30.4
Total	388	100	

*per-protocol population.

The mean duration of hypertension was 7.5 (±7.7) years, and the mean blood pressure was 144/84 mmHg. The proportion of patients receiving an antihypertensive treatment was high (97.2%): 56.9% and 43.1% of them were on monotherapy and combination therapy, respectively. The distribution of therapy is shown in Fig. 2. Almost three-quarters of the patients screened (72%) had albuminuria. The prevalence of macroalbuminuria and microalbuminuria are described in Table II.

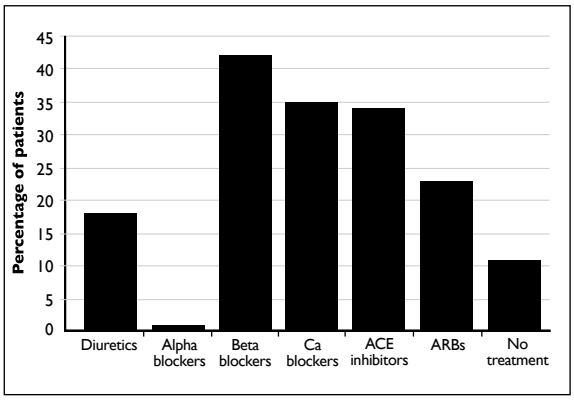

Fig. 2 Current types of antihypertensive treatment.

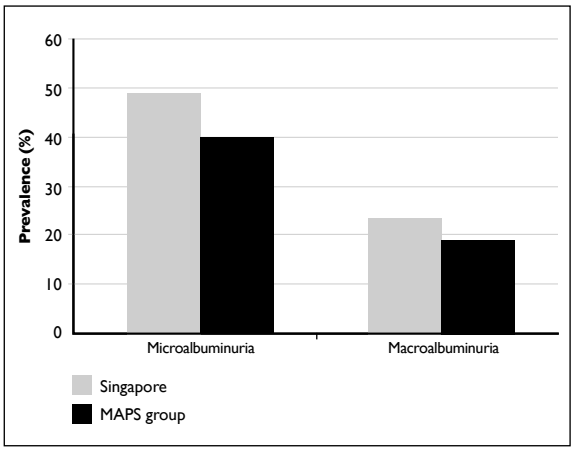

Fig. 3 Prevalence of micro- and macroalbuminuria in Singapore compared with the MAPS group.

DISCUSSION

MAPS is the first large multicentre epidemiological study in Asia to determine the prevalence of microalbuminuria and macroalbuminuria in patients with hypertension and type 2 diabetes mellitus. This sub-analysis of data from Singapore indicates that 48.5% of the 388 patients analysed had microalbuminuria and 23.5% had macroalbuminuria.

This is slightly higher than the overall prevalence rates of 39.8% and 18.8%, respectively, reported for the Asia Pacific region in MAPS (Fig. 3)[15]. The Diabcare-Singapore study carried out in 1998 also showed a high prevalence (36.0%) of microalbuminuria in diabetic patients in Singapore[14]. The wide range in the prevalence of microalbuminuria in people with type 2 diabetes mellitus is possibly due to genetic and CV risk factors (e.g. elevated blood pressure, cholesterol).

Almost 6% of patients had a family history of renal disease and 57% had a family history of diabetes mellitus. Microalbuminuria is the first clinical sign of diabetic damage to the kidney and predicts progressive kidney damage, myocardial infarction and CV death[2]. Once present, microalbuminuria progresses over 5-10 years to macroalbuminuria in 22-50% of patients[16-19]. The development of macroalbuminuria is usually followed by a further decline in glomerular filtration rate[20,21].

Good glycaemic control has been shown to prevent the development of nephropathy and reverse established pathology. In the United Kingdom Prospective Diabetes Study (UKPDS), there was a 34% reduction of nephropathy in the group of patients that achieved a HBA1c of 7% compared to those with a HbA1c of 7.9%. Our national guidelines recommend a target of <7% for persons with diabetes mellitus. Nevertheless, as evidenced by the mean HbA1c of 7.9%, many of patients did not achieve adequate glycaemic control.

Hypertension is common among patients with diabetes mellitus and the prevalence is increased further with the presence of renal disease[22]. In this sub-analysis of MAPS data from Singapore, the mean blood pressure of patients was 143/84 mmHg and the mean duration of hypertension was 8.6 years. Almost all of the patients in this sub-analysis (97.2%) were receiving antihypertensive therapy. The total of patients with SDP/DBP 130/85 mmHg was 22.2%.

The benefits of reducing blood pressure to the recommended level of <130/80 mmHg in patients with diabetes are well established[23]. In the UKPDS 38[24], each decrease of 10 mmHg in mean SBP was associated with a 15% reduction in risk for death

related to diabetes mellitus, an 11% reduction in risk for myocardial infarction, a 13% reduction in risk for microvascular complications and a 12% reduction in risk for any diabetes-related complication. In the Hypertension Optimal Treatment study[25], a 51% reduction in CV events was observed in patients with diabetes randomised to a group with target DBP of ≤80 mmHg compared with those randomised to a target diastolic blood pressure of ≤90 mmHg. It is, therefore, important to develop strategies that increase the percentage of patients who achieve optimal blood pressure control as Asian patients with type 2 diabetes mellitus have higher risk for renal complications and stroke compared with their Caucasian counterparts[26]. A study in Singapore suggested that there may be ethnic differences in risk of mortality in persons with diabetes. Malays and Indian patients with diabetes had mortality rates that were almost double those of Chinese patients[27].

Although the major cause of ESRD is diabetes mellitus, it is predicted that the renal complications associated with hypertension may become more common in Singapore in the future[5]. The National Healthy Lifestyle Programme, an intervention programme for major cardiovascular risk factors in Singapore, was implemented in 1992, with mixed results[28]. Data from the Singapore National Health Survey in 1998 showed a decrease in smoking and an increase in regular exercise, and indicated that the rate of the rise in the prevalence of diabetes in Singapore did not change significantly (8.4% in 1992 versus 8.1% in 1998, $p>0.05$)[28]. However, the prevalence of hypertension in people aged 30-69 years increased significantly ($p<0.001$) from 22.5% in 1992, to 26.6% in 1998[28].

It is now widely established that optimal blood pressure, tight glycaemic control and pharmacological blockade of the renin-angiotensin system with ACE inhibitors or ARB can decrease UAE rates and, subsequently, slow the progression from incipient to overt nephropathy[29]. For example, in the IRMA 2 study (Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients), hypertensive patients with type 2 diabetes mellitus and microalbuminuria taking irbesartan 300 mg daily had a significant (70%, $p<0.001$) relative risk reduction for the development of diabetic nephropathy as measured by the changes in UAE[29].

Additionally, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan in Diabetic Nephropathy (IDNT) trials have conclusively demonstrated the advantage of ARB therapy[30,31]. When used as part of a multi-drug strategy to lower blood pressure, iosartan 100 mg or irbesartan 300 mg have been shown to prevent doubling of serum creatinine, ESRD or death in hypertensive patients with type 2 diabetes mellitus and macroalbuminuria[30,31]. In this study, ACE inhibitors and ARB were used in only 34% and 23% of patients, respectively. Less than 50% of patients were receiving two or more antihypertensive agents, even though a number of clinical trials have confirmed the need for multi-drug therapies in diabetes mellitus to reach target blood pressure[32].

In conclusion, this sub-analysis of data from the Singapore cohort of MAPS demonstrated a very high prevalence of diabetic renal disease in patients with hypertension and type 2 diabetes mellitus – in total, 72% of the patients screened had albuminuria (48.5% with microalbuminuria and 23.5% with macroalbuminuria). This high prevalence is of great concern and implores us to be more aggressive in controlling glycaemia and blood pressure in patients with diabetes mellitus. Screening for microalbuminuria in all patients with type 2 diabetes mellitus is recommended, as early treatment that includes CV risk reduction strategies is critical. In addition, it is critical to ensure good blood pressure and glycaemic control of hypertensive patients with type 2 diabetes mellitus. The advantages of lowering blood pressure and the benefits of renin-angiotensin system blockade have been clearly demonstrated in clinical trials. It is suggested that in type 2 diabetics with hypertension, and signs of renal disease such as micro or macroalbuminuria the use of ARB therapy may contribute to improving the management.

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