Original Article

Incipient Albuminuria in Persons with Newly Diagnosed Type 2 Diabetes Mellitus: A 5-Year Retrospective Cohort Study

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Abstract

Introduction: This study aimed to determine the 5-year incidence of albuminuria among Asian persons with newly diagnosed type 2 diabetes mellitus (DM), and to identify the risk factors at diagnosis for progression to albuminuria. Materials and Methods: A retrospective 5-year closed cohort study was conducted among 1016 persons aged ≥18 years old who were diagnosed with type 2 DM between 1 January 2007 and 31 December 2009 at primary care facilities in Singapore. The cumulative incidence of progression from normoalbuminuria to albuminuria—termed "progression"—was determined. The risk factors associated with progression were evaluated using multiple logistic regression analysis. Results: A total of 541 (53.2%) participants were men. The mean (SD) onset age of type 2 DM was 54 (11) years. From diagnosis of type 2 DM, the 5-year cumulative incidence of progression was 17.3% and mean (SD) duration to progression was 2.88 (1.23) years. Higher onset age (OR 1.02; 95% CI, 1.00-1.04), history of hypertension (OR, 1.88; 95% CI, 1.32-2.70) and higher glycated haemoglobin (HbA1c) (OR, 1.17; 95% CI, 1.09-1.26) at diagnosis were associated with progression. In addition, being on angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) treatment at baseline modified the effect of hypertension on progression. Conclusion: This study highlighted the importance of early screening and treatment of diabetes as well as prevention of hypertension, which could potentially delay the onset of microalbuminuria in persons with type 2 DM. Persons on ACEI or ARB treatment should continue to be monitored regularly for progression to albuminuria.

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Key words: Incidence, New onset, Proteinuria, Risk factors

Introduction

The global prevalence of diabetes among adults over 18 years of age has increased from 4.7% in 1980 to 8.5% in 2014.[1] In Singapore, about 440,000 residents aged 18 years and above had diabetes in 2014, and the number is projected to increase to 1 million in 2050.[2] The incidence of end-stage kidney disease among adults with diabetes is up to 10 times as high as those without diabetes.[1] Singapore ranks first in the world for prevalence of diabetes-induced kidney failure, with diabetes accounting for about 60% of incident cases of end-stage kidney disease which require renal replacement therapy.[3]

Diabetic kidney disease is detected in its early stage by the presence of microalbuminuria, which is defined as urine albumin creatinine ratio of 3.4 mg/mmol or more,[4] or if using gender-specific cutoffs, 2.5 mg/mmol or more for men and 3.5 mg/mmol or more for women.[5] About 20% to 40% of persons with diabetes develop microalbuminuria within 10 to 15 years of diagnosis of diabetes, and approximately 80% to 90% of those with microalbuminuria progress to more advanced stages of kidney disease.[6] Microalbuminuria has also been shown to be an independent determinant of coronary heart disease and death.[7]

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Early kidney disease can be treated with drugs such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), which have been shown to reduce the risk or retard the progression of diabetic nephropathy.[8] Hence, it is recommended that urine albumin excretion should be assessed annually for all persons with type 2 diabetes mellitus (DM), starting at diagnosis of diabetes.[9] The most widely recommended method of testing is the urine creatinine/albumin ratio (UACR), which is determined from a freshly collected random spot urine sample.[10] Due to variability in urinary albumin excretion, 2 or 3 specimens collected within a 3- to 6-month period should be abnormal before a patient is considered to have developed albuminuria.[11]

Given the high health and socioeconomic burden associated with diabetic kidney disease, and the potential for intervention in early disease, it is important to understand the rate of progression to microalbuminuria, and the clinical characteristics of persons with type 2 DM who develop microalbuminuria within the first few years after being diagnosed with type 2 DM. Previous studies in Denmark, Israel, and the United Kingdom[12-14] have shown that the incidence of microalbuminuria in persons with newly diagnosed type 2 DM was about 2% per year, and the prevalence of microalbuminuria was 20% to 24% after 10 years from diagnosis of type 2 DM. A variety of risk factors for microalbuminuria, such as increased age, higher baseline glycated haemoglobin (HbA1c) and serum cholesterol were identified. While there have been a few cross-sectional studies in Asian populations—including a study of 6482 patients in 10 Asian countries where the prevalence of microalbuminuria was found to be 39.8%[15-16]—to our knowledge, no similar cohort study on the incidence of and risk factors for microalbuminuria was done in a Singaporean or Southeast Asian population.[17]

The objectives of this study were to determine: 1) the 5-year cumulative incidence of albuminuria among patients with newly diagnosed type 2 DM in the primary care setting in Singapore; and 2) the risk factors at diagnosis for progression to albuminuria.

Materials and Methods

A retrospective closed cohort study among patients with newly diagnosed type 2 DM was conducted, using electronic medical data from the National Healthcare Group (NHG) Diabetes Registry. This enterprise-wide electronic database links key administrative and clinical information from hospitals, specialty centres and primary care clinics in 1 of the 3 public healthcare clusters in Singapore, and is used to harmonise clinical health records and facilitate seamless care for about 1.2 million patients with diabetes.[18] The following algorithm was used to capture patients into the Registry: 1) rule 1: patients from existing stand-alone diabetes registries; 2) rule 2: patients with diagnosis code of 250.x0, 240.x2 or 363.xx under the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9CM), coded as either the primary or secondary diagnosis; 3) rule 3: patients on antidiabetes medication; and 4) rule 4: patients with 2-hour blood sugar level of ≥11.1 mmol/L on oral glucose tolerance test (OGTT), or a random blood sugar level of ≥11.1 mmol/L on 2 occasions within 2 years, or fasting plasma glucose ≥7.0 on 2 occasions within 2 years, or random blood sugar level of ≥11.1 mmol/L and fasting plasma glucose ≥7.0 within 2 years. Data elements such as the dates and values of key laboratory tests are captured in the system, and a summary of care records, including reminders to order the necessary tests for patients are provided to clinicians.[19]

The study included all patients with: 1) type 2 DM aged ≥18 years old, newly diagnosed between 1 January 2007 to 31 December 2009; 2) normal UACR within 2 months of diabetes onset date; and 3) at least 3 UACR readings during the 5-year follow-up period, where the last UACR was within 15 months of the end of the follow-up period.

Participants seen at 9 public primary care institutions under the NHG who were diagnosed between 1 January 2007 and 31 December 2009 with type 2 DM and had a normal UACR result (UACR <2.5mg/mmol for men and <3.5mg/mmol for women)[5] within 2 months after diagnosis, were followed-up for a period of 5 years. The outcome was progression to albuminuria—termed "progression"—defined as 2 abnormal consecutive UACR tests (UACR ≥2.5 mg/mmol for men and ≥3.5 mg/mmol for women) done maximally 15 months apart.

Ideally, a baseline UACR test should be done at the time of diagnosis,[9] and repeated yearly, if normal. However, in order to allow for any operational or patient-related constraints on the completion of the baseline UACR test at the point of type 2 DM diagnosis, a 2-month postdiagnosis cutoff was used. Sensitivity analysis using a 3-month cutoff did not show any significant differences in participant characteristics, hence a 2-month cutoff period was used. While the diagnostic criteria for diabetic nephropathy is generally accepted as positive results on 2 or 3 UACR tests in a 6-month period,[9] a 15-month cutoff period was used, in line with local recommendations to repeat UACR yearly and to similarly allow for some time buffer for the test to be performed.

There were 31,973 records of patients diagnosed with type 2 DM between 1 January 2007 and 31 December 2009. A total of 27,089 patients did not have a baseline UACR result and hence were excluded. Out of the remaining 4884 records of patients with newly diagnosed type 2 DM, an additional 3426 patients who had abnormal UACR tests at

diagnosis, and 442 patients with missing data during the follow-up period, were excluded. A total of 1016 patient records were used for this analysis (Fig. 1). Participants were termed "Progressors" if they developed albuminuria during the 5-year follow-up period and "Non-progressors" if they did not.

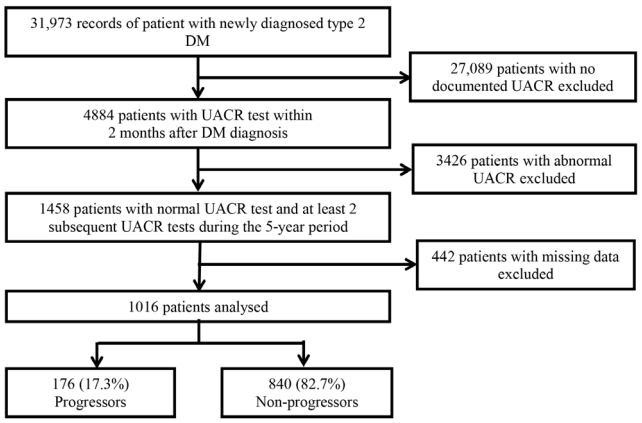

Fig. 1. Study selection flow chart. DM: Diabetes mellitus; UACR: Urine creatinine/albumin ratio.

The 5-year cumulative incidence, and the time from diagnosis to onset of albuminuria (defined as the duration between onset date of diabetes and the test date of the second abnormal UACR) was determined. Participant demographics (age, gender, ethnicity), medical history and other baseline measures which were collected as part of routine standard of care at diagnosis of diabetes—HbA1c, blood pressure, lipid panel, estimated glomerular filtration rate (eGFR), serum creatinine, and body mass index (BMI)—were analysed.

Records of medication prescriptions were also used as a proxy indicator for whether participants were taking ACEIs or ARBs at the time of diagnosis. Participants were considered to be on ACEIs or ARBs if they were prescribed either class of medications within 4 months before diagnosis or within 2 months after diagnosis of type 2 DM (as locally, patients are usually not prescribed more than 6 months' supply of medications at 1 time).

Baseline measures and use of ACEIs or ARBs were compared between progressors and non-progressors to determine factors associated with increased risk of progression to kidney disease. Patient with hypertension were thus stratified by the presence of ACEI or ARB, to determine if the use of ACEI or ARB was a confounder or effect modifier.

Forward stepwise multiple logistic regression analysis was performed to identify significant risk factors. As the first HbA1c reading was positively skewed, the median was used. Statistical significance was defined as $P < 0.05$. Pearson's chi squared test was used for categorical variables, Fisher's exact test was used for discrete variables, and T test and Mann-Whitney U tests were used for continuous variables. Stepwise forward logistic regression analysis was used to identify factors associated with progression to microalbuminuria. Data was analysed using SPSS Statistics 20.0. The study was approved by the NHG Domain Specific Review Board.

Results

Of the 1016 participants, there were 176 progressors and 840 non-progressors. The baseline characteristics of progressors and non-progressors are shown in Table 1.

The mean onset age of diabetes among progressors was higher than that of non-progressors, and there was a slightly larger proportion of males in the study population. Indians accounted for a disproportionately higher number of participants, since they made up 9.2% of the population. This is consistent with the local National Health Survey in 2010 which found that a higher proportion of males were diabetic, and diabetes was most prevalent among Indians (17.2%), compared to Malays (16.6%) and Chinese (9.7%).[20] There were no statistically significant differences in the incidence of microalbuminuria between the different ethnic groups. This is in contrast to a previous cross-sectional study in Singapore, which found that fewer Indians have microalbuminuria (21.0%) compared with Chinese and Malay patients (30.0% and 35.3%, respectively).[21]

More than 40% and 50% of participants had hypertension and hyperlipidaemia, respectively. The mean BMI was 26.9 ± 5.1 kg/m^2, which is higher than the Asian cutoff for moderate risk of cardiovascular disease (i.e. >23 kg/m^2). The mean HbA1c at diagnosis was 8.0%.

Univariate analysis showed that higher onset age of diabetes, higher baseline HbA1c, systolic blood pressure and serum creatinine was associated with increased risk of progression. A history of hypertension (RR 1.54, 95% CI, 1.18-2.01) and use of ACEIs or ARBs (RR 1.49, 95% CI, 1.10-2.02) at diagnosis were significantly associated with progression.

Among participants with hypertension, stratified analysis showed that being on ACEI or ARB at baseline modified the effect of hypertension on development of microalbuminuria Participants on ACEI or ARB had a RR of 3.31, 95% CI, 0.81 to 12.20, while those not on ACEI or ARB had a RR of 1.33, 95% CI, 0.97 to 1.83.

The cumulative incidence of microalbuminuria within 5 years from diagnosis of type 2 DM was 17.3%, or a rate of 3.5% per year. The mean duration between diagnosis of type 2 DM and microalbuminuria incidence was $2.88 \pm$

Table 1. Baseline Variables of 1016 Patients with Newly Diagnosed Type 2 Diabetes Mellitus According to Progression to Albuminuria

Variable	All n = 1016	Progressors n = 176	Non-Progressors n = 840	*P* Value
Onset age (years)	54 ±11	56 ± 11	54 ± 11	0.004
Gender, n (%)				
Male	541 (53.2)	98 (55.7)	443 (52.7)	0.507
Female	475 (46.8)	78 (44.3)	397 (47.3)	0.507
Ethnicity n (%)				
Chinese	663 (65.3)	113 (64.2)	550 (65.5)	0.124
Malay	143 (14.1)	30 (17.0)	113 (13.5)	0.124
Indian	141 (13.9)	17 (9.7)	124 (14.8)	0.124
Others	69 (6.8)	16 (9.1)	53 (6.3)	0.124
Medical history,* n (%)				
Hypertension	434 (42.7)	94(53.4)	340 (40.5)	0.002
Hyperlipidaemia	576 (56.7)	107 (60.8)	469 (55.8)	0.242
Stroke	26 (2.6)	8 (4.5)	18 (2.1)	0.109
On ACEI or ARB	181 (17.8)	43 (24.4)	138 (16.4)	0.017
BMI (kg/m^2)	26.9 ± 5.1	27.2 ± 5.2	26.8 ± 5.1	0.418
SBP (mmHg)	130 ± 17	133 ± 16	129 ± 17	0.004
DBP (mmHg)	77 ± 9	77 ± 9	77 ± 9	0.723
HbA1c† (%)	8.0 (5.1 – 17.6)	8.6 (5.1 – 16.9)	7.9 (5.1 – 17.6)	0.010
LDL-C (mmol/L)	3.31 ± 0.92	3.26 ± 0.86	3.32 ± 0.93	0.465
HDL-C (mmol/L)	1.21 ± 0. 31	1.20 ± 0.32	1.22 ± 0.31	0.537
Triglycerides (mmol/L)	1.61 ± 0.89	1.70 ± 0.87	1.59 ± .089	0.168
Total cholesterol (mmol/L)	5.24 ± 1.02	5.22 ± 0.97	5.25 ± 1.03	0.721
eGFR (ml/min/1.73m^3)	92.51 ± 24.31	90.13 ± 27.82	93.00 ± 23.49	0.154
Serum creatinine (umol/L)	72 ± 20	75 ± 23	72 ± 19	0.022

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; CI: Confidence interval; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SBP: Systolic blood pressure

Values are mean (standard deviation) unless stated otherwise.

*Medical history of hypertension, hyperlipidaemia and stroke were determined by diagnosis codes.

†Median (interquartile range).

1.22 years. With exception of the first year, the cumulative incidence of microalbuminuria over the subsequent 4-year follow-up period increased in a linear fashion (Fig. 2).

In the multiple logistic regression analysis (Table 2), onset age, a history of hypertension and higher baseline HbA1c were found to be significant and independent risk factors associated with progression. For every 1-year increase in type 2 DM onset age, participants had a 1.02 times increased probability of becoming progressors. Likewise, for every 1% increase in baseline HbA1c, participants had a 1.17 times increased risk of becoming progressors. Participants with hypertension were found to be 1.88 times more likely to become progressors.

Discussion

The 5-year cumulative incidence of albumunuria was 17.3%, or 3.5% per year. This is higher than the incidence rate of 2.0% per year in the United Kingdom Prospective Diabetes Study (UKPDS).[12] This may be due to the stricter exclusion criteria for the UKPDS, such as age of more

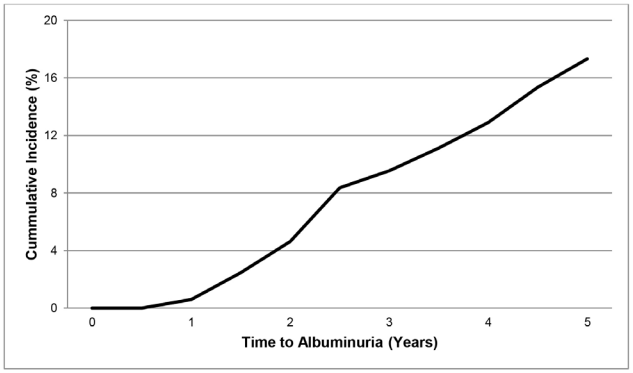

Fig. 2. Cumulative incidence of albuminuria among 1016 patients with newly diagnosed type 2 diabetes mellitus.

Table 2. Multiple Logistic Regression of Variables Associated with Progression to Albuminuria among 1016 patients with Newly Diagnosed Type 2 Diabetes Mellitus

Characteristics*	Univariate Model		Multivariate Model (Stepwise Forward)	
	Odds ratio (95% CI)†	*P* Value	Odds ratio (95% CI)‡	*P* Value
Onset age (year)	1.03 (1.01 – 1.05)	0.010	1.02 (1.00 – 1.04)	0.012
Gender (male vs female)	1.10 (0.69 – 1.76)	0.694	Eliminated	0.290
Hypertension (yes vs no)	1.40 (0.90 – 2.14)	0.134	1.88 (1.31 – 2.70)	0.001
Hyperlipidaemia (yes vs no)	1.10 (0.76 – 1.58)	0.629	-	0.584
On ACEI or ARB (yes vs no)	1.33 (0.86 – 2.07)	0.204	-	0.145
Body mass index (kg/m^2)	1.02 (0.98 – 1.05)	0.343	-	0.206
SBP (mmHg)	1.01 (1.00 – 1.03)	0.028	-	0.081
DBP (mmHg)	0.99 (0.97 – 1.01)	0.99	-	0.876
Baseline HbA1c (%)	1.16 (1.06 – 1.27)	0.001	1.17 (1.09 – 1.26)	0.000
LDL-C (mmol/L)	1.09 (0.47 – 2.50)	0.845	-	0.342
HDL-C (mmol/L)	1.05 (0.38 – 2.92)	0.923	-	0.273
Triglycerides (mmol/L)	1.16 (0.80 – 1.68)	0.442	-	0.311
Total cholesterol (mmol/L)	0.82 (0.36 – 1.88)	0.638	-	0.383
eGFR (ml/min/1.73m^3)	1.01 (1.00 – 1.02)	0.178	-	0.535
Serum creatitine (umol/L)	1.02 (1.00 – 1.04)	0.079	-	0.069
Average HbA1c (%)	1.10 (0.91 – 1.33)	0.326	-	0.282

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CI: Confidence interval; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SBP: Systolic blood pressure

*All variables are baseline characteristics except for 5-year average HbA1c.

†Forward stepwise analyses showed the 3 variables which were independently associated with progression.

‡Odds ratio (95% CI) indicates change in risk per unit increase in each variable.

than 65 years, elevated serum creatinine levels, myocardial infarction in the preceding year, existing cardiac failure or malignant hypertension. Gender-specific cutoff values for the UACR were also not used in the UKPDS. On the other hand, the incidence was lower than the 23% found in the study by Gall et al,[13] possibly due to the difference in diagnostic criteria for persistent microalbuminuria. Despite this, both studies showed similar linear increases in incidence after the first year of follow-up.

It is not surprising that higher onset age and baseline HbA1c were associated with faster progression to albuminuria, as these participants could have developed early kidney disease during the lag time between disease development and diagnosis of diabetes. Hypertension is also a known risk factor for kidney disease.[22] On the other hand, baseline eGFR was not found to be risk factor, likely due to the underestimation of GFR at near-normal ranges.[23]

The association between the use of ACEI or ARB and progression to albuminuria was not observed in the logistic regression analysis, likely due to the confounding effect of hypertension, or pre-existing microalbuminuria which was masked by ACEI or ARB treatment prior to the start of the study.[24-25] It is also disconcerting that the use of ACEI or ARB among patients with hypertension was not protective against subsequent kidney disease. This is in contrast with other studies which showed that use of ACEI reduced the absolute risk of developing microalbuminuria by 2% to 4% over 4 to 5 years among normoalbuminuria patients with type 2 DM and hypertension.[26-28]

The risk factors identified in this study were similar to those found in other studies.[13,14] However, some factors such as baseline lipid control, gender, and BMI were not found to be associated with risk of progression, possibly due to genetic and lifestyle differences between the study populations.

There were 27,089 patients who did not have a documented UACR at diagnosis and hence were excluded from the study. Hence, a key recommendation from this study would be that routine UACR be performed for all patients with newly diagnosed type 2 DM. Other findings of particular concern was that 70% of patients were found to have an abnormal UACR at baseline, compared to 38% of patients in the study by Gall et al.[13] Coupled with the finding that the baseline mean HbA1c of participants was 8.0%, these suggest that current screening efforts for diabetes were not identifying persons with diabetes sufficiently early. In addition, more than 40% and 50% of participants had hypertension and hyperlipidaemia, respectively, which is significantly higher than the prevalence of these conditions in the general local population.[20]

The limitations of the study were mainly related to the use of secondary data from a registry. These included the lack of complete data, such as socioeconomic status, cigarette

smoking status,[29] and reasons why patients were on ACEIs or ARBs. In addition, 442 participants were excluded due to missing data. There is scope for further prospective cohort studies on patients across different care settings, and inclusion of these variables which were unavailable for this study. Future studies could also examine patients who had albuminuria at the onset of type 2 DM, to determine their risk factors for albuminuria or progression to chronic kidney disease.

While the NHG Diabetes Registry captures 69% of all detected cases of diabetes in Singapore,[30] it is not a national registry, hence the findings may not be fully generalisable to the Singapore population. Moreover, patients could have been diagnosed with type 2 DM prior to entry into the registry, in which case, the incidence rate of albuminuria could have been overestimated.

Some of the strengths of this study include the large sample size, and the analysis of multiple risk factors at diagnosis, which could potentially impact disease management. It is also one of the few studies which looked at the development of incipient nephropathy in newly diagnosed type 2 DM patients, and to our knowledge, is the first such study in the Asian context.

Conclusion

Among the 1016 patients with newly diagnosed type 2 DM, the 5-year incidence of microalbuminuria was 17.3%. Higher onset age, hypertension and higher baseline HbA1c were found to be significant, independent risk factors for progression to microalbuminuria.

This study highlighted the importance of close monitoring of patients who are older, have hypertension or have poorer diabetic control at diagnosis of type 2 DM. Clinicians should remain vigilant in monitoring patients using ACEIs or ARBs, as these patients were also found to have a higher relative risk, likely due to underlying hypertension, for which the ACEI or ARB was prescribed.

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