ORIGINAL ARTICLE

Chronic Kidney Disease Stage 3B among Malaysian Diabetics in Primary Care and its Associated Factors: A Pilot 5-Year Case Control Study

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ABSTRAK

Kajian ini bertujuan untuk mengenal pasti faktor-faktor yang berkait dengan penyakit ginjal kronik tahap 3b di kalangan pesakit kencing manis yang dirawat di Pusat Perubatan Primer UKM, khususnya peranan dos ubatan yang menyekat angiotensin. Kajian ini merupakan kajian kes-kawalan pilot yang tidak dipadankan dan dijalankan di sebuah pusat pengajaran perubatan primer. Data klinikal 25 kes pesakit dengan penyakit ginjal kronik tahap 3b (GFR 30-45ml/min/1.73m2) dalam tahun 2012 dipilih sebagai kes untuk kajian ini. Di samping itu, 103 pesakit diabetes yang mempunyai GFR lebih daripada 45ml/min/1.73m2 dalam tahun 2012 dipilih sebagai kawalan. Sampel dipilih secara rawak sistematik. Data pesakit diperolehi melalui rekod pesakit diabetes, sistem maklumat kesihatan komputer, dan fail perubatan pesakit. Analisis univariat menggunakan ujian chi square, t-test, Fisher's exact test dan Mann-Whitney U-test. Regresi logistik digunakan untuk mengenal pasti faktor-faktor yang berkait dengan pembentukan penyakit ginjal kronik tahap 3b. Kes dan kawalan berbeza dari segi umur, jangkamasa diabetes, penggunaan dan dos ubat penyekat angiotensin, tekanan darah sistolik dan GFR permulaan. Regresi logistic menunjukkan bahawa tekanan darah sistolik (Adjusted OR= 1.08, 95% CI= 1.02-1.14, p=0.013) and GFR tahap asas (Adjusted OR= 0.90, 95% CI= 0.85-0.95, p<0.001) berkait secara signifikan dengan pembentukan penyakit ginjal kronik tahap 3b di kalangan pesakit diabetes. Penggunaan dos ubat penyekat angiotensin yang maksimum memperlihatkan kesan perlindungan (Adjusted OR= 0.14, 95% CI=0.85-0.95, p=0.025). Kajian ini menyokong keperluan kawalan tekanan darah sistolik yang baik untuk melambatkan kemerosotan fungsi ginjal. Dos ubat penyekat angiotensin perlu dioptimumkan di kalangan pesakit-pesakit ini.

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Kata kunci: *kajian kes-kawalan, kencing manis, perubatan primer, kelemahan fungsi ginjal, kronik*

ABSTRACT

The present study aimed to determine the factors associated with CKD stage 3b among type 2 diabetics attending primary care follow-up, specifically the role of angiotensin blockade dosage. This was a pilot unmatched case-control study conducted in a teaching primary care centre. Clinical data of 25 cases of diabetic patients with CKD stage 3b (GFR 30-45ml/min/1.73m^2) in 2012 were selected for this study, as well as 103 controls who were diabetic patients with GFR more than 45ml/min/1.73m^2 in 2012. Systematic random sampling was employed. Data was obtained from patients' diabetic records, computerised clinical medical information system and medical case notes. Univariate analysis was done using Chi-square, t-test, Fisher's exact test and Mann-Whitney U-test. Multiple logistic regression was used to determine the associated factors for development of CKD stage 3b. Cases and controls were different in terms of age, duration of diabetes, use and dosage of angiotensin blockade medications, systolic blood pressure and baseline GFR. Multiple logistic regression revealed that systolic blood pressure (Adjusted OR= 1.08, 95% CI= 1.02-1.14, p=0.013) and baseline GFR (Adjusted OR= 0.90, 95% CI= 0.85-0.95, p<0.001) was significantly associated with the development of CKD stage 3b among diabetics. Maximizing the dose of angiotensin blockade had a protective effect (Adjusted OR= 0.14, 95% CI=0.85-0.95, p=0.025). The results of the present study supports the need for good control of systolic blood pressure among diabetic patients to reduce the risk of chronic kidney disease progression. Dose of angiotensin blockade medications should be optimised in these patients.

Keywords: case-control studies, diabetes mellitus, primary health care, renal insufficiency, chronic

INTRODUCTION

The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide, ranges from 12.1% to 17.5% (Ingsathit et al. 2010; Centers for Disease Control and Prevention (CDC) 2007; Chen et al. 2009; Ong-Ajyooth et al. 2009). Diabetes mellitus (DM) is the leading cause of CKD, accounting for approximately 30% to 40% of CKD and up to 45% of ESRD (National Kidney Foundation 2004). In Malaysia, diabetic nephropathy contributed to more than half of new dialysis patients since 2003, and this number is progressively increasing (National Renal Registry 2011). In view of the increasing burden of chronic kidney disease, factors influencing the disease progress need to be identified to reduce end-stage renal failure.

The average time for diabetics with CKD3 to progress to CKD stage 4 is about three years (Meguro et al.

2009). Previous studies have shown that certain risk factors are associated with accelerated progression of CKD including older age, ethnicity, cigarette smoking, duration of diabetes, obesity, systemic hypertension, poor diabetes control and various levels of albuminuria (Meguro et al. 2009; Hsu et al. 2003; Keane et al. 2003; Orth & Hallan 2008).

A retrospective cohort study conducted by Chia and Ching (2012) in the primary care setting focused on the role of hypertension in development of chronic kidney disease. This study found that older age, diabetes, hyperuricaemia and lower eGFR status was associated with the development of new onset chronic kidney disease. The aim of the present study was to identify the risk factors associated with CKD stage 3b and the effect of maximal dose of angiotensin blockade.

MATERIALS AND METHODS

SETTING

This was a pilot unmatched case-control study conducted in a teaching primary care centre in Kuala Lumpur. Prior ethical approval was obtained from the Ethics Committee of UKMMC. A total of 25 cases of patients who had established CKD stage 3b (GFR between 30-45ml/min/1.73m^2) and 103 controls of patients with GFR of more than 45ml/min/1.73m^2 in the year 2012 were identified from the primary care clinic diabetic registry. Systematic random sampling was used, where every fifth patient in the registry was selected.

INCLUSION AND EXCLUSION CRITERIA

Diabetic patients who were on regular follow-up for at least five years at the primary care clinic were included. Patients with impaired fasting glucose or impaired glucose tolerance, those who developed CKD stage 4 and 5 on or before 2012, pregnant patients at any time during the 5-year of follow-up and patients with other causes of chronic kidney disease such as autoimmune disease, obstructive uropathy, congenital kidney disease as well as drug-induced nephropathy, were excluded from this study.

DATA COLLECTION

Information on socio-demographic data, body mass index (BMI), systolic blood pressure (SBP) and the use of ACEIs or ARBs were collected from patients' diabetic records. Dosages of angiotensin-blockade medications were further classified into submaximal and maximal dose. The glycosylated haemoglobin concentration (HbA1c) and serum creatinine levels were traced from the computerized clinical medical information system. Patients' case files were reviewed for data the duration of DM.

The mean BMI over the five year period was calculated for analysis. The mean SBP and HbA1c of the first reading each year from 2008 to 2012 were used for statistical analysis. Albuminuric status was defined as the latest investigated urine albumin within the five years, prior to recruitment and categorized into normoalbuminuric, microalbuminuric

and macroalbuminuric. The first serum creatinine levels for each year from 2008 to 2012 were recorded.

CLASSIFICATION OF CKD

When eGFR declines to less than 60 mL/min/1.73m^2, half of the renal function is lost and the prevalence of the complications of CKD, such as hypertension, anaemia, malnutrition, bone disease, neuropathy, and decreased quality of life, begins to rise (Cockcroft & Gault 1976; Swedko et al. 2003; Levey et al. 2003). In this study, CKD stage 3b was selected as the outcome variable because it signifies the definite presence of pathological reduction of GFR (Levey et al. 2003). Studies have shown that there is a steep increase in risk of mortality in patients who have CKD stage 3b compared to with those having CKD stage 3a (Levey et al. 2011).

The estimated glomerular filtration rate (eGFR) was used to determine renal function. In this study, eGFRwas calculated using Modification of Diet in Renal Disease (MDRD) equation and expressed in units of ml/min/1.73m^2 (Levey et al. 2003).

STATISTICAL ANALYSIS

All statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) version 21.0. Normally distributed data was described using mean and standard deviation, whereas skewed data was described using median and interquartile range. Univariate analysis was done using Chi-square, Fisher Exact test and Student t-test for parametric data, and Mann-Whitney U-test was used for non-parametric data. Multiple logistic regression was used to determine the association between the variables and the outcome.

RESULTS

A total of 865 diabetic patients were identified to have continued follow up care in the last five years at PPP-UKMMC. Only twenty five of them had developed CKD stage 3b. Since this number was small, the ratio of controls for each case was increased to 4:1 in order to improve the power of the study.

Table 1 showed the socio-demographic and clinical characteristics of the patients. They were significantly older (p=0.009) and had diabetes for a longer duration (p=0.002). They were more frequently prescribed with angiotensin blockade medications at the maximum dosage (64.0% p=0.001), had higher systolic blood pressure (155.2 mmHg vs 140.8 mmHg, p<0.001) and lower baseline GFR (64.6 vs 92.4 ml/min/1.73m^2, p<0.001) compared to the controls.

Multiple logistic regression using enter method was used to determine factors associated with the development of CKD stage 3b. The independent variables that were included into the model for multiple logistic regression were age, duration of diabetes, dosage of ACEI/ARB used, BMI, SBP, HbA1c, albuminuric status and baseline GFR. Use of ACEI/ARB could not be entered into the model for multiple logistic regression because all cases were on ACEI/ARB. Due to missing data, only 23

Table 1: Socio-demographic and clinical characteristics of study population

Variable	Sample		p value
	Case	Control	
Age (years)	69.69±8.56	64.49±9.70	**0.009**[a]
Gender			
Male	9 (36.0%)	39 (37.9%)	0.863[b]
Female	16 (64.0%)	64 (62.1%)	
Ethnicity			
Malay	7(28.0%)	41(39.8%)	
Chinese	14(56.0%)	57(55.3%)	0.183[b]
Indian	4(16.0%)	5(4.9%)	
Duration of Diabetes (years)	11 (IQR6-20)	6 (IQR 5-9.25)	**0.002**[c]
Use of ACEI/ARB			
Use of ACEI/ARB	25 (100%)	86 (83.4%)	0.042[d]
No use of ACEI/ARB	0 (0%)	17 (16.5%)	
Dosage of ACEI/ ARB			
Maximal	16(64.0%)	21(24.4%)	**<0.001**[b]
Submaximal	9(36.0%)	65(75.6%)	
Body Mass Index (kg/m^2)	25.9 (IQR 24.8-29.9)	26.4 (IQR 23.4-29.3)	0.798[c]
Systolic Blood Pressure (mm Hg)	155.2±14.6	140.8±15.0	**<0.001**[a]
HbA1c level	7.0 (IQR 5.8-8.5)	6.7 (IQR 6.1-7.7)	0.417[c]
Albuminuric Status			
Normoalbuminuria	9(36.0%)	52(50.5%)	
Micro/macroalbuminuria	14 (56.0%)	34 (33.0%)	0.067[b]
Not done	2 (8.0%)	17 (16.5%)	
Baseline GFR (ml/min/1.73m^2)	64.56±18.64	92.40±24.57	**<0.001**[a]

a = Student t-test; b = Chi-square test; c= Mann-Whitney U test; d= Fisher Exact test

cases and 73 controls were retained for multivariate analysis.

The logistic regression model was statistically significant ($X^2(8)= 57.7$, $p<0.001$). The model explained 68.5% (Nagelkerke R^2) of the variance in development of CKD stage 3b among diabetics. We were able to correctly classify 89.6% of the cases, with a sensitivity of 72.7% and specificity of 94.6%. Three of the nine variables were found to be significantly associated with the development of CKD stage 3b, namely systolic blood pressure, baseline GFR and use of maximal dosage of angiotensin blockade agents. The results were tabulated (Table 2).

Every increase of 1 mmHg in systolic blood pressure would increase the risk of developing CKD stage 3b by 8% (Adjusted OR=1.08, 95% CI= 1.02-1.14, p= 0.013). Conversely, every reduction in baseline GFR would increase the risk of developing CKD stage 3b by 11% (adjusted OR 0.90, 95% CI= 0.85-0.95, p<0.001). The use of maximum dosage

Table 2: Multiple logistic regression for predicting factors associated with CKD stage 3b

Variables	Beta	S.E	Wald	p value	Adjusted Odd Ratio	95% CI
Age	0.061	0.047	1.655	0.198	1.06	0.97-1.17
Duration of DM	0.018	0.043	0.177	0.674	1.02	0.94-1.11
Body mass index (BMI)	0.017	0.097	0.032	0.858	1.02	0.84-1.23
Systolic blood pressure	0.072	0.029	6.226	0.013	1.08	1.02-1.14
HbA1c	0.353	0.297	1.405	0.236	1.42	0.79-2.55
Baseline GFR	-0.104	0.029	12.662	<0.001	0.90	0.85-0.95
Dose of ACEI/ARB						
Submaximal dose					1	
Maximal dose	-1.973	0.881	5.015	0.025	0.14	0.03-0.78
Albuminuric Status						
Normoalbuminuria					1	
Micro- and macroalbuminuria	-0.073	0.922	0.006	0.937	0.94	0.15-5.66

of angiotensin blockade reduced the risk of developing CKD stage 3b by 7.2 times (adjusted OR=0.14, 95% CI=0.03-0.78, p= 0.025).

DISCUSSION

Systolic blood pressure is an established risk factor for the development of chronic kidney disease (Haroun et al. 2003; Bakris et al. 2003; Ingsathit et al. 2010; Hooi et al. 2013). The finding of this study was consistent with earlier studies, supporting the importance of blood pressure control in preventing renal complications among diabetics. Unfortunately, only a quarter of patients with diabetes in the primary care setting manage to achieve targets for blood pressure control (Cheong et al. 2013). This places Malaysian diabetics at higher risk of developing chronic kidney disease.

Hypertension and chronic kidney disease form a vicious cycle. Hypertension is a proven predictor of development of renal impairment, whereas presence of renal impairment increases blood pressure and affects blood pressure control (Bakris et al. 2003; Haroun et al. 2003; Sarafidis et al. 2008). Despite the variability of GFR decline, progression to end stage renal disease is increased whenever the baseline GFR is lower (Li et al. 2012). The findings of the present study were similar to an earlier cohort study which looked into trajectories of GFR among patients with CKD (Li et al. 2012).

Many landmark trials demonstrated the benefits of angiotensin blockade medications in delaying the progression of diabetic nephropathy (Heart Outcomes Prevention Evaluation Study Investigators 2000; Ravid et al. 1998; The Diabetes Control and Complications (DCCT) Research Group 1995). Our findings confirmed that by optimising the dose of angiotensin blockade among hypertensive diabetics, the risk of developing severe chronic kidney disease was reduced

by seven times. Although the use of angiotensin blockade agents among diabetics with hypertension have increased in the recent years, there is no published data regarding the dosage of such agents used in the local population (Chan 2005; Chew et al. 2010). There is a need to increase awareness to family physicians that the renoprotective effects of ACE inhibitors and angiotensin receptor blockers are best when maximum recommended dosage is used. However, this practice needs to be done with monitoring to avoid problems such as angiotensin-blockade related renal failure and hyperkalaemia.

A cross-sectional study in Malaysia showed that prescription of ACE inhibitors and ARBs were still very low among diabetic patients in 2003 (Chan 2005). Another study showed that 68.1% of diabetics were on ACE inhibitors, whereas 7.6% of diabetics were on ARBs (Cheong et al. 2013). This could be attributed to higher adoption of local clinical practice guideline by physicians. The improvement in prescribing patterns for such agents is thought to reduce the incidence of diabetic nephropathy and new-onset chronic kidney disease.

Currently, there is no published data regarding the proportion of diabetic patients who are being prescribed the maximum dose of ACEI or ARBs. Clinical audits should be done in order to study the prescribing patterns of such agents in order to maximize its benefits on reducing the risk of developing severe chronic kidney disease.

This study was carried out in a primary care setting, where development of chronic kidney disease is usually first diagnosed. The clinical profiles of patients in a primary care clinic are different from those found in secondary or tertiary care, which caters to patients with more complicated problems. CKD stage 3b is usually detected in primary care clinics. Intervention at this stage could delay the progression to more severe stages of CKD.

Limitations of this study include the small sample size due to lack of eligible cases. Therefore, this study may be underpowered to detect significant associations for other factors such as age, duration of diabetes, HbA1c and BMI. However, clinicians should continue to address modifiable risk factors such as glycemic control and body weight among diabetic patients who are at risk of developing CKD. Secondly, the baseline characteristics of cases and controls were different in many aspects. Therefore, multiple logistic regression was used in order to control for the effect of confounding factors. All cases were on ACE/ARB in this study. The researchers were unable to analyse whether use or non-use of ACEI/ARB affected the development of CKD stage 3b. Being a retrospective study, there were some problems of missing data. Hence, a definite causal relationship between the associated factors and the development of CKD stage 3b could not be demostrated. Patient adherence to ACEI/ARB, interaction with other medications and possible concomitant use of nephrotoxic drugs were other possible confounding factors which could not be addressed in this study.

It is recommended that predictors of CKD in the primary care setting

are studied further by conducting a multi-centered, cohort study in order to further establish the relationship of maximal dose of ACEI/ARB with delaying onset of CKD stage 3b among diabetics.

CONCLUSION

Systolic blood pressure and lower baseline GFR are significantly associated with the development of CKD stage 3b in the primary care setting. The use of maximum dosage of angiotensin blockade agents was found to have protective effect towards the development of CKD stage 3b. Primary care doctors should aim for better control of blood pressure among and to optimise the dose of angiotensin blockade agents among diabetic patients. However, use of maximum dose of such agents should be done with appropriate monitoring to prevent drug-related adverse events.

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