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PREDICTING THE DEVELOPMENT OF RENAL IMPAIRMENT IN TYPE 2 DIABETIC PATIENTS WITH PRESERVED KIDNEY FUNCTION

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INTRODUCTION

Diabetes mellitus (DM), especially type 2 diabetes, is the most common cause of end stage renal disease. DM patients with renal impairment (GFR<60 ml/min/1.73 m^2) are at greater risk of developing cardiovascular disease leading to premature mortality[1]. Age, age at diabetes diagnosis, duration of diabetes, glomerular filtration rate, HbA1C, total cholesterol, systolic blood pressure and albuminuria have been reported to be associated with renal impairment in diabetes patients with preserved kidney function[2-7]. Identification and assessment of individual risk factors for developing renal impairment may be useful for more appropriate patient monitoring and treatment. To date, limited data has been available on this subject regarding the Thai population. Therefore, this study aimed to develop an equation for predicting the development of renal impairment in Thai type 2 diabetic patients.

MATERIALS AND METHODS

Study design and participants This research was a retrospective cohort study. Patients were recruited who were treated at the Outpatient Department at Saraburi Hospital during January 1, 2006-December 31, 2007 with follow-up conducted until January 1, 2011-December 31, 2012. A total of 322 subjects with type 2 diabetes mellitus (T2DM) according to ICD-10 identified from the hospital database aged 20 years or older with baseline eGFR of 60 ml/min/1.73 m^2 or greater and who received hypoglycemic agent for at least 3 months were included. Subjects were excluded if they 1) were pregnant; 2) had limbs amputated; 3) had malignancy, kidney transplantation or kidney disease due to causes other than T2DM; or 4) had incomplete variables data for analysis. This study was approved by the Ethics Committee of Saraburi Hospital.

Parameters All parameters were established using information from the patient database and medical records of Saraburi Hospital.

Demographic and clinical parameters: Information about age, gender, duration of diabetes, age at diabetes diagnosis, comorbidities and blood pressure (BP) was collected. Treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) was also recorded.

Biochemical parameters: Serum creatinine (Scr) was measured using Jaffe's method in mg/dl. Hemoglobin A1C (HbA1C) was measured using immunoturbidimetric method in percentage. Total cholesterol (TC) was measured using enzymatic colorimetric method in mg/dl. Urine albumin was measured using microalbumin dipstrip (Micral test-II®) in mg/l and was categorized as normal and increased urinary albumin excretion. Increased urinary albumin excretion (UAE) was defined as urine albumin concentration 20 mg/l or greater. These measurements were all collected at baseline.

Definition of evaluated outcome Development of renal impairment (RI) was evaluated at the end of the study (about 5 years after baseline) which was defined as estimated GFR (eGFR) < 60 ml/min/1.73 m^2 at follow-up[2]. The eGFR was calculated using Thai eGFR equation[8] as follows: 375.5 x $Cr_{Enz}^{-0.848}$ x $age^{-0.364}$ x 0.712 (if female), where Cr_{Enz} refers to serum creatinine measured using enzymatic method (mg/dl), and age is in years. Since Scr in the hospital's laboratory was measured by Jaffe's method, values were calibrated measuring by enzymatic method using the following equation[9]: Scr (enzymatic method) = Scr (Jaffe's method) x 0.906.

Statistical analysis Before analysis, gathered data was verified by visual checks two times and validated by range, logical and missing data checks. The results were expressed as mean ± standard deviation for continuous data and percentage for category data. The significant difference between groups was analyzed by independent t-test and chi-square test. Logistic regression analysis was used to identify significant risk factors and develop a predictive model based on renal impairment status. Age, age at

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diabetes diagnosis, duration of diabetes, baseline eGFR, HbA1C, TC, systolic blood pressure and increased urinary albumin excretion were applied as predictors in the forward procedure. All analysis was performed with statistical package SPSS 17. Statistical significance was assessed as $p<0.05$.

RESULTS

Of the total of 322 patients, mean age was 59.1±8.7 years, most were female 181 (56.2%) and had increased UAE (79.5%), and mean baseline eGFR was 86.3±18.4 ml/min/1.73 m^2. The baseline characteristic of patients between the renal impairment group and non-renal impairment group at follow-up are shown in Tables 1 and 2. Patients who developed renal impairment at follow-up were older, more likely to be female, be of a higher age at diagnosis, have a longer duration of diabetes, lower baseline eGFR, higher systolic blood pressure (SBP), greater frequency of increased UAE, hypertension and use renin-angiotensin system blockers than those who did not. Hemoglobin A1C, diastolic blood pressure, total cholesterol, proportion of dyslipidemia and diabetes treatment were not significantly different between the groups.

During the mean follow-up of 5.2 ± 0.3 years, 88 patients developed renal impairment. Their mean eGFR at follow-up was 51.3 ± 6.6 ml/min/1.73 m^2. Table 3 shows the results of univariate and multivariate logistic regression analysis. In univariate analysis, older, higher age at diagnosis, longer duration of diabetes, lower baseline eGFR, higher systolic blood pressure and increased UAE were factors significantly associated with renal impairment at follow-up. In multivariate analysis, predictors significantly associated with renal impairment were baseline increased UAE (OR: 5.204, $p= 0.001$), baseline eGFR (OR: 0.878, $p<0.001$), diabetes duration (OR: 1.130, $p= 0.004$), baseline SBP (OR: 1.030, $p= 0.029$) and age (OR: 1.054, $p=0.030$).

Table 1 Baseline characteristics of patients in renal impairment group and non-renal impairment group at follow-up.

Variables	Non-RI (n=234)	RI (n=88)	All (N=322)	P value
Age (years)	57.4 ± 8.6	63.6 ± 7.4	59.1 ± 8.7	<0.001*
Age at diagnosis(years)	53.2 ± 9.0	56.9 ± 8.2	54.2 ± 8.9	0.001*
Diabetes duration (years)	4.2 ± 3.8	6.7 ± 4.7	4.9 ± 4.2	<0.001*
eGFR (ml/min/1.73 m^2)	92.0 ± 18.1	71.1 ± 6.9	86.3 ± 18.4	<0.001*
Hemoglobin A1C (%)	7.8 ± 1.4	7.7 ± 1.2	7.8 ± 1.3	0.458
Systolic blood pressure (mmHg)	135.8 ± 15.4	142.6 ± 12.3	137.7 ± 14.9	<0.001*
Diastolic blood pressure (mmHg)	80.6 ± 9.7	81.3 ± 10.1	80.8 ± 9.8	0.572
Total cholesterol (mg/dl)	208.3 ± 49.4	218.6 ± 51.3	210.6 ± 50.2	0.083

Cohort size, n=322. Data are expressed as mean ± SD. *P* values refer to the unpaired t test, *p<0.05
RI; renal impairment.

Table 2 Baseline characteristics of patients in renal impairment group and non-renal impairment group at follow-up.

Variables	Non-RI	RI (n=88)	All (N=322)	P value
Sex (female/male)	47.0/53.0	80.7/19.3	56.2/43.8	<0.001*
eGFR 60-89/90-120/>120 ml/min/1.73m^2	48.3/44.0/7.7	98.9/1.1/0	62.1/32.3/5.6	<0.001*
Increased urinary albumin excretion	75.6	89.8	79.5	0.005*
Comorbidity				
Hypertension	75.6	88.6	79.2	0.010*
Dyslipidemia	64.1	67.0	64.9	0.622
Cardiovascular disease	7.7	6.8	7.5	0.790
Treatments				
Oral hypoglycemic agent(s) only	89.3	83.0	87.6	0.123
Insulin only	3.8	5.7	4.3	0.541
Insulin + Oral agent(s)	6.8	11.4	8.1	0.184
ACEI/ARB agents	63.2	79.5	68.0	0.005*

Cohort size, n=322. Data are expressed as percentages. *P* values refer to the chi-square test, *p<0.05
RI; renal impairment, ACEI; angiotensin-converting enzyme inhibitor, ARB; angiotensin receptor blocker.

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Table 3 Univariate and multivariate logistic regression analysis with odds ratio (95% CI) for baseline variables as the predictor for renal impairment.

Variables	Univariate	P value	Multivariate	P value
Increased UAE (y/n)	2.827 (1.333-5.992)	0.007	5.204 (2.044-13.253)	0.001
Baseline eGFR (ml/min/1.73 m^2)	0.876 (0.846-0.907)	< 0.001	0.878 (0.847-0.910)	< 0.001
Diabetes duration (years)	1.143 (1.078-1.212)	< 0.001	1.130 (1.041-1.226)	0.004
Age (years)	1.104 (1.065-1.145)	< 0.001	1.054 (1.005-1.105)	0.030
Systolic blood pressure (mmHg)	1.034 (1.015-1.053)	0.001	1.030 (1.003-1.058)	0.029
Age at diagnosis (years)	1.048 (1.019-1.079)	0.001		
Total cholesterol (mg/dl)	1.004 (0.999-1.009)	0.084		
Hemoglobin A1C (%)	0.937 (0.778-1.129)	0.493		

Cohort size, n=322. eGFR; estimated glomerular filtration rate, UAE; urinary albumin excretion.

The final model contained 5 baseline variables as shown in equation 1 was fit well with our data (Chi-square 6.172, p= 0.628). This model can explain variation (Nagelkerke's R^2) 58.3% indicating the model is useful in predicting renal impairment. At the cut-off point of 0.5, the sensitivity, specificity and overall accuracy for prediction of renal impairment were 72.72, 92.31 and 86.96%, respectively.

$$\text{Probability of renal impairment} = \frac{1}{1+e^{-Z}} \qquad \text{(equation 1)}$$

Where $Z = -0.027 + 0.052 \times$ age (in years) $+ 0.122 \times$ diabetes duration (in years) $- 0.130 \times$ eGFR (in ml/min/1.73 m^2) $+ 1.649 \times$ increased UAE (yes=1, no=0) $+ 0.030 \times$ SBP (in mmHg)

DISCUSSION

This study included 322 type 2 diabetic patients with various diabetes durations. These patients had mean diabetes duration of 4.9 years at baseline. Eighty eight patients (27.3%) developed renal impairment over a 5-year period. Modifiable risk factors of development of renal impairment include decreased eGFR, increased UAE and high SBP. In addition, prolonged diabetes duration and old age were associated with the development of renal impairment.

The results show that increased UAE is a major predictor for developing renal impairment. Patients with increased UAE had a 5.2-fold increased risk of developing renal impairment. This is supported by previous studies which showed patients with microalbuminuria and macroalbuminuria had a 1.7-2.2 and 4.3-5.8-fold increase in risk of renal impairment, respectively [4, 5, 7].

Although the association of higher baseline eGFR with an increased rate of GFR decline has been shown[10], patients with lower baseline eGFR are more likely to develop eGFR less than 60 ml/min/1.73 m^2. Our findings show that each 1 ml/mim/1.73 m^2 increase in baseline eGFR was associated with a 12.2% decreased risk of developing renal impairment which was corroborated by previous studies of patients with a mean baseline eGFR of 82-94 ml/min/1.73m^2 showing a 6-28% reduction of renal impairment risk for each unit increase in eGFR[5, 6].

Our results indicate that each 1 year increase in diabetes duration is associated with a 13% increased risk of developing renal impairment. This is a comparable portion of patients developing renal impairment as in previous studies, showing a hazard ratio of 1.02 and 1.2 after 4.6 and 6.4 years of follow-up in patients with a mean diabetes duration of 6.3 and 12.5 years, respectively[4, 5]. It is contrary to other studies that reported that diabetes duration was not significantly associated with developing renal impairment[2, 6].

In agreement with previous studies, it was found that old age was associated with developing renal impairment[2, 4, 5, 7]. This is compatible with the concept that kidney morphology and function can be changed by aging and diseases including DM and HT can hasten this change[11].

Our results highlight the fact that high blood pressure is a risk factor for development and progression of renal impairment[2, 5]. Systolic blood pressure, not diastolic BP, in the renal impairment group was significantly higher than non-renal impairment group.

To our knowledge, there was one other predictive model for CKD development in Thai patients. Thakkinstian et al.[12] developed a prediction score for classifying risk of developing CKD in the Thai population from areas across Thailand (N=3,459). Four predictors were included in their final model,

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which were age, kidney stones, DM and hypertension. However, only 11.9% of the participants were diabetic, so it may be less specific for prediction of CKD in diabetic patients than our model.
The qualifications of this study were that, first, urine albumin and Scr be collected from only one measurement. There are several factors leading to variation of these values and therefore they may not reflect real conditions such as urine concentration and protein intake. Second, the predictive equation still needs to be validated. However, this study was a longitudinal study and investigated the predictors in Thai patients so that the results may be informative for monitoring and treatment, particularly in Thai diabetic patients that have similar characteristics. Finally, in this study urine albumin was measured as 2 levels (normal and increased urinary albumin excretion) which corresponded to American Diabetes Association guidelines 2013, which define UAE as albumin-creatinine ratio $\geq$ 30 mg/g, which is comparable to albumin concentration $\geq$ 20 mg/l in our study[13]. Future studies with quantification of albuminuria would be needed to further evaluate its effect on the development of renal impairment.

CONCLUSION

The predictive model had 5 baseline risk factors including increased UAE, eGFR, duration of diabetes, age and SBP. Study results suggest that albuminuria, eGFR and systolic blood pressure are modifiable risk factors and that reducing albuminuria, preserving GFR and controlling blood pressure may be beneficial in preventing renal impairment. Furthermore, it is recommended that patients be diagnosed with DM as soon as possible to receive appropriate monitoring and treatment.

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