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KEYWORDS: Type 2 diabetes, Preserved kidney function, Glomerular filtration rate, Prediction

INTRODUCTION

Chronic kidney disease (CKD) is one of the major complications founded in patients with type 2 diabetes (T2DM) and is characterized by progressive deterioration in renal function *(1)*. Early detection and management of CKD has been suggested to prevent the major consequences including progression to renal failure and cardiovascular complications *(2)*. In clinical practice, the most widely used parameter for evaluation of renal function loss is the decline in glomerular filtration rate (GFR). Some clinical factors associated with GFR decline in T2DM patients with early-staged CKD or preserved kidney function have been identified *(3-5)*. However, these researches in Thai patients are limited. The aim of this study was to determine the predictors of annual GFR decline in a cohort of Thai patients with T2DM and a baseline GFR $\geq$ 60 ml/min/1.73 m^2.

MATERIALS AND METHODS

Study subjects The populations for this study were all T2DM patients from outpatient diabetes clinic of Maharajnakhonsithammarat Hospital who came to see physicians during 2007-2012. One thousand patients who met all inclusion criteria were randomly sampling by computerized method from the hospital database. Individuals who had already been treated for T2DM with baseline GFR $\geq$ 60 mL/min/1.73 m^2 were included in this study. Patients having non-diabetic renal diseases including glomerulonephritis, amputation, pregnancy, or incomplete medical records were excluded from the study. The study protocol was reviewed for approval by the Maharajnakhonsithammarat Hospital Ethical Committee.

Measurements The retrospective medical record review were employed to obtain the associated clinical and biochemical data. Hypertension, hyperlipidemia, and prior cardiovascular diseases including strokes, myocardial infarction, coronary artery disease, and peripheral vascular disease, were defined by physician diagnosis of each condition documented in the medical record. Non-fasting blood samples were obtained for measurements of serum concentrations of creatinine, hemoglobin A1C, and lipids. Serum creatinine was measured by using the Jaffe's kinetic assay. Urinary albumin concentration was semi-quantified by using a urine dipstick and classified into 2 groups thereafter including normoalbuminuria (< 30 mg/L) and abnormal albuminuria ($\geq$ 30 mg/L). Smoking status was recorded as current smoker and non-current smoker. Blood pressure was measured by trained nurses using a mercury sphygmomanometer with an appropriate cuff size at the left upper arm of patients after their resting for more than 5 minutes. All data transferred from medical records were verified, validated and cleaned. Double visual check was implemented as the verification method to ensure the accuracy of the data gathered. Data validation including range check, logical check, and missing data check were as well performed to confirm that all data were sensible. GFR was calculated by using the Thai equation recently generated by Praditpornsilpa, et al: $375.5 \times Cr^{(-0.848)} \times Age^{(-0.364)} \times 0.712$ (if female) *(6)*. According to the enzymatic method of serum creatinine measurement used in this equation, Jaffe-measured serum creatinine in this study was multiplied by correction factor 0f 0.906 prior to GFR calculation *(7)*. Annual GFR decline for each patient was calculated by the formula: $GFR_{baseline} - GFR_{follow\text{-}up}$ / years of follow-up *(5)*. Percentage of annual GFR decline was calculated by the formula: annual GFR decline / $GFR_{baseline} \times 100$.

Statistical analysis Categorical data were presented as frequency and percentage while continuous data were presented as mean and standard deviation (SD). Stepwise multiple regression analysis (MRA) was performed to determine the prediction equation of annual GFR decline. The following variables were considered for possible inclusion in the regression model: age, age of first diagnosis of T2DM, T2DM duration, GFR, hemoglobin A1C, systolic blood pressure, diastolic blood pressure, serum total cholesterol, serum LDL- cholesterol, serum HDL- cholesterol, serum triglyceride, abnormal albuminuria, and current smoker. Four major assumptions of MRA including normality, linearity, homoscedasticity and multicollinearity were formally inspected prior to model proceeding. Statistical analysis was

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performed with SPSS 17.0 statistical package software. P values < 0.05 were considered statistically significant.

RESULTS

Summary of study subjects Baseline characteristics of 1000 patients were shown in Table 1. All patients had received ACEI/ARB. GFR was followed with the mean observation period of 5.3±0.1 years, ranging from 5.0-5.6 years. In addition, there were no patients characterized by GFR increase during this observational period.

Table 1 Baseline characteristics of T2DM patients with preserved kidney function (N=1000)

Parameter	Frequency (%)	Mean±SD (Range)
Age (years)	-	59.4±4.4 (51/66)
Male	353 (35.3)	-
Age of diabetes diagnosis (years)	-	53.1±3.2 (50/65)
Duration of diabetes (years)	-	6.3±3.7 (1/16)
OAD only/ insulin only/ OAD + insulin	808/120/72 (80.8/12.0/7.2)	-
GFR at baseline (mL/min/1.73 m^2)	-	92.5±20.5 (66.7/157.2)
GFR at follow-up (mL/min/1.73 m^2)	-	72.1±18.8 (43.7/145.5)
GFR decline (mL/min/1.73 m^2 per year)	-	3.8±1.0 (1.0/6.8)
GFR decline (% per year)	-	4.2±1.1 (1.1/7.6)
Abnormal albuminuria	907 (90.7)	-
Hemoglobin A1C (%)	-	7.8±0.8 (6.7/9.5)
Hemoglobin A1C < 7%	223 (22.3)	-
Hypertension	974 (97.4)	-
Systolic blood pressure (mmHg)	-	147.5±3.3 (139/153)
Diastolic blood pressure (mmHg)	-	85.4±7.8 (70/99)
Hyperlipidemia	896 (89.6)	
Total cholesterol (mg/dL)	-	252.5 ±37.8 (172/367)
LDL-cholesterol (mg/dL)	-	204.8 ±20.0 (176/237)
HDL-cholesterol (mg/dL)	-	47.2 ±6.3 (36/60)
Triglyceride (mg/dL)	-	229.9 ±40.4 (190/397)
Statin users	883 (88.3)	-
Prior cardiovascular diseases	66 (6.6)	-
Current smokers	85 (8.5)	-

Abbreviations: OAD, oral antidiabetic drug

Prediction equation of annual GFR decline Stepwise MRA revealed that age and baseline GFR were the significant predictors of the annual GFR decline with the adjusted R-square = 0.480. The regression coefficient (B) of these two predictors was 0.141 (95% CI: 0.129-0.152) and 0.032 (95% CI: 0.030-0.034), respectively and p<0.001 for both predictors. Furthermore, the standardized regression coefficient (Beta) of these two predictors was 0.589 and 0.626, respectively. Thus, the prediction equation of the annual GFR decline is presented as follows:

Annual GFR decline = 0.141 (Age) + 0.032 (baseline GFR) - 7.48

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DISCUSSION

Prediction of GFR decline in patients with T2DM and preserved kidney function is of clinical importance in order to improve the therapeutic strategies for early approach of CKD. In this long-term retrospective study of a large cohort of patients with T2DM and preserved kidney function, clinical variables including old age and high baseline GFR were significantly identified to be the predictors of the annual GFR decline.

Most patients in this study cohort were characterized by old age, female predominance, poor control of diabetes, hypertension, and hyperlipidemia, and also abnormal albuminuria. In addition, all patients had received ACEI/ARB, the antihypertensive drug classes that provide a benefit for delaying the progression of CKD *(1-2)*. However, all patients were considered to be in the GFR decline stage of renal disease since the absence of patients with increase in GFR during the period of follow-up *(8)*.

High baseline GFR was the strongest predictor of the annual GFR decline as a result of its greatest Beta value. From the prediction equation, it should be interpreted that the higher baseline GFR the patients had, the faster annual GFR decline they got. Previous studies show that high baseline GFR is the significant predictor of the annual GFR decline in T2DM patients with preserved kidney function. Zoppini, et al. reported that baseline GFR is the independent predictor of the annual GFR decline (Beta = -0.07, $p<0.05$) *(3)*. The minus symbol of Beta reported in this study means that the higher baseline GFR the patients have, the more decline of annual GFR they get. In addition, Babazono, et al. reported the negative impact of baseline GFR on the annual GFR change (B = -0.060, Beta = -0.403, $p<0.001$) *(4)*, meaning that baseline GFR has a positive impact on the annual GFR decline. The cause of high GFR leading to subsequent GFR decline is attributed to the glomerular hyperfiltration influenced by increase in circulating nitric oxide as a resulted of hyperglycemia founded in patients with diabetes *(10)*.

For old age, this study demonstrates a positive impact on the annual GFR decline, meaning that the older age the patients had, the faster annual GFR decline they got. The significant association between age and annual GFR decline in T2DM patients with preserved kidney function is reported in the previous published data. Zoppini, et al. reported that age is the independent predictor of the annual GFR decline (Beta = -0.07, $p<0.05$) *(3)*. The minus symbol of Beta reported in this study means that the older age the patients have, the more decline of annual GFR they get. Moreover, Meguro, et al. reported the positive impact of age on the annual GFR decline in patients with baseline GFR from 60 to less than 90 mL/min/1.73 m^2 (Beta = 0.153, $p<0.001$) *(5)*. The mechanisms involving age-related deterioration in renal function include decrease in renal plasma flow and loss of filtration surface area with age *(11)*.

Strengths of this study included the large number of patients in the study cohort and the long duration of follow-up. The study also has some limitations. First, the availability of some relevant data may be limited because of the retrospective design of this study. Second, selection bias may occur as a result of the exclusion of individuals with incomplete medical data. Finally, some variables including albuminuria and smoking habit were not fully quantified. Future studies with a complete quantification of these data would be needed to further evaluate their effects on the annual GFR decline.

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CONCLUSION

This study demonstrates that, in a large cohort of patients with T2DM and preserved kidney function who were followed for at least 5 years, the annual GFR decline is strongly predicted by high GFR and old age.

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