Prevalence and Risk Factors of Diabetic Nephropathy among Thai Patients with Type 2 Diabetes Mellitus

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Background: *Diabetic nephropathy (DN) is the leading cause of end stage renal disease. Clinically, DN is classified into 3 stages: microalbuminuria (MA), macroalbuminuria and ESRD. The prevalence and risk factors of DN among patients with type 2 diabetes mellitus (T2DM) in Thailand have not been well studied.*
Objective: *To assess the prevalence of DN in patients with T2DM and to determine their associated risk factors.*
Material and Method: *A cross-sectional study evaluating 877 T2DM patients from the out-patient department of seven public hospitals in Thailand was performed. Three random spot urine samples from all patients were collected during 3 consecutive months. Normoalbuminuria, MA and macroalbuminuria were defined as the presence of at least two out of three spot urine tests for urine albumin/creatinine ratio showing less than 30, 30-300 and more than 300 mg/gm respectively.*
Results: *Most patients were female, 60 years of age or older, with BMI above 25 kg/m^2, a family history of DM, uncontrolled blood pressure, HbA1c above 7.0% and LDL above 100 mg/dl. The prevalence of normoalbuminuria, MA and macroalbuminuria was 62.8, 26.0 and 11.2% respectively. The prevalence of diabetic retinopathy in T2DM with normoalbuminuria, MA and microalbuminuria was 18.5, 35.5 and 48.0% respectively. Associated risk factors of DN were the duration of DM, HbA1c levels and uncontrolled hypertension.*
Conclusion: *The prevalence of all DN was 37.2%. Associated risk factors of DN were the duration of DM, HbA1c levels and uncontrolled hypertension.*

Keywords: *Diabetic nephropathy, Diabetes mellitus*

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Diabetes mellitus (DM) is a risk factor for chronic kidney disease. Diabetic nephropathy (DN) is now the leading cause of end stage renal disease (ESRD) throughout the world. Clinically DN is classified into 3 stages: microalbuminuria (MA), macroalbuminuria and ESRD. DM patients without DN have normal urinary albumin excretion which is less than 20 mg/day. The earliest detectable sign of diabetic nephropathy is MA which is diagnosed if urinary albumin excretion increases to between 30 and 300 mg/day. The next stage is macroalbuminuria which is diagnosed if urinary albumin excretion increases above 300 mg/day[1]. The last stage of DN is decreasing renal function leading to ESRD. Previous studies of DM patients have identified a number of factors as being associated with increased risk of clinical DN[2-4]. The likelihood of developing DN is markedly increased in patients who are elderly, male, with a family history of DN, long duration of DM, poor glycemic control (high HbA1c levels), high blood pressure, high body mass index (BMI), dyslipidemia, who smoke and who take certain types of antihypertensive drugs, especially angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Some studies suggest a relationship between DN and diabetic retinopathy (DR). Some studies show that DR typically precedes macroalbuminuria[5-8]. Patients with proteinuria and DR most likely have DN, while patients with proteinuria but without DR look more like patients with other glomerular diseases[9]. The

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prevalence and risk factors of DN among patients with type 2 diabetes mellitus (T2DM) in Thailand have not been well studied. The purpose of this present study was to assess the prevalence of DN in patients with T2DM and to determine their associated risk factors.

Material and Method

This is a cross-sectional study in Thai T2DM patients, Performed from January 2007 to September 2008. The Ethics Review Committee for Research in Human Subjects, Ministry of Public Health approved this study and all patients gave written informed consent after reviewing a written summary of the study plan. The authors recruited T2DM patients diagnosed with the American Diabetes Association's criteria[10] from the out-patient departments of seven public hospitals, including Rajavithi Hospital (Bangkok), Lerdsin Hospital (Bangkok), Nopparatrajathanee Hospital (Bangkok), Mettaphacharak Hospital (Nakhonpathom), Pathumthani Hospital (Prathumthani), Lardlumkaew Hospital (Prathumthani) and Nongsau Hospital (Prathumthani). Exclusion criteria were pregnancy, breast feeding, acute systemic diseases and other renal diseases. Histories of these patients and complete physical examinations were obtained. Height, weight and blood pressure were measured using standard procedures. The mean of two separate blood pressure results was taken as the final blood pressure recording. Two fasting blood and three random spot urine samples from all patients were collected over 3 consecutive months.

Fasting blood sugar, HbA1c and serum creatinine were determined by hexokinase enzymatic, immunoturbidimertric (DCCT/NGSP) assay and the Jaffe method (rate-blanked and compensated) using a COBAS INTEGRA 400® analyzer (Roche Diagnostics, Indianapolis, IN, US). The quantity of urinary albumin concentration was determined by immunoturbidimetric assay and urine creatinine concentration by the Jaffe method (rate-blanked and compensated) using COBAS INTEGRA 400® analyzer.

Using the World Health Organization classification for adult Asians, BMI above 25 kg/m^2 was considered to constitute obesity. Subjects with systolic blood pressure over 130 mmHg and/or diastolic blood pressure over 80 mmHg were considered to have uncontrolled hypertension. Glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula[10]. Urine albumin to creatinine ratio (UACR) was classified into three groups: less than 30, 30-300 and more than 300 mg/gm. Normoalbuminuria, MA and macroalbuminuria were defined as the presence of at least two out of three spot urine tests for UACR showing less than 30, 30-300 and more than 300 mg/gm respectively.

The critical statistic for this research was the determination factor shown as mean $\pm$ standard deviation. Univariate comparisons of the independent variables of continuous and categorical dependent variables were made using unpaired Student's t-test and Pearson Chi-square test respectively. Multivariate regression was used to assess the associated risk factors of DN with odds ratio and 95% confidence interval (95% CI). A p-value of less than 0.05 was considered as statistically significant. Analysis was made with the software program SPSS for Windows version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Among the total of 899 T2DM patients, 22 patients were excluded for not completing the three required urine examinations. A total of 877 patients were therefore enrolled. Their basic characteristics were shown in Table 1. Most patients were female (71.3%), 60 years of age or older (51.4%), with BMI above 25

Table 1. Baseline characteristics of all 877 patients in this study

Factors	n = 877
Female (n, %)	625 (71.3)
Age (yrs)	59.57 $\pm$ 9.90
Duration of DM (yrs)	8.06 $\pm$ 6.11
Family history of DM (n, %)	524 (59.8)
Smoking (%)	74 (8.4)
ACEI/ARB taking (n, %)	326 (41.3)
Diabetic retinopathy (n, %)	229 (26.3)
Body weight (kg)	66.87 $\pm$ 13.17
Body mass index (kg/m^2)	27.35 $\pm$ 4.72
Systolic BP (mmHg)	130.91 $\pm$ 16.31
Diastolic BP (mmHg)	71.94 $\pm$ 9.45
HbA1c (%)	8.77 $\pm$ 1.85
Fasting blood sugar (mg/dl)	154.02 $\pm$ 52.74
Serum creatinine (mg/dl)	0.95 $\pm$ 0.58
GFR (ml/min/1.73 m^2)	82.01 $\pm$ 27.54
LDL (mg/dl)	139.19 $\pm$ 41.18
Serum albumin (gm/dl)	4.53 $\pm$ 0.39
Diabetic nephropathy (n, %)	326 (37.2)

Values are represented as n (%), Means $\pm$ SD
DM = Diabetes mellitus , GFR = Glomerular filtration rate

kg/m^2 (66.9%), a family history of DM (59.8%), uncontrolled blood pressure (51.5%), HbA1c above 7.0% (83.1%) and LDL above 100 mg/dl (82.8%). The prevalence of MA and macroalbuminuria were 26.0 and 11.2% respectively. No ESRD patients were found. Finally the overall prevalence of DN was 37.2%. Only 41.3% of all patients had received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. The overall prevalence of DR in the patients was 26.3%. The prevalence of DR in T2DM with normoalbuminuria, MA and microalbuminuria was 18.5, 35.5 and 48.0% respectively. Furthermore, 39.6% of DN patients had DR.

In univariate analysis, duration of DM, blood pressure, uncontrolled hypertension, DR and HbA1c level were associated with the presence of DN (Table 2). In multivariate regression analysis, associated risk factors of DN were the duration of DM, HbA1c levels and uncontrolled hypertension (Table 3).

Discussion

DM appears to be a factor in the increase in ESRD, making the care of these patients very expensive[11]. Epidemiological studies show marked variations in the prevalence of DN, especially for MA, with reports of less than 10.0% in the United Kingdom[12] and 35.0% in Hispanic Americans[13]. The variation in prevalence may be explained by the differences in several factors, especially the particular populations studied and the definition of MA. The generally accepted criterion for MA requires two out of three urine examinations within a target range for UACR (30-300 mg/gm). The prevalence and risk factors of DN among patients with T2DM in Thailand have not been well studied. This present study used the generally accepted criteria to evaluate the prevalence of DN in patients with T2DM and to determine their associated risk factors. Eight hundred seventy-seven patients with T2DM from primary to tertiary pubic hospitals in the Bangkok Metropolitan area were included. Most patients were female, 60 years of age or older, obese, with uncontrolled hypertension, poor glycemic control and hyperlipidemia. Using accepted UACR criteria of 3 urine examinations, the prevalence

Table 2. Univariate analysis of factors associated with DN (n = 877)

	DM without DN	DM with DN	p-value
Number (%)	551 (62.8)	326 (37.2)	
Age (yrs)	59.39 $\pm$ 9.89	59.88 $\pm$ 9.91	0.481
Duration of DM (yrs)	7.55 $\pm$ 5.73	8.94 $\pm$ 6.63	0.002*
Diabetic retinopathy (n, %)	101 (18.5)	128 (39.6)	0.001*
Body mass index (kg/m^2)	27.22 $\pm$ 4.59	27.57 $\pm$ 4.91	0.298
Uncontrolled BP (n, %)	251 (45.6)	201 (61.7)	< 0.001*
Systolic BP (mmHg)	127.99 $\pm$ 14.50	135.83 $\pm$ 17.96	< 0.001*
Diastolic BP (mmHg)	71.25 $\pm$ 9.22	73.09 $\pm$ 9.74	0.005*
HbA1c (%)	8.60 $\pm$ 1.71	9.06 $\pm$ 2.05	0.001*
LDL (mg/dl)	138.25 $\pm$ 39.71	140.77 $\pm$ 43.56	0.382

Values are represented as n (%), Means $\pm$ SD, * Significant at $p < 0.05$

Table 3. Multivariate analysis of adjusted factors associated with DN (n = 877)

Factors	Crude OR	Adjusted OR	95% CI of Adjusted OR	p-value
Sex (Male)	1.25	1.24	0.90-1.69	0.183
Age (year)	1.00	0.99	0.98-1.01	0.648
Duration of DM (yrs.)	1.04	1.03	1.00-1.06	0.010*
HbA1C (%)	1.14	1.15	1.06-1.24	0.001*
Uncontrolled BP	1.94	1.91	1.43-2.56	< 0.001*

Adjusted for sex, age and duration of diabetes, OR = odds ratio, CI = confidence interval, * Significant at $p < 0.05$

of DN, MA and macroalbuminuria were 37.2, 26.0 and 11.2% respectively. The associated risk factors of DN were duration of DM, HbA1c levels and uncontrolled hypertension. These results extended previous studies in Thai T2DM patients. A previous cross-sectional study of 4,875 T2DM patients of 11 medical school hospitals that are referral hospitals in Thailand showed the prevalence of DN, MA and macroalbuminuria as 42.9, 19.7 and 23.2% respectively. However DN in this previous study was defined as the presence of at least two out of three of these symptoms: positive MA, positive dipstick test for proteinuria, or serum creatinine of 2 mg/dl or more[14]. MA was defined as the presence of single random urine UACR between 30-300 mg/gm. Macroalbuminuria was defined as a positive dipstick test for proteinuria in single random urine examination. This previous study found that factors associated with DN were age, duration of diabetes, male sex, smoking, systolic blood pressure, HbA1c, dyslipidemia and the presence of DR. Another study (the DEMAND study) evaluated 32,208 patients with T2DM from 33 countries including Thailand[15]. Patients were selected from primary care settings. MA was determined by the result of single random urine dipstick test for MA. The overall prevalence of MA and macroalbuminuria of the patients in this study was 39.0 and 10.0% respectively. Asian patients had the highest prevalence of MA (43.0%) and macroalbuminuria (12.0%). Glycemic control, arterial BP and smoking were associated with the presence of MA and macroalbuminuria.

Our findings show that there is an association between DN and DR. DR was found in 39.6% of Thai T2DM patients with DN, but in only 18.5% of patients without DN. These results confirm previous studies of Thai T2DM patients. Previously, 47.0% of patients with DN were found to have DR[16].

Conclusion

The prevalence of DN, MA and macroalbuminuria were 37.2, 26.0 and 11.2% respectively. Associated risk factors of DN were the duration of DM, HbA1c levels and uncontrolled hypertension.

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Potential conflicts of interest

None.

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ความชุกและปัจจัยเสี่ยงของโรคไตจากเบาหวานชนิดที่สอง

อุดม ไกรฤทธิชัย, สมเกียรติ โพธิสัตย์, อัมพร จงเสรีจิต, ชาญเวช ศรัทธาพุทธ

ภูมิหลัง: *โรคไตจากเบาหวาน (diabetic nephropathy) เป็นสาเหตุสำคัญของไตวายระยะสุดท้าย อาการของโรคไตจากเบาหวานแบ่งออกเป็นสามระยะ คือ microalbuminuria (MA), macroalbuminuria และไตวายระยะสุดท้าย ความชุก และปัจจัยเสี่ยงของโรคไตจากเบาหวานชนิดที่สองในประเทศไทยยังมีการศึกษาน้อย*

วัตถุประสงค์: *เพื่อหาความชุกและปัจจัยเสี่ยงของโรคไตจากเบาหวานชนิดที่สอง*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยเบาหวานชนิดที่สองจำนวน 877 ราย จากคลินิกผู้ป่วยนอกของโรงพยาบาลรัฐบาล 7 แห่ง ทำการตรวจปัสสาวะแบบสุ่มจำนวนสามครั้งในสามเดือน โดยนิยาม normoalbuminuria, microalbuminuria (MA) และ macroalbuminuria เท่ากับการมีผล urine albumin/creatinine ratio เท่ากับ 30, 30-300 และมากกว่า 300 mg/gm ตามลำดับอย่างน้อยสองในสามครั้งของการตรวจปัสสาวะแบบสุ่ม*

ผลการศึกษา: *ผู้ป่วยส่วนใหญ่เป็นเพศหญิง, อายุมากกว่า 60 ปี, BMI มากกว่า 25 kg/m^2, มีประวัติครอบครัวเป็นเบาหวาน, ควบคุมความดันโลหิตไม่ได้, ระดับ HbA1c มากกว่า 7.0% และ LDL มากกว่า 100 mg/dl ความชุกของ normoalbuminuria, MA และ macroalbuminuria เท่ากับ 62.8, 26.0 และ 11.2% ตามลำดับ ความชุกของโรคตาจากเบาหวานชนิดที่สองใน normoalbuminuria, MA และ macroalbuminuria เท่ากับ 18.5, 35.5 และ 48.0% ตามลำดับ ปัจจัยเสี่ยงของโรคไตจากเบาหวาน คือ ระยะเวลาที่เป็นเบาหวาน, ระดับ HbA1c และการควบคุมความดันโลหิตไม่ได้*

สรุป: *ความชุกและปัจจัยเสี่ยงของโรคไตจากเบาหวานชนิดที่สองเท่ากับ 37.2% โดยปัจจัยเสี่ยงของโรคไตจากเบาหวาน คือ ระยะเวลาที่เป็นเบาหวาน, ระดับ HbA1c และการควบคุมความดันโลหิตไม่ได้*