Prevalence of Overt Nephropathy and Its Associated Factors in Type 2 Diabetes Mellitus at Maharat Nakhon Ratchasima Hospital

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Abstract

Objective: To determine the prevalence of overt nephropathy and the factors associated with this condition among diabetic patients at the Diabetic Clinic, Department of Medicine, Maharat Nakhon Ratchasima Hospital. **Patients & Methods:** A cross-sectional hospital-based study of diabetic registry in 2003. Overt nephropathy was defined as positive urine dipstick test at least 1+ in two collections excluding patients with non-diabetic kidney disease. **Results:** The study include 962 patients with type 2 diabetes, consisted of 699 females and 263 males. The prevalence of overt nephropathy founded in this study was 25.6%, and 59.9% of the patients had developed chronic kidney disease (CKD) stage 3 or higher. The factors associated with the presentation of overt proteinuria were the duration of diabetes ≥20 years, systolic blood pressure of ≥160 mmHg, serum triglyceride of ≥150 mg/dL and the presence of diabetic retinopathy. **Conclusions:** Overt nephropathy was a very common complication of type 2 diabetes. Early urine screening test for urine microalbumin and estimated GFR should be done for early diagnosis and early treatment of diabetic nephropathy which could prevent the progression to end-stage renal disease.
Key words: overt nephropathy, prevalence, chronic kidney disease

บทคัดย่อ: โรคไตเรื้อรังจากเบาหวานและปัจจัยที่มีความสัมพันธ์กับการเกิดในผู้ป่วยเบาหวานชนิดที่ 2 ในโรงพยาบาลมหาราชนครราชสีมา

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความชุกของโรคไตเรื้อรังจากเบาหวานและปัจจัยที่มีความสัมพันธ์กับการเกิดในผู้ป่วยเบาหวานชนิดที่ 2 ในคลินิกผู้ป่วยเบาหวาน กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา **ผู้ป่วยและวิธีการ:** การศึกษาภาคตัดขวางผู้ป่วยเบาหวานที่ลงทะเบียนรับการรักษาในปี พ.ศ. 2546 โรคไตเรื้อรังจากเบาหวานใช้เกณฑ์การตรวจปัสสาวะโดยใช้แถบจุ่มพบผลบวกไข่ขาวอย่างน้อย 2 ครั้ง และแยกโรคไตเรื้อรังจากสาเหตุอื่น **ผลการศึกษา:** ผู้ป่วยเบาหวานชนิดที่ 2 จำนวน 962 ราย เป็นเพศหญิง 699 ราย เพศชาย 263 ราย พบความชุกของโรคไตเรื้อรังจากเบาหวานร้อยละ 25.6 เมื่อจำแนกผู้ป่วยตามระดับความรุนแรงของโรคไตเรื้อรังพบร้อยละ 59.9 ของผู้ป่วยเป็นโรคไตเรื้อรังระยะที่ 3 ขึ้นไป ปัจจัยที่มีความสัมพันธ์กับการเกิดโรคไตเรื้อรังจากเบาหวานได้แก่ ระยะเวลาที่เป็นเบาหวานตั้งแต่ 20 ปีขึ้นไป ระดับความดันโลหิตช่วงหัวใจบีบตัวค่าตั้งแต่ 160 mmHg ขึ้นไป ระดับไขมันไตรกลีเซอไรด์ตั้งแต่ 150 mg/dL ขึ้นไป และการตรวจพบเบาหวานแทรกซ้อนทางตา **สรุป:** โรคไตเรื้อรังจากเบาหวานเป็นภาวะแทรกซ้อนที่พบบ่อยในผู้ป่วยเบาหวานชนิดที่ 2 ควรวินิจฉัยภาวะนี้ตั้งแต่ระยะเริ่มแรกโดยการตรวจคัดกรองหาปริมาณไข่ขาวในปัสสาวะซึ่งเป็นวิธีที่ไวกว่า ร่วมกับวัดระดับการทำงานของไต และรีบให้การรักษาในระยะเริ่มแรกเพื่อป้องกันการเกิดไตวายระยะสุดท้าย

Background

Diabetes has become the most common cause of end-stage renal disease (ESRD) worldwide; this is due to the facts that diabetes, particularly type 2, is increasing in prevalence and diabetes patients now live longer.[1] Patients with diabetic ESRD are now being accepted for treatment in ESRD programs where formerly they had been excluded both in western countries and Thailand.[2] In the United States (US) about 20-30% of patients with type 1 and type 2 diabetes developed evidence of nephropathy.[3] Persistent albuminuria in the range of 30-299 mg per 24 hours (microalbuminuria) has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes. Micro-albuminuria is also a well-established marker of increased CVD risk.[4] There is a considerable racial/ethnic variability in this regard, with Native Americans, Hispanics (especially Mexican-Americans), and African-Americans having much higher risks of developing ESRD than non-Hispanic whites with type 2 diabetes.[5]

The purpose of this study is to determine the prevalence of overt nephropathy and the factors associated with this condition among diabetic patients in the Department of Medicine, Maharat Nakhon Ratchasima Hospital.

Patients and Methods

Setting and Subjects

This cross-sectional study is a part of the Diabetic Registry Project at Maharat Nakhon Ratchasima Hospital, which was carried out from April to December 2003. It was conducted at the Diabetic Clinic of Maharat Nakhon Ratchasima Hospital which is a tertiary care center in the North-eastern of Thailand. The subjects of this study were diabetic patients who treated at our Diabetic Clinic and accepted to be participants in this registry. The diagnosis of diabetes mellitus was made according to the American Diabetes Association criteria 1997.[6] The total number of diabetic patients who registered at Maharat Nakhon Ratchasima Hospital was 1,066 patients. From those patients, 992 patients were type 2 diabetes and were included in the study.

Methods and Measurements

The registry data were recorded in the case record form by interviewing and examining the

patients and reviewing their medical records. The data composed of demographic data, pertinent parts of physical examinations, laboratory examinations performed during the last 12 months of recruitment, specific medications including insulin, oral hypoglycemic agents, antihypertensive agents, lipid lowering agents and aspirin, and diabetic complications. All of the information was verified by physician's reports.

Blood pressure was measured at right arm twice for 30 seconds apart, after resting for 5 minutes, by using an automated blood pressure machines (OMRON T4 , Omron Corporation, Japan). Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg, or was considered to be present if the patient had a history of high blood pressure and was being treated with antihypertensive drugs. Height and weight were measured in light clothing and body mass index was calculated as weight (kg)/height $(m)^2$. Information on smoking, medication and history of diabetes were obtained by an interview.

Results of eye examinations reported within one year from the registry day were recorded; including the results of retinal examinations, visual acuity, and cataract findings by direct opthalmoscopy after full dilatation of pupils. Level of retinopathy was classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) categories. Level of retinopathy was based on the grading of the worst eye.

Fasting plasma glucose, serum total cholesterol, HDL cholesterol (HDL-C) and triglyceride levels were determined by the enzymatic methods. LDL cholesterol (LDL-C) was calculated using the Friedewald's formula (LDL=total cholesterol-HDL-TG/5). Glycosylated hemoglobin (HbA1c), plasma creatinine, and urine microalbumin levels were determined by the central laboratory of the hospital using standard methods with local quality control.

Urine analysis was performed by using urine specimens in the morning void fresh urine (midstream). Overt nephropathy was evaluated and defined as positive urine dipstick test at least 1+ level in the absence of active sedimentation in two consecutive collections and excluded non-diabetic kidney diseases. Chronic kidney disease was defined by NKF-K/DOQI Stages of Chronic Kidney Disease (CKD)[7]. GFR was calculated by the MDRD equation[8] using serum creatinine.

The study was approved by the Ethics Committee of the Endocrine Society of Thailand and by the Institutional Review Board of Maharat Nakhon Ratchasima Hospital. Informed consent for the study was also obtained from all participants in this study.

Statistical Analyses

Descriptive statistics were used for the study's subjects. Proportions of studied variables were compared by using Chi-square test and Fisher's exact test. Differences in mean values of studied variables were compared by using t-test and Mann-Whitney U test. The crude odds ratio was calculated to define each associated factor with diabetic nephropathy. Then confounding factors were adjusted by applied multiple logistic regression and adjusted factors were calculated to define the associated factors with diabetic nephropathy. Statistical analyses were performed using computer software.

Results

A total of 992 patients with type 2 diabetes mellitus were tested for proteinuria by urine strips. Since 30 patients were non-diabetic kidney disease, therefore, only 962 patients were included in the study which consisted of 699 females and 263 males. Mean age of patients was 59.4$\pm$10.9 years (median 59.6, range 33.4-83.0 years) and mean duration of diabetes was 8.2$\pm$6.8 years (median 6.8, range 0-46 years). The prevalence of overt nephropathy in this study was 25.6% (246 patients) and 71 patients (29.0%) had renal insufficiency (serum creatinine >2 mg/dL). The prevalence of overt nephropathy in patients with type 2 diabetes increased with a longer duration of

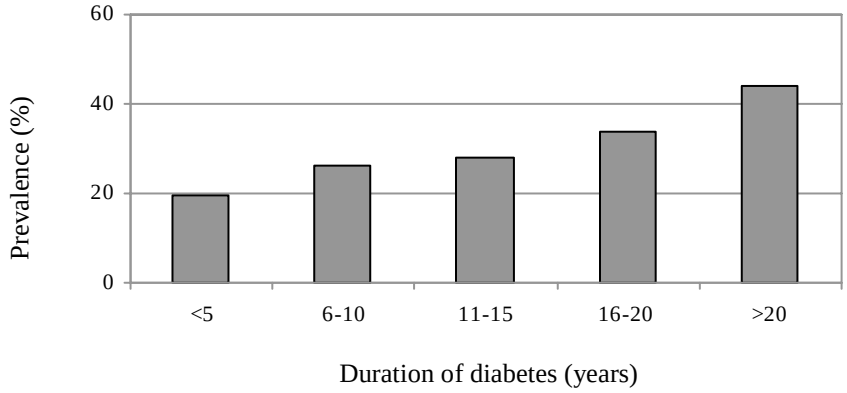

Figure 1. Prevalence of overt nephropathy by the duration of diabetes of type 2 diabetic patients

diabetes from less than 5 years to more than twenty years as shown in **Figure 1**. GFR calculation by using MDRD equation classified 577 patients or about 59.9% into NKF-K/DOQI Stages of Chronic Kidney Disease stage 3 or higher as shown in **Figure 2**.

The clinical characteristics of patients according to the presentation of overt nephropathy are demonstrated in **Table 1**. When compared with patients without overt proteinuria, patients with overt proteinuria had higher percentages of male patients and smokers, and had a longer mean duration of diabetes, higher mean systolic and diastolic blood pressure, higher mean serum creatinine and higher mean triglyceride levels.

The proportions of diabetic patients categorized by levels of metabolic control using the cut points according to the recommendations for adults with diabetes from the American Diabetes Association[6] are demonstrated in **Table 2.** We found that the percentages of patients with overt proteinuria are significantly higher than those without overt proteinuria in three parameters, e.g. systolic blood pressure more than or equal to 130 mmHg, diastolic blood pressure more than or equal to 80 mmHg, and triglyceride level more than or equal to 150 mg/dL. Moreover, patients with overt proteinuria also represent significantly higher percentages than those without proteinuria in the other three characteristics,e.g., diabetic retinopathy, hypertension and renal insufficiency.

Figure 2 Chronic kidney disease staging according to NKF-K/DOQI

Table 1. Clinical characteristics of type 2 diabetic patients according to the presentation of overt nephropathy

Parameters	Overt proteinuria		*P*
	Positive (n = 246)	Negative (n = 716)	
Male (%)	34.6	24.9	0.003
Age (yr) (mean±SD)	60.2±11.1	59.1±10.8	0.599
Duration of DM (yr) (mean±SD)	9.8±7.4	7.7±6.4	<0.001
Body mass index (mean±SD)	25.4±4.9	25.0±4.3	0.284
Current smokers and ex-smokers (%)	22.8	15.4	0.008
Systolic BP (mmHg) (mean±SD)	148.7±26.6	139.3±22.5	<0.001
Diastolic BP (mmHg) (mean±SD)	79.6±13.1	77.2±11.8	0.010
Fasting plasma glucose (mg/dL) (mean±SD)	157.3±65.4	150.2±50.2	0.120
Hemoglobin A1c (%) (mean±SD)	8.05±2.1	7.86±2.1	0.225
Serum creatinine (mg/dL) (mean±SD)	1.9±1.6	1.3±0.7	<0.001
Total cholesterol (mg/dL) (mean±SD)	209.5±58.3	202.5±42.7	0.086
Triglyceride (mg/dL) (mean±SD)	187.8±131.1	156.7±95.6	<0.001
LDL cholesterol (mg/dL) (mean±SD)	117.6±42.9	114.8±37.2	0.368
HDL cholesterol (mg/dL) (mean±SD)	54.2±16.8	56.4±15.5	0.052

A multiple logistic regression was performed by adjusting with the duration of diabetes, gender, smoking status, systolic blood pressure, diastolic blood pressure, serum triglyceride levels, and a status of retinopathy. The factors associated with the presentation of overt proteinuria were the duration of diabetes of more than or equal to twenty years, systolic blood pressure of more than or equal to 160 mmHg, serum triglyceride of more than or equal to 150 mg/dL, and the presence of diabetic retinopathy as demonstrated in **Table 3**.

Discussion

Diabetic nephropathy is the most common microvascular complications of diabetes. The prevalence of overt nephropathy in this study was

Table 2. Clinical characteristics of type 2 diabetic patients according to the presentation of overt nephropathy (using the cut points recommended by the American Diabetes Association)

Parameters	Overt proteinuria		*P*
	Positive (n = 246)	Negative (n = 716)	
Systolic BP ≥130 mmHg (%)	75.6	63.7	0.001
Diastolic BP ≥80 mmHg (%)	50.4	41.3	0.013
Fasting plasma glucose >130 mg/dL (%)	64.2	61.7	0.486
Hemoglobin A1c ≥7% (%)	71.4	67.3	0.236
Total cholesterol ≥200 mg/dL (%)	50.4	50.7	0.937
Triglyceride ≥150 mg/dL (%)	51.2	40.7	0.004
LDL cholesterol ≥100 mg/dL (%)	62.9	64.9	0.558
HDL cholesterol ≤40 mg/dL in male (%) and ≤50 mg/dL in female (%)	35.0	33.4	0.681
Diabetic retinopathy (%) (n = 608)	29.7	13.0	
NPDR	10.8	6.5	<0.001
PDR	28.9	6.5	
Renal insufficiency (%)	29.0	2.4	<0.001
Hypertension (%)	88.2	63.8	<0.001

Table 3. Factors associated with the presentation of overt nephropathy in type 2 diabetes

Risk Factors	Adjusted Odd Ratio* (95% CI)	*P*
Duration of diabetes (years)		
<5	1	
5-9.9	0.93 (0.55-1.58)	0.793
10-14.9	42 (0.82-2.44)	0.209
15-19.9	1.1.61 (0.78-3.34)	0.192
≥20	2.52 (1.20-5.30)	0.015
Gender		
Female	1	
Male	0.90 (0.51-1.59)	0.721
Current smokers and ex-smokers	1.76 (0.90-3.42)	0.093
Systolic blood pressure (mmHg)		
<140	1	
140-159	1.18 (0.74-1.89)	0.476
≥160	1.95 (1.11-3.43)	0.021
Diastolic blood pressure (mmHg)		
<90	1	
90-99	1.03 (0.55-1.94)	0.919
≥100	1.02 (0.40-2.64)	0.963
Triglyceride (mg/dL)		
<150	1	
150-299	1.60 (1.04-2.48)	0.032
≥300	3.15 (1.72-5.78)	<0.001
Presence of retinopathy	2.41 (1.49-3.89)	<0.001

* Adjusted for the duration of diabetes, gender, smoking, systolic blood pressure, diastolic blood pressure, serum triglyceride levels, and presence of retinopathy

25.6%, while previously reported prevalence of nephropathy in types 2 diabetes varied from 5-20%.[1,3] From Thailand Diabetes Registry Project 2003, a large cross-sectional, multicenter, hospital-based diabetic registry included tertiary care and academic centers revealed the prevalence of diabetic nephropathy of 42.9% (microalbuminuria 19.7% and overt nephropathy 23.2%).[9] Maharat Nakhon Ratchasima Hospital, one of the TDR project, was not included in the analysis of the prevalence of diabetic nephropathy because of the limitation in demonstrating diabetic patients with microalbuminuria. Therefore, some patients classified to have no proteinuria might have an incipient nephropathy (microalbuminuria). A high prevalence of overt nephropathy in this study could be explained by more advanced diseases that required special care in tertiary center.

Non-diabetic kidney diseases in this study were 30 patients which were excluded by having active urine sediment or severe impair GFR but no overt nephropathy. Twenty four patients found to have renal calculi and chronic tubulointerstitial disease. Six patients had associated with other secondary glomerular diseases (proliferative glomerulonephritis).

American Diabetic Associations recommended Standards of medical care in Diabetes in 2007[10] to early detection of complication by multidisciplinary approach including annual check up urinary microalbumin and serum creatinine to screen for diabetic kidney disease. The combination of abnormal creatinine and microalbuminuria found to improve performance in identifying CKD but still failed to detect a large number with CKD.[11,12] Incorporating estimated GFR by MDRD equation

into screening for CKD as NKF-K/DOQI recommendation would identified patients with early disease that we can enable early effective treatment to delay progression of CKD. This study also found that most patients developed CKD stage 3 or higher accounted for 59.9% including patient that did not have overt nephropathy.

The factors associated with overt nephropathy in the study were duration of diabetes of more than or equal to twenty years, systolic blood pressure of more than or equal to 160 mmHg, serum triglyceride of more than or equal to 150 mg/dL and the presence of diabetic retinopathy. Glycaemic control, fasting plasma glucose and HbA1c, had not been shown to be the risk factors in the study compared to previously reported.[3,13] These findings could be explained by a cross-sectional study that did not known glycaemic control on the start and the progression of overt proteinuria. The finding that nearly 44% of the patients that had duration of diabetes more than or equal to twenty years developed overt nephropathy is comparable to previous data from United Kingdom Prospective Diabetes Study (UKPDS) 74.[14]

Strict blood pressure control is clearly important for preventing the progression of diabetic nephropathy and other complications. In the study systolic blood pressure of more than 160 mmHg was an independent risk factor for overt nephropathy as in many studies. [3,9,13-15] Many patients received treatment for hypertension, potentially obscuring role of blood pressure in the development of diabetic kidney disease. In UKPDS each 10 mmHg reduction in systolic pressure was associated with a 12 percent risk reduction in diabetic complications (P<0.001), the lowest risk occurred at a systolic pressure below 120 mmHg.[16]

Many of the changes in plasma lipoproteins associated with renal disease are believed to be caused by renal dysfunction. However, hyperlipidaemia may be associated with development of glomerular injury. Ravid et al found that the concentration of cholesterol was positively related with the subsequent increase in urine albumin excretion in patients with diabetes type 2.[17] In the study serum triglyceride of more than or equal to 150 mg/dL was associated with an increased risk of developing overt nephropathy but serum cholesterol did not show this association.

Diabetic retinopathy was also a strong risk factor and is probably a marker of the presence of microvascular disease rather than a risk factor per se, because nephropathy and retinopathy seem to share the same environmental predisposing factors, such as hyperglycemia and arterial hypertension. These findings were found in nearly all previously reported. [3-5,9,13-14,16]

Conclusions

A total of 962 patients with type 2 diabetes mellitus were tested for proteiuria by urine strips consisted of 699 females and 263 males. The prevalence of overt nephropathy in this study was 25.6% (246 patients) and 59.9% (577 patients) of the patients had developed CKD stage 3 or higher estimated by the MDRD equation. The factors associated with the presentation of overt proteinuria were the duration of diabetes of more than or equal to twenty years, systolic blood pressure of more than or equal to 160 mmHg, serum triglyceride of more than or equal to 150 mg/dL and the presence of diabetic retinopathy. Early urine screening test for urine microalbumin and estimated GFR should be done for early diagnosis and early treatment of diabetic nephropathy which could prevent the progression to end-stage renal disease.

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