Thailand Diabetes Registry Project: Prevalence, Characteristics and Treatment of Patients with Diabetic Nephropathy

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Objectives: To identify the prevalence and characteristics of patients with Diabetic Nephropathy (DN) and to evaluate adequacy of glycemic and blood pressure control of these patients in the authors' registry.

Material and Method: A cross-sectional, multicenter, hospital-based diabetic registry was carried out in diabetes clinics of 11 tertiary centers in Thailand. DN was defined as the presence of at least two out of three of these symptoms; positive microalbuminuria, positive dipstick proteinuria or creatinine levels equal to or greater than 2 mg/dl. One center that did not perform urine microalbumin measurement was excluded from the analysis. Overt nephropathy was defined as the presence of gross proteinuria or renal insufficiency.

Results: The study included 4,875 patients (females 63.8%) with a mean (SD) duration of diabetes of 12.8(8.2) years. The prevalence of DN was 42.9% (microalbuminuria 19.7% and overt nephropathy 23.2%). There were 373 (7.7%) patients with renal insufficiency and 24 (0.47%) with end-stage renal disease. By multivariate analysis, factors associated with DN were age, duration of diabetes, male sex, smoking, blood pressure, HbA1c, dyslipidemia and presence of diabetic retinopathy. Prevalence of ischemic heart disease and cerebrovascular disease in patients with DN was 11.5% and 6.6% respectively. Mean (SD) HbA1c in patients with nephropathy was 8.2 (2.6)%. Only 25% of subject had HbA1c of less than 7%, 46% had blood pressure of more than 140/90 mmHg and 84% received at least one antihypertensive drug. However, the target blood pressure of less than 130/80 mmHg could be achieved in only 18% of these patients. The mean (SD) number of antihypertensive drugs was 1.7 (1.1). Nearly 60% of patients received either ACE inhibitors or ARBs.

Conclusion: DN was very common. The overall picture of DN in the present survey suggests the seriousness of the problem and prompts more aggressive intervention.

Keywords: Diabetes registry, Nephropathy, Prevalence, Thailand, Glycemic control, Blood pressure

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Diabetic Nephropathy (DN) is one of the notorious complications of diabetes. It is a leading cause of end-stage renal disease and is also associated with increased morbidity and mortality from cardio-vascular disease[1]. The spectrum of this complication ranges from the presence of microalbuminuria to overt nephropathy, and ultimately end-stage renal disease. Besides poor glycemic control, other factors have been associated with DN such as duration of diabetes, blood pressure, ethnic and genetic factors[1]. Current evidence indicates that aggressive intervention in the early stage can prevent or delay progression of DN. Intensive control of blood glucose has been demon-strated to prevent or delay progression of microvas-cular complications, including DN[2,3]. In addition, tight control of blood pressure and use of ACE inhibitor or angiotensin II receptor blocker (ARB) can also retard the progression of nephropathy[1]. Therefore, screen-ing and identifying the patient at risk will be crucial to decrease the health burden of diabetic nephropathy and related morbidity. The aims of the present study were to identify the prevalence, associated factors and characteristics of patients with DN in the authors' registry and also to evaluate adequacy of glycemic and blood pressure control in our nephropathy patients.

Material and Method

A cross-sectional, multi-center, hospital-based diabetes registry was carried out from April 2003 to December 2003. The authors registered diabetic patients from diabetes clinics of 11 tertiary centers. The method of registration and data collection were described in detail in the previous section of this issue[4]. The present study was approved by the ethics committee of each participating hospital. Signed informed consent was obtained from all participants. Diabetic nephropathy was defined as the presence of at least two out of three of these symptoms, positive microalbuminuria (urine albumin to creatinine ratio between 30-300 mg/g), positive dipstick proteinuria or creatinine levels equal to or greater than 2 mg/dl. The laboratory measurements were done in each hospital. No standardization of urinary protein measurements and values was performed. All centers were encouraged to obtain urine microalbumin measurement in every registered patient if diagnosis of DN has not been established. Data from one center that could not per-form urine microalbumin measurement was excluded from the analysis.

Data were expressed as mean ± SD. Statistical analyses were performed using SPSS version 11.5.0 (SPSS Inc, Chicago, IL, U.S.) A comparison between groups was analyzed by t-test, Chi-square test or Fisher's exact test with 0.05 level of significant, where appropriate.

Results

In the 4,875 patients, composed of 1764 males and 3,111 females, the prevalence of DN was 42.9% [2091], the prevalence of microalbuminuria was 19.7% [960], and the prevalence of overt nephropathy was 23.2% [1131] (proteinuria 16.3% and renal impairment 6.9%). The number of patients who had end-stage renal disease requiring renal replacement therapy was 24/4875 (0.49%). The characteristics of patients with and without nephropathy are shown in Table 1. By multivariate analysis, factors associated with diabetic nephropathy were age, duration of diabetes, male sex, smoking, systolic blood pressure, hemoglobinA1c (A1c), dyslipidemia (hypercholesterolemia, hypertrigly-ceridemia and low HDL-C) and the presence of diabetic retinopathy. Furthermore, 47% of the presented neph-ropathy patients had diabetic retinopathy. Prevalence of ischemic heart disease was 11.5% and prevalence of cerebrovascular disease was 6.6%. Mean (± SD) HbA1c in the patients with nephropathy was 8.2 (± 2.6)%. Only 25% of the patients had HbA1c of less than 7%. The data revealed that 64% of the patients had blood pressure of more than 140/90 mmHg while 84% received at least one antihypertensive drug. The target blood pressure of less than 130/80 mmHg could be achieved in only 18% of these patients. The mean (± SD) number of antihypertensive drugs type taken was 1.7 (± 1.1); 32.6% of the patients took one type, 27.5% took two types and 24% took at least three types. The choices of antihypertensive drugs type were ACE inhibitors (43.2%), diuretics (37.3%), calcium channel blockers (35.2%), beta blockers (25.7%), angiotensin receptor blockers (ARBs) (18%) and alpha 1-blockers (6.2%). Nearly 60% of patients received either ACE inhibitors or ARBs while only 1.3% received both ACE inhibitors and ARBs.

Discussion

DN is one of the most serious microvascular complications of diabetes. DN is not only the leading cause of end-stage renal disease, but is also associated with increased mortality. Even in the earliest detectable stage of DN, microalbuminuria, is associated with increased cardiovascular events[5]. The prevalence of microalbuminuria and overt nephropathy in the authors' registry was 19.7%, 23.2% respectively. The reported

Table 1. Comparisons between characteristics of adult type 2 diabetic subjects without and with nephropathy (n = 4875)

Characteristics	Subjects without nephropathy (n = 2877)	Subjects with nephropathy (n =1998)	p value
Age (yr)	58.9 ± 12.5	61.8 ± 12.4	<0.001
Sex (% male)	33.4	40.2	<0.001
Smoking (%)	13.3	20.0	<0.001
Duration of diabetes (yr)	9.62 ± 7.3	12.8 ± 8.2	<0.001
Mean Systolic BP (mmHg)	138.5 ± 21.1	148.7 ± 25.1	<0.001
Mean Diastolic BP (mmHg)	77.0 ± 11.0	78.4 ± 12.0	<0.001
HbA_{1c} (%)	7.8 ± 1.9	8.19 ± 2.5	<0.001
Cholesterol (mg/dl)	187.0 ± 45.8	192.9 ± 57.5	<0.001
Triglyceride (mg/dl)	132.5 ± 83.6	161.8 ± 136.9	<0.001
HDL-C (mg/dl)	52.6 ± 17.7	49.1 ± 17.8	<0.001
LDL-C (mg/dl)	107.3 ± 36.8	109.3 ± 46.0	NS
Diabetic retinopathy	19.8	38.7	<0.001
NPDR (% of subjects)	16.1	25.0	
PDR (% of subjects)	3.7	13.7	

Data shown as mean $\pm$ SD
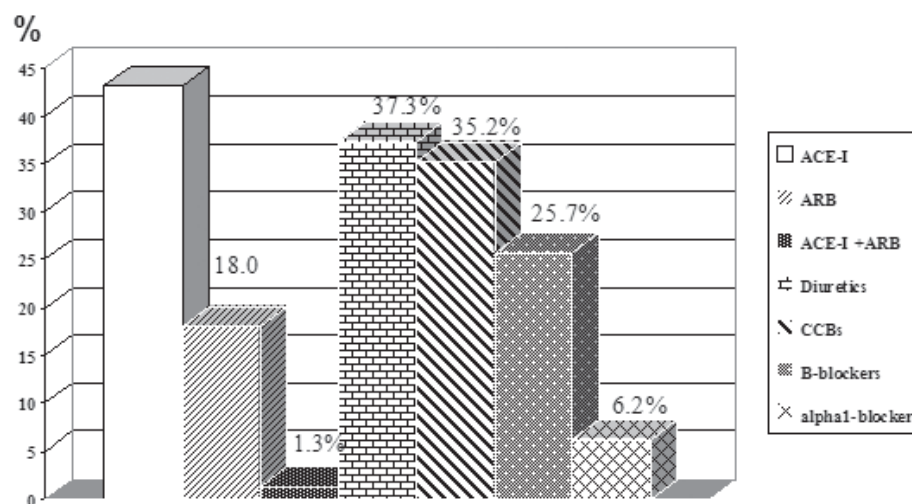
Fig. 1 Choice of antihypertensive agents in nephropathy patients

Percentage of subjects with diabetic nephropathy using each drug. ACE-I , angiotensin converting enzyme inhibitor ; ARB, angiotensin 2 receptor blocker; Diuretics, CCBs, calcium channel blocker; B-blocker, beta-blocker; alpha1-blocker, alpha-1 receptor blocker

prevalence of nephropathy in type 2 diabetes has varied from 5-20%[5,6]. The observation of high prevalence in the present study could be because the data was collected from the diabetes clinics in a tertiary centers and it is likely that the presented patients might have more advanced diabetes-related complications thus require care by an endocrinologist. Another possible explanation may be because of a racial difference in the

frequency of nephropathy. Epidemiologic studies in the United States revealed a higher prevalence of DN in Asian[1,7]. In addition, the Diabcare-Asia 1998, a large cross-sectional diabetes survey in many Asian countries, revealed prevalence of microalbuminuria at 39%[8], which was comparable to our study. The factors associated with DN in the present study were age, duration of diabetes, male sex, smoking, systolic blood

pressure, HbA1c, dyslipidemia (hypercholesterolemia, hypertriglyceridemia and low HDL-C) and the presence of diabetic retinopathy, similar to the previously reported risk factors in both cross-sectional and longitudinal studies[9-11]. With regard to other complications of diabetes in the presented nephropathy patients, 47% of the patients also had diabetic retinopathy. Prevalence of ischemic heart disease and cerebrovascular disease was 11.5% and 6.6% respectively.

Evidence, that a progression of diabetic nephropathy can be prevented or delayed with proper and aggressive interventions, is clear. Intensive control of blood glucose level has been demonstrated to lower the incidence of microalbuminuria in both type 1[2] and type 2 diabetes[3,12]. In the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes, intensive treatment of diabetes reduced the incidence of microalbuminuria by 39%[2]. The UKPDS, a long term follow-up study in newly diagnosed type 2 diabetes, showed a 30% risk reduction in development of microalbuminuria in intensively control diabetes group[3]. Furthermore, in the Kumamoto study, strict glycemic control also reduced the rate of development of both microalbuminuria and macroalbuminuria. Therefore, the American Diabetes Association recommendation is to keep HbA1c less than 7%[13,14]. In the present study, HbA1c of less than 7%, was seen in only 25% of patients indicating that the majority of patients did not have adequate control of hyperglycemia. Although the benefit of tight glycemic control is well known, controlling blood glucose remains a challenge as many epidemiologic studies from different regions of the world also demonstrated[8,15-17]. Despite the difficulties, physicians do need to address barriers to achieve glucose goal in the patients. In addition to good glycemic control, intensive blood pressure control is crucial to retard progression of proteinuria and renal function decline. Numerous studies have demonstrated that treatment of hypertension, irrespective of agents used, produced a beneficial effect on proteinuria[1]. There was no threshold level of blood pressure where the risk of nephropathy diminish, but the goal of 130/80 mmHg as recommend by a major diabetes association[18] and nephrology work group[19] is widely accepted. Only 18% of the presented patients with nephropathy achieved target blood pressure of less than 130/80 mm Hg. Most studies showed that at least 3 antihypertensive drugs were required to achieve good control of diabetes[20,21]. In the present study, the mean ($\pm$ SD) number of antihypertensive drugs was 1.7 ($\pm$ 1.1) and only a quarter of our nephropathy patients used 3 or more antihypertensive drugs. Renin-angiotensin system blockade confers an additional renoprotective effect independent of blood pressure reduction[1]. Although the majority of our patients could not reach the targeted blood pressure, more than half did receive antihypertensive agents that blocked the action of angiotensin II; ACE inhibitors (43.2%), angiotensin II receptor blockers (ARBs) (18%), and combination of ACE inhibitors and ARBs (1.3%). Because ACE inhibitor and ARB block the renin-angiotensin system at different levels and dual blockade with both agents has been shown to be more effective in reducing blood pressure and microalbuminuria than either drug alone[14]. However, this combination therapy has not been widely recommended as a standard treatment and one needs to be more cautious with potentially increased side effects such as hyperkalemia.

Although, intensified blood pressure and glycemic control is beneficial and cost-effective for nephropathy[22,23], applying these strategies to achieve the ideal targets, even by specialists in a tertiary-care center, may still be difficult, as demonstrated in the authors' registry. There are probably many factors involved such as poor compliance, low educational status, inadequate understanding of diabetes education, limited financial resources, and limited time during the clinic visit. These factors need to be further explored and intervened to improve diabetes care and reduce its preventable complications, such as nephropathy.

Conclusion

DN was very common and was associated with modifiable risk factors. The overall picture of DN in the present survey suggests the seriousness of the problem and prompts aggressive intervention of glycemic and blood pressure control to reduce the overall morbidity and mortality.

Acknowledgements

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โครงการลงทะเบียนผู้ป่วยเบาหวานในประเทศไทย: ความชุก ปัจจัยเสี่ยงและการรักษาภาวะแทรกซ้อนทางไต

ฉัตรประอร งามอุโฆษ, พงศ์อมร บุนนาค, ณัฐพงศ์ โฆษชุณหนันท์, สิริเนตร กฤติยาวงศ์, ยุพิน เบ็ญจสุรัตน์วงศ์, รัตนา ลีลาวัฒนา, ธงชัย ประฏิภาณวัตร, ณัฐเชษฐ์ เปล่งวิทยา, สมพงษ์ สุวรรณวลัยกร, ชัยชาญ ดีโรจนวงศ์, ธัญญา เชฏฐากุล, สิริมา มงคลสัมฤทธิ์, เพชร รอดอารีย์

วัตถุประสงค์*: เพื่อศึกษาความชุก ปัจจัยเสี่ยงและการรักษา ของภาวะแทรกซ้อนทางไต และประเมินการควบคุมระดับน้ำตาลและความดันโลหิตในผู้ป่วยที่มีภาวะแทรกซ้อนทางไต ในผู้ป่วยที่มารับการรักษาที่คลินิกโรคเบาหวานของโรงพยาบาลมหาวิทยาลัยและโรงพยาบาลศูนย์*

วัสดุและวิธีการ*: การศึกษานี้เป็นการลงทะเบียนผู้ป่วยเบาหวานที่มารับการรักษาที่คลินิกเบาหวานของโรงพยาบาลระดับตติยภูมิทั้งหมด 11 แห่งในประเทศไทย เกณฑ์การวินิจฉัยภาวะแทรกซ้อนทางไต คือมีผลตรวจปัสสาวะหา microalbumin หรือ protein ให้ผลบวก2 ครั้งเป็นอย่างน้อย หรือมีระดับ creatinine ในซีรั่มเท่ากับหรือมากกว่า 2 มก./ดล. ข้อมูลของศูนย์แห่งหนึ่งที่ไม่สามารถตรวจ microalbumin ในปัสสาวะ ไม่ได้ถูกนำมารวมวิเคราะห์*

ผลการศึกษา*: จำนวนทั้งหมดของผู้ป่วยในการศึกษาคือ 4,875 คน โดยมีความชุกของภาวะแทรกซ้อนทางไต 42.9% ประกอบด้วย microalbuminuria 19.7% และ ภาวะแทรกซ้อนทางไตชัดเจน 23.2% จำนวนผู้ป่วยที่มีการทำงานของไตเสื่อมคือ 373 คน (7.7%) และไตวายระยะสุดท้าย 24 คน (0.47%)*

การวิเคราะห์แสดงว่าปัจจัยที่มีความสัมพันธ์กับภาวะแทรกซ้อนทางไต ได้แก่ อายุ ระยะเวลาของโรคเบาหวาน เพศชาย การสูบบุหรี่ ความดันโลหิต ระดับ HbA1c ความผิดปกติของระดับไขมันในเลือด และการมีภาวะแทรกซ้อนทางตา ในผู้ที่มีภาวะแทรกซ้อนทางไต พบความชุกของโรคหลอดเลือดแดงโคโรนารี 11.5% และโรคหลอดเลือดสมอง 6.6% ค่าเฉลี่ย(ค่าเบี่ยงเบนมาตรฐาน)ของ HbA1c ในผู้ที่มีภาวะแทรกซ้อนทางไตคือ 8.2% และมีผู้ป่วยเพียง 25% ที่มี HbA1c น้อยกว่า 7% ผู้ป่วย 64% มีความดันโลหิตมากกว่า 140/90 มิลลิเมตรปรอท ค่าเฉลี่ยของจำนวนยาลดความดันที่ได้รับคือ 1.7 (1.1) ชนิด ผู้ป่วยเกือบ 60% ได้รับยา ACE inhibitors หรือ Angiotensin2 receptor blockers

สรุป*: จากการศึกษาครั้งนี้พบว่า ภาวะแทรกซ้อนทางไตพบได้บ่อยในผู้ป่วยเบาหวานและเป็นปัญหาที่สำคัญที่ควรได้รับสนใจและมีการปรับปรุงการรักษา*