The Relationship between Microalbuminuria by Using Urine Dipsticks and Diabetic Retinopathy in Type 2 Diabetes

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Objective: *Study the association between microalbuminuria and diabetic retinopathy in type 2 diabetic patients.*
Material and Method: *A cross-sectional analytic study of 1,111 cases with type 2 diabetic patients recruited from seven public hospitals, between June and December 2006 was performed.*
Result: *Two hundred eighty six subjects (79 males and 207 females) with urine dipsticks for microalbuminuria detection tested positive at least 2 of the 3 morning urine samples within 6 months. They were divided into 2 equal groups, micro- and normoalbuminuria based on quantity of albumin. Indirect ophthalmologic examination of all subjects' eyes for diabetic retinopathy was performed by ophthalmologists (retinal specialists). The present study showed that the proportion of diabetic retinopathy was 19.6% (28/143) and 12.6% (18/143) in micro- and normoalbuminuric groups, respectively. The difference of proportion between the groups was 7% but was statistically not significant (p = 0.108).*
Conclusion: *Microalbuminuria detected using urine dipstick was not cross-sectionaly associated with diabetic retinopathy in type 2 diabetic patients.*

Keywords: *Microalbuminuria, Diabetic retinopathy, Urine dipstick, Type 2 diabetes*

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The World Health Organization has reported that diabetes mellitus (DM) is a chronic disease and its complications impose economic consequences on individuals, families, health systems, and countries. The prevalence of diabetes in all age-groups worldwide was estimated to be 2.8% in 2000 (171 million people) and projected to be 4.4% in 2030 (366 million people)[1]. The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths (1 million deaths in developed countries and 1.9 million deaths in developing countries)[2]. The diabetes epidemic is accelerating in the developing world with an increasing proportion of affected people in younger age groups and furthers the burden of chronic diabetic complication worldwide. Microvascular complications of diabetes mellitus, especially retinopathy and nephropathy, are the leading cause of blindness and end stage renal disease (ESRD), respectively, in many populations both developed and developing countries[3-4]. Type 2 diabetes may be present for several years before diagnosis, by which time many patients have already developed complications[5]. Most diabetic patients will lose the chance to early detect microvascular complications (diabetic nephropathy and retinopathy) and prevent ESRD and blindness even though they are in the early stage. Since most such people are asymptomatic at diagnosis, active cases detection would be required to identify them.

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Increasing urinary albumin excretion in type 2 diabetic population has been found to be associated with an increasing prevalence of diabetic retinopathy, neuropathy, and cardiovascular diseases[6]. Microalbuminuria has been reported to be a predictor of clinical diabetic nephropathy (DN) in type 1[7] and type 2 diabetes[8]. The systematic review of National Coordinating Centre for Health Technology Assessment (NCCHTA) has shown that microalbuminuria is a powerful predictor for the future development of diabetic nephropathy and retinopathy in type 1 diabetes mellitus[9]. However, little information is available on type 2 DM. The available data provide no evidence that microalbuminuria or raised albumin excretion rate has any independent prognostic significance for the incidence of retinopathy in type 2 diabetic patients. The demonstrated relationship between microalbuminuria and the development of retinopathy in type 1 diabetes makes this an important issue to be studied in type 2 diabetic patients as well.

Material and Method

The present cross-sectional multi-sites study was approved by the Ethics Review Committee for Research in Human Subjects, Ministry of Public Health. All voluntary subjects had given written informed consent. The total subjects of 1,111 cases were type 2 diabetic patients (diagnosed by using the American Diabetic Association criteria)[10] who were recruited from seven public hospitals, including the Rajavithi Hospital, Lerdsin Hospital, Nopparatrajathanee Hospital, Mettaphacharak (Watraikhing) Hospital, Prathumthani Hospital, Lardlumkaew Hospital, and Nongsau Hospital during the period from June to December 2006. All the subjects' personal data, physical, urine examinations, blood examinations, and fundus examination were completely performed. The subjects with pregnancy, proteinuria, serum creatinine more than 1.5 mg/dl, and the causes of transient elevations in urinary albumin excretion, (i.e., urinary tract infection, haematuria, marked hypertension, acute febrile illness, and heart failure) were excluded. The subjects were divided into two groups (micro- and normoalbuminuria). Urine dipsticks (Micral test II®) were used for microalbuminuria detection. Subjects were positive in at least 2 of the 3 morning urine samples within 6 months. The interpretation of the microalbuminuria test strip was visually compared by means of color to the color blocks on a chart attached to the vial. The color presentation between 20 mg/l to 100 mg/l albumin was classified as microalbuminuric group[12] and normoalbuminuric group if less than 20 mg/l. Mydriatic ophthalmoscopy through dilated pupils was performed and the subjects were diagnosed with retinopathy by a board-certified ophthalmologist who had subspecialty training in retina with experience in diabetic retinopathy grading. Diabetic retinopathy was classified into five grades, no DR (no diabetic retinopathy), mild NPDR (non-proliferative diabetic retinopathy), moderate NPDR, severe NPDR, and PDR (proliferative diabetic retinopathy)[13]. The authors expected 80% power to detect diabetic retinopathy with a 95% confidence interval and calculated based on the study of Manaviat[11] in which the prevalence of diabetic retinopathy in micro- and normoalbuminuric groups were 43.4% and 27.6%, respectively. The sample size was at least 286 cases. The data was then randomized by computer from micro- or normoalbuminuric group for analysis of the retinopathic outcomes.

Statistical analysis

The patients' demographic data and baseline characteristics were presented using means, SD, and percentage. Chi-square test was employed to test the association between microalbumonuria and diabetic retinopathy in type 2 diabetes. The magnitude of the difference in proportion of diabetic retinopathy between type 2 diabetes with micro- and normoalbuminuria was presented along with 95% confidence interval.

Results

Two hundred eighty six diabetic patients (79 males and 207 females) participated in the present study. Each of the 143 subjects was allocated into micro- and normoalbuminuria groups. The characteristics of subjects were similar between the two groups, as shown in Table 1. The average age for the present study was 58.7 years and the duration of diabetes was about 5 years. Blood urea nitrogen (BUN) and creatinine of normoalbuminuric group were 13.2 (4.1) mg/dl and 0.8 (0.2) mg/dl, respectively, whereas they were 14.6 (4.2) mg/dl and 0.9 (0.2) mg/dl, respectively in the microalbuminuric group. Hemoglobin A_{1c} was 8.6% (1.6) in the normoalbuminuric and 8.7% (1.8) in the microalbuminuric group. Fasting plasma glucose (FPG) of patients with microalbuminuria was 158.8 (56.1) mg/dl and 146.1 (46.3) mg/dl among patients with normoalbuminuria. The average systolic and diastolic blood pressure between the two groups was about 130 and 72 mmHg, respectively.

The association between albuminuria and diabetic retinopathy is shown in Table 2. The proportion

of DR in micro- and normoalbuminuric groups was 19.6% (28/143) and 12.6% (18/143), respectively. The difference between the two groups was 7%, which was not statistically significant (p = 0.108). The 95% CI of the difference in proportion of DR between micro- and normoalbuminuria was -1.5% to 15.5%. Thus, the microalbuminuric group may have at most 1.5% less DR or at most 15.5% more DR when compared to the normoalbuminuria group. The Odds ratio (OR) of diabetic retinopathy between micro- and normoalbuminuria groups was 1.69 along with 95% confident interval from 0.89 to 3.20.

Table 3 shows the grading of diabetic retinopathy in micro- and normoalbuminuric group. No DR was found at 87.4% (125/143) in the normoalbuminuric group and at 80.4% (115/143) in the microalbuminuric group. Mild NPDR and moderate NPDR were 9.8% (14/143) and 7% (10/143) in the microalbuminuric group, respectively. Whereas, 7.7% (11/143) were mild NPDR 4.9% (7/143) NPDR were found in the normoalbuminuric

Table 1. Baseline characteristics of type 2 diabetic patients as compared between micro- and normoalbuminuria

	Normoalbuminuria (n = 143)	Microalbuminuria (n = 143)
Female gender	112.0 (78.3)	95.0 (66.4)
Age (years)	58.3 (9.8)	59.2 (10.1)
Duration of type 2 DM (years)	4.4 (3.6)	5.4 (4.4)
BUN (mg/dl)	13.2 (4.1)	14.6 (4.2)
Serum creatinine (mg/dl)	0.8 (0.2)	0.9 (0.2)
HbA_{1c} (%)	8.6 (1.6)	8.7 (1.8)
FPG (mg/dl)	146.1 (46.3)	158.8 (56.1)
Systolic blood pressure (mmHg)	130.3 (17.2)	131.2 (15.3)
Diastolic blood pressure (mmHg)	71.9 (10.3)	71.8 (10.0)

Data shown as mean (SD) or number (%)
BUN = blood urea nitrogen, HbA_{1c} = hemoglobin A_{1c}, FPG = fasting plasma glucose

Table 2. Relationship between diabetic retinopathy and albuminuria

Albuminuria	DR	No DR	Total	p-value
Normoalbuminuria (n = 143)	18 (12.6%)	125 (87.4%)	143	0.108
Microalbuminuria (n = 143)	28 (19.6%)	115 (80.4%)	143	
Total	46	240	286	

Data shown as number (%)
DR = diabetic retinopathy

Table 3. Relationship between microalbuminuria and grading of diabetic retinopathy

Albuminuria	No DR	DR				Total	ME
		Mild NPDR	Moderate NPDR	Severe NPDR	PDR		
Normoalbuminuria	125 (87.4)	11 (7.7)	7 (4.9)	0	0	143	0
Microalbuminuria	115 (80.4)	14 (9.8)	10 (7.0)	3 (2.1)	1 (0.7)	143	3
Total	240	25	17	3	1	286	3

Chi-square for trend of DR, p-value = 0.043,
Data shown as number (%), DR = Diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy, ME = macular edema

group. However, severe NPDR (2.1%), PDR (0.7%), and macular edema were found only in the group of patients with microalbuminuria.

Discussion

The present cross-sectional study showed that there was no relationship between microalbuminuria and diabetic retinopathy in type 2 diabetes. However, microalbuminuria is still an expression of an early phase of diabetic renal disease. The authors were very much interested in the association between microalbumin in urine and retinopathy because of the insufficient number of ophthalmologists for screening diabetic retinopathy complication in Thailand. Thus, a new method or procedure that can be used as an early screening for retinopathy is needed. It should carry low price and be simple to use.

The present study has also confirmed other published studies that microalbuminuria may not be sufficient for the early detection of retinopathy. Cruickshanks et al[14] cross-sectionally studied the association of microalbuminuria with diabetic retinopathy from 1,139 participants in the Wisconsin Epidemiological Study of Diabetic Retinopathy. They reported that microalbuminuria which was measured using agglutination inhibition assay is associated with retinopathy in type 1 but not among type 2 diabetes. Savage[6] reported the study of 947 type 2 DM that overt albuminuria, but not microalbuminuria, is independently related with the presence of retinopathy. Because type 2 DM occurs several years before diagnosis, the longer is the duration of DM is, the greater is the chance to find complications. Voutilainen-Kaunisto[15] reported that the prediction of diabetic retinopathy at 10-year follow-up in patients with newly diagnosed type 2 diabetes is not associated with microalbuminuria.

Some studies have supported the notion that microalbuminuria was associated with diabetic retinopathy in type 2 diabetes. It is possible that ethnicity or race is different with regard to developing diabetic retinopathy in type 2 diabetes[16]. The cross-sectional study of Manaviat[11] in Iran showed a significant association between microalbuminuria using dipsticks and diabetic retinopathy in 553 patients. The 2-years of longitudinal study in Chile (36 and 64 subjects with microalbuminuria and normoalbuminuria, respectively) has shown that microalbuminuria from urine excretion in 24 hours is significantly associated with retinopathy[17]. The cross-sectional study in Brazil[18] and Finland[19] showed that microalbuminuria is associated with proliferative diabetic retinopathy. On the other hand, some studies showed that protein and albumin excretion rate are increased in patients with retinopathy[20].

However, there are many factors that may cause transient elevations in urinary albumin excretion such as short-term hyperglycemia, marked hypertension, urinary tract infection, haematuria and heart failure[3]. Although the findings by using urine dipsticks for microalbuminuria are semi-quantitative, they are reasonable to be used for initial screening with regard to the influential factors in mind.

The serious grading of diabetic retinopathy (severe NPDR and PDR) and macular edema (ME), which may be classified as "Sight-threatening", were only found in the microalbuminuric group, whereas, the Odds ratio (OR) of diabetic retinopathy between micro- and normo-albuminuria groups was rather high. It is possible that there is a trend to develop the severity of diabetic retinopathy in micro- more than normoalbuminuric group. In summary, micro-albuminuria was not associated with diabetic retinopathy in type 2 diabetes. However, the screening of diabetic retinopathy by ophthalmologists should be done when type 2 diabetes is diagnosed[21]. Further well-designed cohort studies for expressing the relation of microalbuminuria and retinopathy should be performed before type 2 diabetic patients develop microvascular complication.

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ความสัมพันธ์ระหว่างอัลบูมินปริมาณน้อย (microalbuminuria) โดยใช้แถบจุ่มปัสสาวะกับภาวะจอประสาทตาผิดปรกติในผู้ป่วยเบาหวานชนิดที่ 2

สมเกียรติ โพธิสัตย์, อรรถสิทธิ์ ศรีสุบัติ, อุดม ไกรฤทธิชัย, อัมพร จงเสรีจิตต์

การศึกษาเชิงวิเคราะห์ ณ จุดเวลาใดเวลาหนึ่ง (cross-sectional analytic study) เพื่อหาความสัมพันธ์ระหว่างภาวะปัสสาวะมีอัลบูมินปริมาณน้อย (microalbuminuria) กับภาวะจอประสาทตาผิดปรกติจากเบาหวานในผู้ป่วยเบาหวานชนิดที่ 2 โดยอาสาสมัครเป็นผู้ป่วยเบาหวานชนิดที่ 2 ในโรงพยาบาลของรัฐ 7 แห่ง จำนวน 286 คน (ชาย 79 คน หญิง 207 คน) และถูกแบ่งออกเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ตรวจปัสสาวะด้วยแถบจุ่มตรวจปัสสาวะแล้วพบ microalbuminuria จำนวน 143 คน ซึ่งผลการตรวจต้องเป็นบวกอย่างน้อย 2 ครั้งจากการตรวจ 3 ครั้งภายในระยะเวลา 6 เดือน และกลุ่มที่ไม่พบ microalbuminuria จำนวน 143 คน อาสาสมัครทุกคนจะได้รับการตรวจหาภาวะจอประสาทตาผิดปรกติจากเบาหวานโดยจักษุแพทย์ผู้เชี่ยวชาญด้านจอประสาทตา ผลการศึกษาพบภาวะจอประสาทตาผิดปรกติร้อยละ 19.6 (28/143) ในกลุ่มอาสาสมัครที่ตรวจพบ microalbuminuria และร้อยละ 12.6 (18/143) ในกลุ่มที่ตรวจไม่พบ microalbuminuria สัดส่วนความแตกต่างของภาวะจอประสาทผิดปรกติในกลุ่มที่ตรวจพบและตรวจไม่พบ microalbuminuria เป็นร้อยละ 7 ($p = 0.108$) แต่มีแนวโน้มที่พบภาวะจอประสาทตาผิดปรกติจากเบาหวานระดับรุนแรง (sight-threatening) สูง ในกลุ่มอาสาสมัครที่ตรวจพบ microalbuminuria โดยสรุปการศึกษานี้พบว่าภาวะปัสสาวะมีอัลบูมินปริมาณน้อย (microalbuminuria) จากการใช้แถบจุ่มปัสสาวะไม่มีความสัมพันธ์กับภาวะจอประสาทตาผิดปรกติจากเบาหวานในผู้ป่วยเบาหวานชนิดที่ 2 ซึ่งควรได้รับความสนใจศึกษาต่อไป