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Prevalence and risk factors of proteinuria in patients with type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (DM) is a common disease in clinical practice. Proteinuria or urine protein-tocreatinine ratio (UPCR) is an indicator for tubular biomarker for diabetic kidney disease. There is limited data on risk factors of proteinuria in patients with DM particularly in Thai or Asian populations. This study aimed to evaluate prevalence and risk factors of proteinuria in patients with type 2 DM in Thai population. This was a retrospective study conducted at Roi Et Hospital, Roi Et, Thailand. The study criteria were adult patients diagnosed as diabetes mellitus type 2 and treated at Diabetes Mellitus clinic, Roi Et Hospital for at least three months. The primary outcome of the study was presence of proteinuria of over 150 mg/g by UPCR. Factors predictive of proteinuria were computed by logistic regression analysis. During the study period, there were 299 patients met the study criteria. Of those, 92 patients (30.77%) had proteinuria. There were eight factors eligible for multivariate logistic regression analysis for proteinuria. Of those, only fasting plasma glucose (FPG) was independently associated with proteinuria with adjusted odds ratio of 1.009 (95% CI 1.004, 1.0156). The FPG of 136 mg/dL or over had sensitivity of 80.43%. In conclusion, prevalence of proteinuria in patients with type 2 DM was 30.77% in provincial hospital setting. FPG may be associated with presence of proteinuria. A cut off point of FPG of 136 mg/dL had good sensitivity as a predictor of proteinuria in patients with type 2 DM.

Keywords: UACR, UPCR, FPG, A1C, Snoring, Diabetic kidney disease, Diabetic nephropathy

1. Introduction

Diabetes mellitus (DM) is a common disease in clinical practice. The mainstay of treatment in patients with DM is to prevent its complications and consequences such as coronary artery disease. Diabetic kidney disease is one of the common complications in patients with type 2 DM. A systematic review from China showed that the prevalence of diabetic nephropathy was 21.8% from 79,364 patients [1]. Urine albumin-to-creatinine ratio (UACR) is a laboratory test to detect diabetic kidney disease. Recent studies found that UACR is associated with increasing risk of cardiovascular diseases and mortality even within normal range of less than 30 mg/g [2,3]. Increasing of UACR per 10 mg/g had adjusted hazard ratio of cardiovascular mortality of 1.34 (95% confidence interval of 1.17, 1.55).

Even though UACR is an important indicator for diabetic kidney disease, it may indicate mainly on glomerular changes [4]. Proteinuria or urine protein-to-creatinine ratio (UPCR), an indicator for chronic kidney disease, is a tubular biomarker for diabetic kidney disease [4]. Another advantage of UPCR is that it can be tested for only single test, while UACR requires two or three times of tests to detect diabetic nephropathy [5]. A previous study found that single UPCR was well correlated with UACR with sensitivity of 89%-92% [5]. The presence of

proteinuria was shown to be related with carotid artery atherosclerosis by 2.342 times; *p* value 0.030 and renal function deterioration by 1.95 times; *p* value 0.011 [6,7]. Even though proteinuria in patients with DM may be another indicator for diabetic kidney disease or cardiovascular consequences, there is limited data on risk factors of proteinuria in patients with DM particularly in Thai or Asian populations. This study aimed to evaluate prevalence and risk factors of proteinuria in patients with type 2 DM in Thai population.

2. Materials and methods

This was a retrospective study conducted at Roi Et Hospital, Roi Et, Thailand. The study criteria were adult patients with age of 18 years or over, diagnosed as DM type 2 and treated at DM clinic, Roi Et Hospital for at least three months. Pregnant women or those with type 1 diabetes mellitus/ other specific types of diabetes mellitus were excluded from the study. Diagnosis of diabetes mellitus was based on the criteria purposed by the American Diabetes Association [8]. The study period was between January and December 2019.

Eligible consecutive patients were chosen from the Diabetes Mellitus clinic database. Clinical data were retrieved including baseline characteristics, physical signs, and laboratory tests. Baseline characteristics were age, sex, duration of diabetes mellitus, medications, complications of diabetes mellitus, consequences of diabetes mellitus such as coronary artery disease, and associated diseases such as hypertension. Physical signs included body mass index, abdominal circumference, and neck circumference. Abdominal and neck circumference were measured at midabdomen and cricothyroid membrane in centimeters. The primary outcome of the study was presence of proteinuria of over 150 mg/g by UPCR. The latest UPCR was used to define the outcome.

Statistical analyses. Patients were divided into two groups: with and without proteinuria. Descriptive statistics were used to calculate mean with standard deviation (SD) or number (percentage) and compared values between both groups. Wilcoxon rank sum test and Fisher Exact test were used to compare differences of numerical and categorical variables, respectively. Factors predictive of proteinuria were computed by logistic regression analysis. A univariate logistic regression analysis of each factor was calculated. Those factors with a *p* value of less than 0.20 were put in the subsequent multivariate logistic regression analysis.

Multicollinearities of the studied factors were tested. Results were shown in unadjusted/ adjusted odds ratio with 95% confidence interval. The final predictive model was tested for goodness of fit with the HosmerLemeshow test. A *p* value of over 0.05 for Hosmer-Lemeshow chi square indicated goodness of fit. Numerical independent predictors for proteinuria were executed for sensitivity and specificity for various cut points. A receiver operating characteristic (ROC) curve with an area under the ROC curve and the 95% confidence interval was also calculated.

All statistical analyses were performed using STATA software version 10.1 (College Station, Texas, USA).

3. Results and discussion

During the study period, there were 299 patients met the study criteria. Of those, 92 patients (30.77%) had proteinuria. Regarding baseline characteristics, there were three factors significantly different between those with and without proteinuria (Table 1). The proteinuria group had higher proportion of aspirin therapy (10.87% vs 1.43%) but lower proportions of snoring (38.04% vs 54.59%) and dyslipidemia (19.57% vs 32.85%) than the non-proteinuria group. Note that complications and consequences of diabetes between both groups were comparable such as neuropathy or stroke.

Table 1 Baseline characters of patients with diabetes mellitus type 2 categorized by presence of proteinuria (PU).

Factors	No PU n = 207	PU n = 92	*p* value
Age, years*	57.31 (10.01)	56.36 (13.88)	0.608
Male sex	89 (41.55)	39 (42.39)	0.900
Duration of diabetes, years*	11.42 (21.90)	10.29 (7.34)	0.880
Nocturia	82 (39.61)	44 (47.83)	0.205
Alcohol consumption	70 (33.82)	27 (29.67)	0.505
Alcohol consumption, years*	18.1 (9.70)	15.64 (9.81)	0.225
Smoking history	63 (30.43)	22 (23.91)	0.269
NSAIDs	19 (9.18)	5 (5.43)	0.358
Aspirin	3 (1.43)	10 (10.87)	0.001
Oral pill	167 (80.68)	69 (75.00)	0.284
Herb	19 (9.18)	11 (11.96)	0.532
Snoring	113 (54.59)	35 (38.04)	0.009
Hypertension	84 (40.58)	28 (30.43)	0.120
Dyslipidemia	68 (32.85)	18 (19.57)	0.019
GERD	17 (8.21)	5 (5.43)	0.478
CAD	5 (2.42)	2 (2.17)	0.999
Heart failure	1 (0.48)	0	0.999
Stroke	9 (4.35)	5 (5.43)	0.768
Neuropathy	134 (64.73)	62 (67.39)	0.694
Retinopathy	19 (9.18)	10 (10.87)	0.674
BMI, kg/m^{2*}	25.43 (4.20)	24.72 (4.56)	0.248
Abdominal circumference, cm*	85.23 (10.09)	83.29 (10.83)	0.127
Neck circumference, cm*	35.59 (3.50)	35.35 (3.29)	0.348

Note. Data presented as number (%), *indicated mean (SD); NSAIDs: non-steroidal anti-inflammatory drugs; GERD: gastroesophageal reflux disease; CAD: coronary artery disease; BMI: body mass index.

For laboratory results, there were three significant factors between both groups: fasting plasma glucose (FPG), A1C, and alkaline phosphatase (Table 2). The proteinuria group had higher levels of these three factors than the non-proteinuria group (188.04 vs 155.22 mg/dL for FPG, 8.57 vs 8.11% for A1C, and 81.06 vs 72.62 U/L for alkaline phosphatase).

Table 2 Laboratory results of patients with diabetes mellitus type 2 categorized by presence of proteinuria (PU).

Factors	No PU n = 207	PU n = 92	*p* value
FPG, mg/dL	155.22 (42.67)	188.04 (69.37)	0.001
A1C, %	8.11 (4.52)	8.57 (2.31)	0.006
Hb, g/%	12.28 (1.84)	12.17 (1.95)	0.635
Hct, %	37.58 (5.05)	37.33 (5.61)	0.613
WBC, $cells/mm^3$	9.29 (2.21)	9.15 (2.34)	0.863
PMN, %	54.89 (8.43)	56.31 (9.44)	0.148
Lymphocytes, %	33.11 (7.57)	32.13 (7.84)	0.271
NLR	1.83 (0.75)	1.93 (0.81)	0.202
Platelet, $x10^6$ $cells/mm^3$	282 (74)	286 (77)	0.494
Cholesterol, mg/dL	172.95 (36.44)	177.01 (43.65)	0.910
Triglyceride, mg/dL	168.99 (121.97)	170.26 (129.70)	0.802
HDL-c, mg/dL	49.86 (13.65)	51.53 (15.75)	0.536
LDL-c, mg/dL	107.51 (37.10)	110.45 (38.67)	0.689
eGFR, $ml/min/1.73m^2$	90.16 (20.92)	86.30 (28.91)	0.211
Albumin, g/dL	4.35 (0.25)	4.33 (0.33)	0.784
ALT, U/L	24.44 (15.06)	23.97 (13.37)	0.721
AST, U/L	24.29 (14.66)	23.96 (18.32)	0.609
ALP, U/L	72.62 (21.77)	81.06 (24.89)	0.003

Note. FPG: fasting plasma glucose; A1C: hemoglobin A1C; Hb: hemoglobin; Hct: hematocrit; WBC: white blood cells; PMN: neutrohils; NLR: neutrophils: lymphocytes ratio; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate transaminase; ALP: alkaline phosphatase.

There were eight factors eligible for multivariate logistic regression analysis for proteinuria (Table 3). Of those, only FPG was independently associated with proteinuria with adjusted odds ratio of 1.009 (95% CI 1.004, 1.0156). The Hosmer-Lemeshow Chi square of the final model was 8.10 (*p* value 0.423). The FPG of 136 mg/dL or over had sensitivity of 80.43% with specificity of 33.33%, while FPG of 180 mg/dL or over had sensitivity of 39.13% with specificity of 80.68%. The area under the ROC curve of FPG on proteinuria was 64.65% (95% CI of 57.60%-71.71%) as shown in Figure 1.

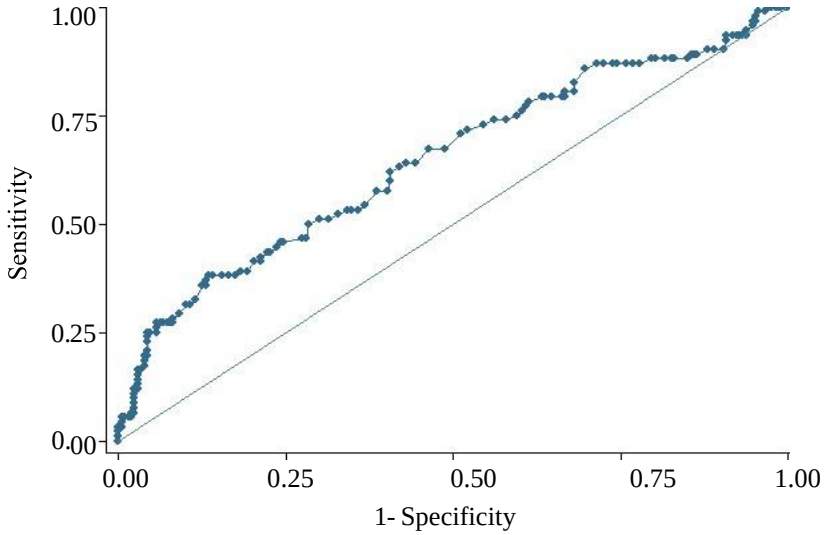

Figure 1 Receiver operating characteristic (ROC) curve and its area under the ROC curve (95% confidence interval) of fasting plasma glucose to predict proteinuria in patients with diabetes mellitus type 2. Note. Area under the ROC curve was 64.65% (95% CI 57.60%-71.71%).

There are several risk factors for diabetic kidney disease. More specifically for albuminuria, advanced age, male sex, smoking, or hyperglycemia increased risk of diabetic kidney disease [9]. A longitudinal study on 1,290 patients with DM type 2 found that lower A1C less than 7% lower risk of new-onset albuminuria by 27.1% [10]. In this study, increasing FPG by 1 mg/dL increased risk of proteinuria by 0.9% (Table 3). Note that A1C was not a significant factor. Unlike albuminuria, proteinuria may be an indicator for tubular damage [4,5]. Knockout mice at proximal tubule had significantly higher fasting plasma glucose than wild type mice (10.5 vs 7.8 mmol/L; p = 0.03) [11]. Therefore, high FPG may be an indicator of tubular damage resulting in increasing risk of proteinuria.

Table 3 Factors predictive of proteinuria in patients with diabetes mellitus type 2.

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Hypertension	0.640 (0.379, 1.081)	0.840 (0.469, 1.504)
Dyslipidemia	0.497 (0.275, 0.898)	0.581 (0.306, 1.102)
Snoring	0.510 (0.309, 0.843)	0.610 (0.354, 1.051)
Abdominal circumference	0.981 (0.958, 1.005)	0.992 (0.966, 1.019)
FPG	1.011 (1.006, 1.016)	1.009 (1.004, 1.015)
A1C	1.027 (0.965, 1.092)	0.996 (0.920, 1.078)
PMN	1.018 (0.990, 1.047)	1.003 (0.973, 1.034)
ALP	1.015 (1.004, 1.026)	1.010 (0.999, 1.022)

Note. FPG: fasting plasma glucose; A1C: hemoglobin A1C; PMN: neutrohils; ALP: alkaline phosphatase.

Roles of detecting proteinuria by using FPG depend on the levels of FPG. Using lower cut point at 136 mg/dL had good sensitivity at 80.43%, while FPG of 180 mg/dL or over had better specificity of 80.68% (Figure 1). To early detection of proteinuria, physicians may consider checking single UPCR in patients with type 2 DM if FPG is over 136 mg/dL. Additionally, screening for UACR should be performed at the time of diagnosis of type 2 DM and then three urine collections in the six-month period [12].

There are some limitations in this study. First, this study conducted at DM clinic at provincial hospital. Most patients in this study had few cardiovascular complications. Results of this study may not be applicable for other population or representative for Thai or Asian population. Further studies are required to represent the results from Thai or Asian population. Second, some factors may not be studies such as sodium intake or obstructive sleep

apnea [13]. Finally, there are some other non-albumin proteinuria markers for diabetic kidney disease such as alpha-1 micro-globulin which were not studied [4]. However, the outcome of this study is UPCR is more widely available.

4. Conclusion

In conclusion, prevalence of proteinuria in patients with type 2 DM was 30.77% in provincial hospital setting. FPG may be associated with presence of proteinuria. A cut off point of FPG of 136 mg/dL had good sensitivity as a predictor of proteinuria in patients with type 2 DM.

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6. Ethic approval

The study protocol was approved by the institutional review board, Roi Et Hospital, Thailand (RE034/2564).

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