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Original Article

Albuminuria as a risk factor for diabetic retinopathy in indonesian type 2 diabetes mellitus patients

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Abstract

Diabetic retinopathy (DR) is the leading cause of new-onset blindness in productive age. The aim of the study is to investigate the clinical relevance of albuminuria as a risk factor for DR in Indonesian Type 2 Diabetes Mellitus (T2DM) patients, as both have similar pathogenesis and are closely related. A number of 168 adult T2DM patients in the diabetes outpatient clinic at the Dr. Soetomo General Academic Hospital were recruited from July to December 2019 for this cross-sectional study. All participants underwent complete history taking and physical examination. A comprehensive metabolic panel and urinalysis parameters were collected from all subjects. Bivariate analysis with the chi-square test was used, followed by multivariate analysis by logistic regression. Albuminuria and DR were present in 125 subjects (74.4%) and 80 subjects (47.6%) respectively. There was a statistically significant difference in the prevalence of albuminuria between the group with and without DR (p=0.000). Through multivariate logistic regression, the presence of albuminuria increased the risk for DR 4.857 folds (95% CI: 2.029–11.626; p=0.000) adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, HbA1c levels, and dyslipidemia. In conclusion, albuminuria increases the risk of developing DR in Indonesian T2DM patients.

Keywords: diabetic retinopathy, diabetic nephropathy, albuminuria, type 2 diabetes.

Introduction

Type 2 diabetes mellitus is one of the fastest-growing global health problems worldwide. According to IDF 2021 data, it is estimated that 537 million people had diabetes in 2021, and this number is projected to reach 643 million in 2030 and 783 million in 2045. Indonesia is among the top ten countries with the highest number of diabetes in the world, with an estimated 19.5 million in 2021, and remains in the fifth rank with an estimated number of people with diabetes as much as 28.6 million in 2045 [1, 2]. As the number of diabetics increases, the development of microvascular complications such as retinopathy, nephropathy, and neuropathy also increases. This causes high rates of morbidity and mortality in diabetic patients. The microvascular complications of diabetes substantially affect the quality of life of patients and cause a large economic burden on the health care system [3, 4].

Diabetic retinopathy is a common vascular complication of diabetes and a leading cause of new-onset blindness [4]. The prevalence of DR is reported to be as high as 59.8% in T2DM, and 10% are in vision-threatening stages [5, 6]. As to renal involvement in T2DM, it is the leading cause of end-stage renal disease in the United States, Europe, and Japan. Microalbuminuria is

the first sign of renal involvement in T2DM [7]. These microvascular complications are related to the duration of diabetes mellitus, poor glycemic control, and systolic hypertension [6, 8]. Unlike in type 1 DM, several studies have shown conflicting results in developing diabetic nephropathy (DN) and DR for patients with T2DM. However, mounting evidence has shown that the two are closely related [9, 10].

Comprehending the association between albuminuria and DR could lead to a better understanding of the disease processes and, subsequently, better initial screening and overall management. The availability of current surgical and medical techniques might reduce blindness due to DR by up to 90% [11]. Therefore, early detection of DR is essential for early intervention. However, the clinical relevance of albuminuria as a risk factor for DR in Indonesian T2DM has not been explored; thus, our present study aimed to investigate the association between albuminuria and DR.

Material and methods

Study design and patients

This cross-sectional design study was conducted in the Endocrinology and Diabetes outpatient clinic at the Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, from July to December 2019. This current research was part of the Diabetic Ocular Renal Surabaya Study (DiORS Study) [12, 13]. The minimum sample for our study was calculated from the following formula:

$$n = \frac{\left(Z_{1-\alpha/2}\right)^2 p\, q}{d^2}$$

Significance – 95%; Expected prevalence – 59.8% from previous study [5]; margin of error – 10%. Therefore, a minimum number of 93 subjects was needed. The sampling was performed using the consecutive method according to the inclusion and exclusion criteria. The inclusion criteria were adult patients (over 18 years of age) who had been diagnosed with T2DM. Meanwhile, subjects with chronic kidney disease (CKD) stage 5 undergoing dialysis, CKD with kidney transplantation, and hazy ocular media precluding a good view of the retina were excluded.

Study variables

The dependent variable was the presence of DR, and the independent variable was the presence of albuminuria.

Data collection

All participants underwent complete history taking and physical examination. Lipid profiles (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides), estimated glomerular filtrate rate (eGFR) using the MDRD equation, glycated hemoglobin (HbA1c) levels, and urinalysis parameters data were obtained from the recent examination in the last three months from the medical record if the data were available. Otherwise, a venous blood or urine sample was obtained and sent to the laboratory of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, for biochemical analysis.

Assessment of albuminuria

Albuminuria was determined by a semi-quantitative procedure based on urine albumin creatinine ratio (ACR) staging for CKD: normal (<30 mg/g), microalbuminuria (30–300 mg/g), and macroalbuminuria (>300 mg/g). Trace or 1+ on protein urine dipstick was also considered positive for albuminuria [14].

Assessment of diabetic retinopathy

Retinal abnormalities due to diabetes complications were assessed using the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS) criteria. Examination and diagnosis were carried out by a retinal consultant ophthalmologist using a slit lamp biomicroscopy and a 90D lens. The results were documented using fundus photography.

Statistical analysis

Data were analyzed using SPSS version 23.0 for Windows (IBM Corporation, New York, USA). The data were tested for normality using the Kolmogorov–Smirnov test. Descriptive statistics were expressed as frequency distribution and mean with standard deviation. Bivariate analysis with a chi-square test was used, followed by multivariate analysis by logistic regression. A p-value<0.05 was considered significant with a 95% confidence interval (CI).

Results

A total of 168 T2DM patients were included in the present study. The majority of the subjects were female (59.5%).

Table 1: Characteristics of the study subjects.

Characteristics	Overall (n=168)
Female (n, %)	100 (59.5%)
Age, years (mean±SD)	54.84±10.10
Body mass index (kg/m²) (mean±SD)	25.37±5.25
Body mass index (n, %)	
Normal	52 (31.0%)
Overweight	42 (25.0%)
Obesity I	53 (31.5%)
Obesity II	21 (12.5%)
Blood pressure (mmHg) (mean±SD)	
Systolic	144.01±22.73
Diastolic	87.71±12.20
Duration of diabetes mellitus (years) (mean±SD)	6.64±6.53
HbA1c (%) (mean±SD)	8.09±1.78
Lipid profiles (mg/dL) (mean±SD)	
Total cholesterol	203.74±50.04
LDL	123.98±38.39
HDL	53.39±24.01
Triglycerides	166.37±98.17
eGFR (mL/min/1.73 m²) (mean±SD)	67.21±29.61
Albuminuria (n, %)	125 (74.4%)
Diabetic retinopathy (n, %)	80 (47.6%)

Note: LDL – low-density lipoprotein; HDL – high-density lipoprotein; eGFR – estimated glomerular filtration rate.

The mean age of the participants was 54.84±10.10 years old. The participants' average BMI was 25.37±5.25 kg/m², with most participants having a BMI category of obesity, as many as 74 participants (44.0%). The participants' average systolic and diastolic blood pressures were 144.01±22.73 mmHg and 87.71±12.20 mmHg, respectively. Albuminuria and DR were present in 125 subjects (74.4%) and 80 subjects (47.6%) respectively. Table 1 summarizes the clinical characteristics of the study population.

The bivariate analysis between the presence of albuminuria and DR was performed using a chi-square test. There were 33 (76.7%) subjects with normoalbuminuria and 55 (44.0%) subjects with albuminuria in the group without DR. Meanwhile, there were 10 (23.3%) subjects with normoalbuminuria and 70 (56.0%) subjects with albuminuria in the group with DR. There was a statistically significant difference between the two groups (p=0.000) (Table 2). We further analyzed the demographic and clinical characteristics that might be

Table 2: Association between the presence of albuminuria and diabetic retinopathy.

Albuminuria category	Diabetic retinopathy category		P-value
	normal (n=88)	DR (n=80)	
Normoalbuminuria	33 (76.7%)	10 (23.3%)	0.000*
Albuminuria	55 (44.0%)	70 (56.0%)	

Note: DR – diabetic retinopathy; * – significant (p<0.05).

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associated with DR. Only age, sex, BMI, systolic blood pressure, diastolic blood pressure, HbA1c levels, and dyslipidemia were the variables that might be associated with the presence of DR and therefore included in the multivariate analysis. Through multivariate logistic regression, the presence of albuminuria increased the risk for DR 4.857 folds (95% CI: 2.029–11.626; p=0.000) adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, HbA1c levels, and dyslipidemia (Table 3).

Discussion

Our study revealed that the prevalence of renal involvement in T2DM patients was 74.4%. According to NHANES data, the prevalence of CKD in T2DM patients in the US remained consistently high from 2007 to 2012 at 38%. Factors associated with the presence of CKD were older age, HbA1c, systolic blood pressure, and significant hypertension [15]. The proportion of patients with albuminuria in the present study was higher than the number reported by Unnikrishnan *et al.* [8], which was around 32%. However, our present finding is similar to the previous study by Sobngwi *et al.* [16], in which microalbuminuria was reportedly present in 53.1% of diabetic patients. Even though those previous studies were conducted in the same developing countries as ours, they were population-based research, while our current study was conducted in tertiary care hospitals. This difference might result from early diagnosis, awareness, and the long duration of DM (6.64±6.53 years) in the tertiary care hospital patients. Our present study's result is supported by Soegondo *et al.* [17], who reported the prevalence of albuminuria at 80% in Indonesia's primary care practice.

As for DR, the prevalence in our study was 47.6%. This number is similar to the number reported by the study of Sasongko *et al.* [18], in which the prevalence of DR in T2DM patients was 43.1%. Although it was a population-based study, the subjects were comparable to our subjects in terms of mean age, gender, duration of DM, and hypertension. Hospital-based studies by Ahmed *et al.* [5] and Alemu *et al.* [19] reported that the prevalence of DR was 39.8–59.8% and 34.1%, respectively. The results of our present study and those of previous studies are higher than the global prevalence of DR [20]. This difference could be related to the utilization of better examination techniques and technology to help ascertain a greater number of cases with DR.

Clinical studies have reported that albuminuria is associated with DR, and albuminuria has an impact on predicting the risk for the development and progression of DR in T2DM patients [21]. High-normal albuminuria is closely associated not only with diabetic kidney disease but also with diabetic vascular complications such as cardiovascular disease in patients with type 2 diabetes [22, 23]. Previously, the correlation between renal involvement and retinopathy in T2DM was controversial [7]. However, recent cumulative evidence proved the association between the two, even though the chronological order is still unclear [24]. These are in accordance with the main finding of our study, in which albuminuria is associated with the presence of DR (adjusted OR: 4.857).

Microvascular damages were responsible for both the retinal and renal complications of DM. The correlation and the chronology of occurrence are well established in type 1 DM, in which retinopathy appears before nephropathy. However, this is not the case for T2DM patients. Insulin resistance plays a pivotal role in the development of T2DM. An elevated level of plasma

Table 3: Multivariate logistic regression analysis of diabetic retinopathy.

Variable	OR	95% CI	P-value
Sex	1.260	0.595–2.669	0.547
Age	0.966	0.930–1.004	0.079
Body mass index	0.910	0.847–0.978	0.010*
Systolic blood pressure	1.040	1.013–1.068	0.004*
Diastolic blood pressure	0.958	0.914–1.005	0.077
HbA1c	1.185	0.962–1.460	0.111
Dyslipidemia	1.003	0.995–1.010	0.488
Albuminuria	4.857	2.029–11.626	0.000*

Note: OR – odds ratio; CI – confidence interval; * – significant (p<0.05).

insulin promotes glomerular hyperfiltration, endothelial dysfunction, and increased vascular permeability that eventually results in albuminuria [25]. Therefore, albuminuria might serve as a marker of generalized vascular dysfunction. Hyperglycemia-induced vascular dysregulation is characterized by the increase in the production of endogenous vasodilators such as vascular endothelial growth factor (VEGF), nitric oxide (NO), and insulin-like growth factor (IGF) [26]. Hyperglycemia also induces apoptosis of pericytes in the retinal tissue followed by microaneurysm formation, the earliest clinical finding of DR. Vascular endothelial growth factor is responsible for the further progression of DR, especially the development of proliferative DR [11].

Our study has several limitations, firstly due to its cross-sectional design in nature. Secondly, a single examination of urine ACR or dipstick proteinuria did not conform to the generally accepted definition of persistent microalbuminuria or proteinuria. Third, the medications (antihypertensive and antidiabetics regimen) taken by the subjects were not considered in this present study; therefore, a bias is likely to be present.

Conclusion

Albuminuria is significantly associated with an increased risk of developing DR in Indonesian T2DM patients. The presence of albuminuria in T2DM patients warrants further investigation of DR and more aggressive management to prevent the development of vision-threatening stages.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (approval ID: 1311/ KEPK/ V/2019.).

Consent to participate

Written informed consent was obtained from all the participants.

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