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HbA1c levels with albuminuria in diabetes mellitus patients

Niveles de HbA1c con albuminuria en pacientes con diabetes mellitus

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SUMMARY

Introduction: *The number of people with diabetes mellitus (DM) worldwide with kidney complications has increased. Glycemic control by assessing HbA1c levels is one factor that influences the occurrence of kidney damage in DM patients. This study aims to determine the relationship between HbA1c levels and the incidence of albuminuria in DM patients.* **Methods:** *This study was a cross-sectional analytic observational study with consecutive sampling techniques in DM patients who did not have urinary tract infections and had no history of other kidney diseases, which were then measured for HbA1c levels and protein in the urine.* **Results***: A total of 20 patients (62.5 %) were female, and 12 patients (37.5 %) were male. The average age of the patients was 59.81±4.89 years, and the average length of suffering from DM was 6.21±2.27 years. The average HbA1c level was 8.63±2.15, with an HbA1c level >7 found in 21 patients (65.7 %). In this study, there were 21 patients (65.7 %) with uncontrolled HbA1c levels. In this study, the prevalence of negative albuminuria was 56.2 %, while the prevalence of positive albuminuria was 43.8 %. There was a significant relationship between uncontrolled HbA1c levels and the incidence of albuminuria in DM patients (p=0.03).* **Conclusion:** *Uncontrolled HbA1c levels were associated with the incidence of albuminuria in DM patients.*

Keywords*: HbA1c, Diabetes Mellitus, albuminuria.*

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RESUMEN

Introducción: *En todo el mundo ha aumentado el número de personas con diabetes mellitus (DM) con complicaciones renales. El control glucémico mediante la evaluación de los niveles de HbA1c es un factor que influye en la aparición de daño renal en pacientes con DM. Este estudio tiene como objetivo determinar la relación entre los niveles de HbA1c y la incidencia de albuminuria en pacientes con DM.* **Métodos:** *Se realizó un estudio observacional analítico transversal con técnicas de muestreo consecutivo en pacientes con DM que no tenían infecciones del tracto urinario y no tenían antecedentes de otras enfermedades renales, a los cuales se le midieron los niveles urinarios de HbA1c y proteína.* **Resultados:** *20 pacientes (62,5 %) eran mujeres y 12 pacientes (37,5 %) eran hombres.*

La edad media de los pacientes fue de 59,81 ± 4,89 años y la duración media de la DM fue de 6,21 ± 2,27 años. El nivel medio de HbA1c fue de 8,63 ± 2,15, encontrándose un nivel de HbA1c> 7 en 21 pacientes (65,7 %). En este estudio 21 pacientes (65,7 %) presentaron niveles de HbA1c no controlados. La prevalencia de albuminuria negativa fue del 56,2 %, mientras que la prevalencia de albuminuria positiva fue del 43,8 %. Hubo una relación significativa entre los niveles de HbA1c no controlados y la incidencia de albuminuria en pacientes con DM (p = 0,03).
Conclusión: *Los niveles de HbA1c no controlados se asociaron con la incidencia de albuminuria en pacientes con DM.*

Palabras clave: *HbA1c, Diabetes Mellitus, albuminuria.*

INTRODUCTION

Diabetes mellitus (DM) is a significant health problem that affects millions of people globally because of its increasing number. Data shows that until 2013 DM sufferers in the world reached 382 million people, and it is estimated that this will increase to 592 million in 2035 (1). DM is a primary chronic disease in the world that can cause heart disease, blindness, kidney failure, and lower extremity amputation. Globally, the number of people with type 2 DM was around 424.9 million in 2017 (2). In Indonesia, the number of people with DM is also increasing. Indonesian Basic Health Research data, known as *Riset Kesehatan Dasar* (RISKESDAS), in 2013 stated that the percentage of DM sufferers is 2.1 % of the total population of Indonesia. This increased from 1.1 % in 2007 while the number of sufferers of chronic kidney disease in Indonesia, according to RISKESDAS 2013, is around 0.2 % of the total population of Indonesia (3).

Diabetes is characterized by the American Diabetes Association (ADA) as type 1 diabetes, type 2 diabetes, gestational diabetes, and type-specific diabetes caused by other factors. In general, the number of diabetic patients is increasing each year, particularly type 2 diabetes (4). DM is a chronic metabolic disorder caused by faulty insulin secretion, insulin action, or both; resulting in elevated blood glucose levels (hyperglycemia condition) (5). Chronic hyperglycemia is frequently associated with damage, dysfunction, and failure of numerous organs, most notably the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), heart, and blood arteries in type 1 diabetes patients. Uncontrolled blood glucose levels are a significant risk factor (6).

Diabetic nephropathy in DM patients causes patients to fall into end-stage chronic kidney disease (ESKD), which has a high mortality rate and requires hemodialysis (HD) therapy. This affects the quality of life and socioeconomic conditions and increases the morbidity and mortality of DM patients with ESKD (7).

An early marker of kidney disease is the presence or absence of albumin in the urine. Under normal circumstances, albumin is not excreted in the urine. Enlargement of the podocyte gap in the renal basement membrane will cause proteins with large molecular weights not to be appropriately filtered to obtain protein content in the urine (albuminuria). If this condition lasts for a long time, there will be a decrease in kidney function and chronic kidney failure (8). Studies have shown that albuminuria is a predictor of pathogenic factors in progressive kidney disease. A cohort study of 100 000 patients showed a greater incidence of ESKD in patients with albuminuria. Albuminuria is also a risk factor for cardiovascular and renal disease in the general population (9).

Various factors play a role in the pathophysiology of albuminuria in DM patients. One of them is poor regulation of blood sugar levels. Chronic hyperglycemic conditions cause changes in the structure of the renal glomerular efferent blood vessels. So that the glomerular pressure will increase and hyperfiltration occurs. The result is a thickening of the glomerular basement membrane and widening of the podocyte gap, making it easier for larger molecules such as protein to pass into the urine (10). The state of hyperglycemia will also increase oxidative stress and oxidant formation. This causes a decrease in kidney function through glomerulosclerosis due to a decrease in podocyte cells, mesangial cells, and activation of transcriptional pathways (10).

Several methods can be used to control blood sugar regulation, one of which is by measuring hemoglobin-A1c (HbA1c). HbA1c examination has been widely used either to diagnose DM or

to assess glycemic control for three months in DM patients (11). Hyperglycemic conditions will trigger the production of HbA1c, formed by the glucose and amide groups on the amino acid valine at the end of the globulin B chain. The continuous increase in glucose levels will stabilize the bond and maintain it as HbA1c. The amount of HbA1c formed will accumulate in red blood cells and slowly spread as red blood ages (12). Normal HbA1c levels are 3.5 %-5 %. HbA1c was significantly influenced by the average blood glucose level during the previous 30 days. The average monthly contribution of blood glucose to HbA1c was 50 % in the preceding 30 days, 25 % in the preceding 30-60 days, and 25 % in the preceding 60-120 days. Measurement of HbA1c is considered important for long-term control of glycemic status in DM patients (11).

Several studies regarding the relationship of HbA1c levels with albuminuria in DM patients have been carried out and have varying results. Most studies show a very strong relationship between HbA1c levels and the occurrence of albuminuria, and several other studies have obtained contradictory results (12). In Indonesia, study on this subject has not been widely carried out, while knowledge about the role of glycemic control in the occurrence of kidney complications in DM patients is essential to understand, especially for clinicians. The purpose of this study is to examine the link between HbA1c levels and the prevalence of albuminuria in patients with DM.

METHODS

This is an analytic observational study using a cross-sectional design. It was conducted on all individuals with type 2 diabetes who met the study's inclusion criteria. The investigation was conducted from November 2018 to January 2019 at Ibnu Sina Hospital Makassar, Indonesia.

Sampling was done by consecutive sampling technique. Based on the calculation of the sample size for nominal correlative analytics, the number of samples obtained was 32. The inclusion criteria in this study were patients diagnosed with DM in the Internal Medicine poly and willing to participate in the study. Exclusion criteria in this study were history of chronic kidney disease, kidney stones, stones in the urinary tract, patients who had complaints of urinary tract infections, and patients who were not willing to participate in the study.

Measurement of albuminuria using urine while from the patient. Urine specimens were stored at 4 °C until the examination was performed. If the examination was delayed more than 24 hours, the urine specimen was stored at -20°C (13). 1.6 mL of urine specimen was added into two test tubes for the test solution and blank, the specimen was also added into the standard solution tube and the control tube. Then 0.4 mL of trichloroacetic acid solution was added to each tube and allowed to stand for 10 minutes at room temperature. The blank tube was centrifuged for 10 minutes at 2 000 rpm. Then the optical density/absorbance was determined using spectrophotometry (620 nm wavelength) (13).

HbA1c assessment was performed on blood specimens taken from peripheral veins to which anticoagulant was added (EDTA and citrate). In the sample tube, 1.5 mL of diluent solution was added, and a mixture of 5 l of blood + EDTA was added. After homogenization HbA1c was determined by High-performance liquid chromatography (HPLC) (14).

Albuminuria was the dependent variable in this study, defined as protein in human urine that exceeds its normal value of more than 150 mg/24 hours or in children more than 140 mg/m^2 (13). The condition of albuminuria in patients is measured using a dipstick instrument, which will give a positive or negative albuminuria result. The HbA1c level is an independent variable and is stable glucose bound to the N-terminal group on the HbA1c chain, forming a post-translational modification so that glucose combines with free amino acids on the N-terminal valine residue of the chain of hemoglobin. Clinically used to evaluate the glycemic control of DM patients for three months according to the life span of erythrocytes with the group (14). The HbA1c level in this study was measured using the HPLC brand BioRad D10 TM. HbA1c levels were controlled if the value was 7 and uncontrolled if the value was >7. Univariate analysis was carried out to explain and analyze descriptively by calculating the distribution and frequency of each

characteristic of the study variables, namely the independent variable (HbA1c) and the dependent variable (patient albuminuria levels), then presented in the form of tabulations and graphs. Furthermore, bivariate analysis was carried out to assess the relationship and significance between the two variables. The independent variable in this study used an ordinal scale, and the dependent variable is also an ordinal scale. The correlation was analyzed by the Spearman Correlation test. Data analysis was carried out using Microsoft Office Excel 2013 and SPSS V.24 for Windows.

RESULTS

In this study, 35 DM patients met the inclusion criteria, but three patients were excluded because they had a history of prostate enlargement and urinary tract infection (UTI) complaints.

As shown in Table 1, patients comprised an age range of 34 - 84 years with an average age of 59.81±3.99. The gender found was 12 men and 20 women, with an average duration of DM of 6.21±2.27 years. There were 21 patients (65.7 %) with uncontrolled HbA1c levels. The prevalence of negative albuminuria was 56.2 % in 18 patients, while the prevalence of positive albuminuria was 43.8 % in 14 patients. The bivariate analysis showed a significant correlation between uncontrolled HbA1c levels with the occurrence of albuminuria (p=0.03).

DISCUSSION

This study shows that there was a strong correlation between HbA1c levels, and the occurrence of albuminuria, and most patients had uncontrolled HbA1c levels. There was a lower incidence of albuminuria in the group of patients with controlled HbA1c levels, while a higher incidence of albuminuria in the group of uncontrolled HbA1c levels. Our results are similar to a study showing a higher incidence of albuminuria in the group with HbA1c >7 (15,16). Also were confirmed by another study which stated that there was a significant relationship between HbA1c levels and albuminuria in type 2 DM patients (17,18). The amount and

Table 1

Patient characteristics

No	Characteristics	n	%	Mean±SD
1.	Age (years)		59.81±4.89	
	31 – 40	1	3.1 %	
	41 – 50	3	9.3 %	
	51 – 60	16	50.0 %	
	61 – 70	6	18.8 %	
	>70	6	18.8 %	
2.	Sex			
	Male	12	37.5 %	
	Female	20	62.5 %	
3.	Long Suffering DM (years)			6.21±2.27
	1 - 5	18	56.2 %	
	6 - 10	10	31.2 %	
	11 - 15	2	6.3 %	
	15 - 20	2	6.3 %	
4.	HbA1c level			8.63±2.15
	≤ 7 (controlled)	11	34.3 %	
	>7 (uncontrolled)	21	65.7 %	
Total		32	100 %	

type of protein that may be found in the urine depending on the severity of the kidney damage and is also related to the duration of DM (19). Clinically manifested diabetic nephropathy usually occurs 10 to 15 years after the diagnosis of DM. Early in the course of the disease, it is often asymptomatic and without proteinuria. In his regard, in the present study, significant proteinuria was observed although the number of patients suffering from DM for more than 5 years was only a small number. This possible is because some patients may not realize that they have had DM before and there is a delay in diagnosis (19).

Albuminuria examination is a screening test to identify kidney involvement in various diseases. In the diabetic population, the presence of albumin in the urine is also an important risk factor for renal and cardiovascular damage. Adults excrete 80 mg of protein in the urine daily. Protein excretion greater than 150 mg/day is considered normal. In healthy individuals, urine albumin accounts for around 15 % of daily protein excretion, whereas serum and other urinary proteins, such as beta-2-microglobulins and uromodulin, account for the remaining 85 % (Tamm-Horsfall protein) (20).

The dipstick methodology, which employs a buffer indicator that changes color in the presence of protein, can be used to qualitatively or semi-quantitatively determine the protein level. This technique is especially sensitive to albumin because, in comparison to other proteins, albumin includes a greater number of amino groups capable of accepting hydrogen ions (13). A urine dipstick test for protein concentrations of 10-20 mg/dL can be used to detect urine albumin levels (14). The results are influenced by the urine concentration, and the threshold value is approximately equivalent to the value on a trace urine reagent strip or 1+. Dipsticks are frequently utilized due to their inexpensive cost and speed of results. Gloves and eye protection should be worn when doing a dipstick urinalysis. The dipstick should be fully inserted into a fresh urine specimen and promptly withdrawn. Since some reactions from a multitest urine dipstick can take up to two minutes to complete, it is critical to know the precise time of the reading in order to avoid missing abnormal results (20).

Albuminuria can occur due to several causes, including changes in glomerular permeability following an increase in filtration of normal plasma proteins, primarily albumin, failure of the tubules to reabsorb small amounts of these proteins that are normally filtered, abnormal glomerular filtration of the circulation, low Molecular Weight Protein (LMWP) in amounts exceeding the tubular reabsorption capacity, increased secretion of uroepithelial maculoprotein and IgA secretion in response to inflammation, large amounts of protein normally pass through the glomerular capillaries. However, they do not enter the urine. If this barrier is broken, there is leakage of plasma proteins into the urine or glomerular protein (21).

In this study, few DM patients had albuminuria, showing that the progression of kidney complications among DM patients is still relatively small. One of the factors that influence albuminuria in DM patients is low glycemic control which is characterized by elevated HbA1c levels. Several factors such as age, gender, and adherence to DM treatment can affect glycemic control (19). We show that most patients had abnormal HbA1C levels, indicating that glycemic control is still low among DM patients. Another study also reported poor glycemic control in Indonesia regarding glycated albumin as a marker of glycemic control in patients with type 2 diabetes (22,23).

Finally, we demonstrate a high prevalence of DM in the age group above 40 years, and female gender higher than male gender, similarly to the studies reported previously (24), and contrary to those reported in India where there were more males than females (25). The duration of suffering from DM in this patient varied between 1 to 20 years, being most of the patients suffering from DM for less than 5 years.

CONCLUSION

HbA1c levels are associated with the occurrence of albuminuria in type 2 DM patients. This underscores the importance of glycemic control to prevent complications of diabetic nephropathy, which will affect the quality of life of DM patients.

REFERENCES

1. Shen Z, Fang Y, Xing T, Wang F. Diabetic Nephropathy: From Pathophysiology to Treatment. J Diabetes Res. 2017;2017(4):10-24.
2. Rondhianto, Kusnanto, Melaniani S. The effect of diabetes self-management education, based on the health belief model, on the psychosocial outcome of type 2 diabetic patients in Indonesia. Indian J Public Heal Res Dev. 2018;9(11):1718-1723.
3. KKRI. Riset Kesehatan Dasar (RISKESDAS) 2018. Jakarta; 2018.
4. Maharani AI, Hasmono D, Diansyah MN. Use of anti-dyslipidemia in type 2 diabetes mellitus. Indian J Public Heal Res Dev. 2019;10(8):1970-1976.
5. Putri EIS, Indriati DW, Wahyunitisari MR. The prevalence of diabetes mellitus among hospitalized tuberculosis-positive cases admitted in Hajj Hospital, Surabaya, Indonesia. Malaysian J Med Heal Sci. 2020;16(1):235-239.
6. Hamdan M, Wisnujono R, Basuki M, Fidiana, Fadil, Sudarmadi I. The association between blood glucose control measured with serum hna1c level with peroneal motor nerve conduction velocity in patients with type 2 diabetes mellitus with polyneuropathy. Indian J Forensic Med Toxicol. 2020;14(2):1649-1654.
7. Bennett K, Aditya BS. An overview of Diabetic nephropathy: Epidemiology, pathophysiology, and treatment. J Diabetes Nurs. 2015;19(2):61-67.
8. Tan J, Zwi LJ, Collins JF, Marshall MR, Cundy T. Presentation, pathology and prognosis of renal disease in type 2 diabetes. BMJ Open Diabetes Res Care. 2017;5(1):1-10.
9. Prodjosudjadi W, Suhardjono, Suwitra K, Pranawa, Widiana IGR, Loekman JS, et al. Detection and prevention of chronic kidney disease in Indonesia: Initial community screening. Nephrology. 2009;14(7):669-674.
10. Putri AY, Thaha M. Role of oxidative stress on chronic kidney disease progression. Acta Med Indones. 2014;46(3):244-252.
11. Berard LD, Siemens R, Woo V. Monitoring Glycemic Control. Can J Diabetes. 2018;42:S47-53.
12. Husen SA, Hayaza S, Susilo JK, Setyawan F, Zuraidah AA, Winarni D, et al. Antioxidant potency of various mangosteen (Garcinia mangostana, L) pericarp extract fractions on HbA1c and fasting blood glucose level in diabetic mice. In: IOP Conference Series: Earth and Environmental Science. Institute of Physics Publishing; 2019.
13. Vardiansyah. Pemeriksaan Fungsi Ginjal. Cermin Dunia Kedokt. 2016;43(2):148-154.
14. Paputungan SR, Sanusi H. Peranan pemeriksaan hemoglobin A1c pada pengelolaan diabetes melitus. Cermin Dunia Kedokt. 2014;41(9):650-655.
15. Alqudah S, Jarab AS, Alefishat EA, Mayyas F, Khdour M, Pinto S. Factors Associated with Poor Hemoglobin A1c Control in Patients with Type 2 Diabetes. Curr Diabetes Rev. 2018;15(2):164-170.
16. Rosdiana D, Mukhyarjon, Asputra H, Hernita NF, Makmur O, Prayogo, et al. Correlation between Proteinuria and Glomerular Filtration Rate in Type 2 Diabetes Mellitus. Maj Kedokt Bandung. 2020;52(2):61-68.
17. Showail AA, Ghoraba M. The association between glycemic control and microalbuminuria in Type 2 diabetes. Saudi J Kidney Dis Transplant. 2016;27(3):473-479.
18. Kundu D, Roy A, Mandal T, Bandyopadhyay U, Ghosh E, Ray D. Relation of microalbuminuria to glycosylated hemoglobin and duration of type 2 diabetes. Niger J Clin Pract. 2013;16(2):216-220.
19. Majid F, Uwan WB, Zakiah M. Hubungan kadar HbA1c terhadap laju filtrasi glomerulus dan proteinuria pada penderita diabetes melitus tipe 2. J Cerebellum. 2020;5(4A):12-16.
20. Cassia MA, Pozzi FE, Bascapè S, Saggiante L, Daminelli G, Cirelli C, et al. Proteinuria and Albuminuria at Point of Care. Nephrol @ Point Care. 2016;2(1):pocj.5000194.
21. Setiati S, Alwi I, Aru WS. Proteinuria. In: Bawazier L, editor. Buku Ajar Ilmu Penyakit Dalam. VI. Jakarta Pusat: Interna Publishing; 2014.p.2308-23145.
22. Elitha C, Pusparini P. Correlation of HbA1c and glycated albumin in hemodialysis patients with diabetes Mellitus. J Kedokt dan Kesehat Indones. 2020;11(1):44-51.
23. Mahmudiono T, Setyaningtyas SW, Rachmah Q, Nindya TS, Megatsari H, Indriani D, et al. Self-efficacy in physical activity and glycemic control among older adults with diabetes in Jagir Subdistrict, Surabaya, Indonesia. Heliyon. 2021;7(7):e07578-e07578.
24. Ningrum VDA, Ikawati Z, Sadewa AH, Ikhsan MR. Glycemic Control and Prevalence of Chronic Kidney Disease in Type-2 Diabetes Mellitus Patients at Primary Healthcare Centers in Yogyakarta Province 2015. Indones J Clin Pharm. 2017;6(2):78-90.
25. Sisodia RK, Gupta A, Singh N. The study of dyslipidemia and its correlation with nephropathy in diabetes mellitus type 2 patients. Int J Adv Med. 2017;4(5):1231.