Jurnal Kedokteran dan Kesehatan Indonesia

Indonesian Journal of Medicine and Health

Journal homepage : https://journal.uii.ac.id/JKKI

Correlation of HbA1c and glycated albumin in hemodialysis patients with diabetes melitus

Clara Elitha[1],Pusparini*[2]

[1]Medical Education Study Program, Faculty of Medicine, Universitas Trisakti, Jakarta Barat, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta Barat, Indonesia

Original Article

ARTICLE INFO

Keywords:
glycated albumin,
HbA1c,
diabetes mellitus,
hemodialysis

***Corresponding author:**
pusparini@trisakti.ac.id

DOI: 10.20885/JKKI.Vol11.Iss1.art7

History:
Received: May 7, 2019
Accepted: January 23, 2020
Online: April 30, 2020

ABSTRACT

Background: Uses of HbA1c compared with glycated albumin as an indicator of glycemic control for hemodialysis patients(HD) needs to be evaluated. HbA1c has some limitations when used for HD because its results can falsely low or falsely high. It can be missunderstood if clinicians use HbA1c as glycemic control.
Objective: This study aimed to evaluate correlation between HbA1c and GA in HD patients with Diabetes Mellitus (DM).
Methods: This study was a cross sectional study conducted on November 2016 until January 2017. Its samples were obtained from 43 patients in HD with DM, fullfilling inclusion and exclusion criteria, located in a private hospital at east Jakarta. The HbA1c was measured by using a turbidimetric inhibition immunoassay method, and the GA was measured by using an enzimatic colorimetric method. In addition, a test of Pearson correlation was used to determine the correlation between HbA1c and GA with a significance of $p<0.05$.
Results: Averages of patients age in this study was 57.16 ± 9.0 years old, including 24 men (55.8%) and 19 women (44.2%). The mean values of HbA1C were 8 ± 2.30%, and the mean values of GA were 30.02 ± 13.3%. The mean duration of the HD was 4.5 ± 1.3 years. The glycemic control based on GA was significantly better than the HbA1c with $p = 0.028$ (Chi-Square test). Pearson correlation showed that there were a significant correlation between HbA1c and GA with $r = 0.759$ and $p = 0.000$.
Conclusion: There were a significant correlation between HbA1c with GA in HD patients with DM. Glycemic control based on GA was better than HbA1c.

Latar Belakang: *Penggunaan HbA1c sebagai kontrol glikemik dibandingkan dengan glycated albumin (GA) pada pasien hemodialisis (HD) perlu dievaluasi. HbA1c mempunyai keterbatasan bila digunakan pada pasien HD karena hasilnya dapat menjadi rendah palsu ataupun tinggi palsu. Bila klinisi menggunakan HbA1c sebagai kontrol glikemik pada pasien HD maka dapat terjadi salah interpretasi mengenai keadaan kontrol glikemiknya.*
Tujuan: *Tujuan penelitian ini adalah untuk mengetahui korelasi antara HbA1c dan GA pada pasien HD dengan DM.*
Metode: *Penelitian ini menggunakan desain potong lintang. Empat puluh tiga pasien HD dengan DM yang memenuhi kriteria inklusi dan eksklusi, diikutsertakan dalam penelitian. Penelitian dilakukan di rumah sakit swasta di Jakarta timur pada bulan November 2016 sampai dengan Januari 2017. Pemeriksaan HbA1c dilakukan dengan metode turbidimetric inhibition immunoassay sedangkan pemeriksaan GA dilakukan*

menggunakan metode enzimatik kolorimetrik. Untuk mengetahui korelasi antara HbA1c dan GA dilakukan uji korelasi Pearson dengan tingkat kemaknaan p<0.05.

Hasil: *Rerata usia subjek adalah 57.16 ± 9.0 tahun, 24 orang (55.8%) berjenis kelamin laki-laki dan 19 orang (44.2%) berjenis kelamin perempuan. Rerata kadar HbA1c adalah 8 ± 2.30% dan rerata GA adalah 30.02 ± 13.3%. Rerata lama pasien menjalani hemodialisis adalah 4.5 ± 1.3 tahun. Kontrol glikemik berdasarkan GA lebih baik secara bermakna dibandingkan dengan menggunakan HbA1c dengan p = 0.028 (Uji Chi Square). Hasil uji Pearson antara HbA1c dan GA menunjukkan korelasi yang bermakna dengan nilai r = 0.759 dan p = 0.000.*

Kesimpulan: *Terdapat korelasi yang bermakna antara HbA1c dengan GA pada pasien HD dengan DM. Kontrol glikemik dengan menggunakan GA lebih baik daripada HbA1c.*

INTRODUCTION

World Health Organization (WHO) had estimated that 422 million adults would suffer diabetes mellitus (DM) in 2014.[1] In Indonesia, there had been 10 million people diagnosed with DM based on data of the International Diabetes Federation (IDF) in 2015, and it had positioned in 7th rank in the world.[2] DM Complications increase along with the increasing number of people with DM. This debilitating disease is one of causes of terminal kidney disease and the most important risk factor for cardiovascular disease, infection and death for patients with chronic kidney disease.[3] In developing countries, almost half of the terminal kidney disease is caused by DM, as the patients mostly use dialysis to help their kidney function.[4]

Strict glycemic control is necessary for DM patients because it can reduce DM complications that can affect quality of life and prognosis of the patients. Several signs can be used as indicators to measure levels of glycemic control of the DM patients including traditional markers such as HbA1c or non-traditional such as GA.[5] Hemoglobin A1c (HbA1c) is a traditional glycemic sign that is often used for glycemic control. The HbA1c is to examine percentages of circulating hemoglobin that chemically reacts with glucose (A1c) and to illustrate blood glucose control by 120 days before an examination.[3] It is also a gold standard to asses glycemic control during DM management. Moreover, since 2009 it has been recommended by the American Diabetes Association (ADA) and WHO as a diagnostic criterion for DM, with a diagnostic cut-off value of > 6.5% (48 mmol/mol).[6] Besides, a main complication of Chronic Kidney Disease (CKD) is anemia that results an erythrocyte turnover. This condition is usually treated with iron and or erythropoietin. This therapy can stimulate productions of erythrocytes; therefore, there is a change in proportions of young erythrocytes and old erythrocytes.[4,5] In these conditions the proportion of hemoglobin molecules that bind to glucose also decreases due to shorter glycation time, resulting lower HbA1c levels than what is expected.[4] If a clinician still uses HbA1c in HD patients, a falsely low HbA1c condition can occur and can not reflect actual glycemic control conditions of the patients.[5]

Non-traditional glycemic signs include serum glycated albumin (GA). GA is a ketamine, which is formed because of a non-enzymatic process of bonding between glucose and serum proteins. In hyperglycemic conditions, serum proteins are exposed to high concentrations of glucose and become more easily duplicated. GA as a non-traditional sign is often used to check glycemic control in DM patients in a shorter period because a half-life of albumin and other serum proteins is shorter than erythrocytes. The GA can reflect a mean of glycemic control within a period of 2-3 weeks.[7] GA concentrations increase and decrease faster with overall glucose fluctuations compared to the HbA1c, allowing rapid changes to be detected at an early stage.[8] Inaba et al reported that uses of HbA1c as a glycemic control in HD patients showed lower results compared to mean random glucose levels and GA. It was reported that percentages of GA were more accurate for a glycemic control in HD patients in Japan.[9] The use of GA as a diagnostic function and a monitoring of successfulness of therapy in DM patients with HD in Indonesia has been limited and has not been a gold standard such as HbA1c according to recommendations

of the American Diabetes Association (ADA) and the Indonesian Endocrinology Association (Perkeni).[6] The purpose of this study was to determine the correlation of HbA1c and GA levels in HD patients with DM.

METHODS

This study obtained a permission of the Research Ethics Commission of the Faculty of Medicine, Trisakti University by number: 12//KER-FK/VII/2016. This research was a cross-sectional design involving 43 patients with inclusion criteria of men and women: aging by 35-76 years old, suffering type 2 diabetes, undergoing hemodialysis, and willing to participate in this study by signing an informed consent. Exclusion criteria were patients with severe complications like a heart failure, suffering blood disorders such as thalassemia and hemoglobinopathy (obtained from medical record data). This study was conducted at a private hospital in East Jakarta from November 2016 to January 2017. Consecutive sampling was used to select the data. The sample size of this study were 43 subjects. Fasting blood was organized for at least 10 hours for a laboratory examination of HbA1c and GA in the morning before HD. Next, the HbA1c was examined by Cobas C111 by using a turbidimetric inhibition immunoassay method, while the GA was examined by Advia 1800 by using a colorimetric enzymatic method. Other laboratory results such as hemoglobin, albumin, urea, creatinine, glomerular filtration rate estimation and hemodialysis duration were obtained from medical record data. The data were analysed by using a statistical program. The glycemic index was considered uncontrolled if HbA1c ≥ 7% and or GA ≥ 16%.[10] To compare the HbA1c and GA, a Pearson correlation test was conducted with p values <0.05 significantly different.

RESULTS

Table 1 showed the characteristics of the patients. Their mean age of was 57.16 ± 9.0 years. Motstly they were male by a number of 55.8%. The details of the characteristics can be seen in Table 1 below.

Table 1. Characteristics of patients

Characteristics	mean ± SD
Age (year)	57.16 ± 9.0
Sex----n (%)	
Male	24 (55.8)
Female	19 (44.2)
Hb (g/dL)	9.2 ± 1.4
Albumin (g/dL)	3.6 ± 0.5
Ureum (mg/dL)	141 ± 25
Creatinin (mg/dL)	8.6 ± 1.3
eGFR (mL/min/1,73m2)	11.3 ± 2.1
HbA1c (%)	8 ± 2.3
Glycated albumin/GA (%)	30.02 ± 13.3
Hemodialysis period (year)	4.5 ±1.3

Hb: haemoglobin, eGFR: estimated glomerulus filtration rate

Table 2 showed group distributions age and sex on HbA1c and GA. In all age groups, it was found that HbA1c level ≥7% was the most dominant group with 6 patients in the age group of <50 years old, and 24 patients in the age group of ≥50 years old with Chi Square test results:

p= 0.542. In the sex groups, a similar result was found that the HbA1c group ≥7% was the dominant group with 18 male patients and 12 female patients with Chi Square test results: p= 0.401.

At the GA level compared all age groups, it was found that the dominant GA level was ≥16% with Fisher's test results: p= 0.659, and in the gender group, both men and women, it was found that the dominant was GA≥16% with the Fisher test result: p= 0.495.

Table 2. HbA1c and GA levels by age and sex

Characteristics	n(%)	HbA1c			GA		
		< 7 %	≥7%	p value	<16%	≥16%	p value
Age (years)							
<50	8 (18.6)	2	6	0.542*	0	8	0.659#
≥50	35 (81.4)	11	24		2	33	
Sex							
Male	24 (55.8)	6	18	0.401*	2	22	0.495#
Female	19 (44.2)	7	12		0	19	

*Chi Square test; # Fisher exact test; GA: glycated albumin.

Table 3 showed that the glycemic control was based on HbA1c and GA levels. Patients with good glycemic control based on HbA1c showed poor glycemic control based on GA results, in which there were 11 patients. Glycemic control based on the results of HbA1c and GA were significantly different with p value = 0.028.

Table 3. Relationship between HbA1c and GA levels based on glycemic control

Characteristics	GA		p value
HbA1c	<16 %	≥16%	
< 7%	2	11	0,028 *
≥7%	0	30	

*Fisher exact test, p<0,05 significant difference.

Figure 1 shows the correlation between HbA1c and GA by using Pearson correlation. Between HbA1c and GA, a significant correlation was obtained by a value of r = 0.759 and p = 0.000.

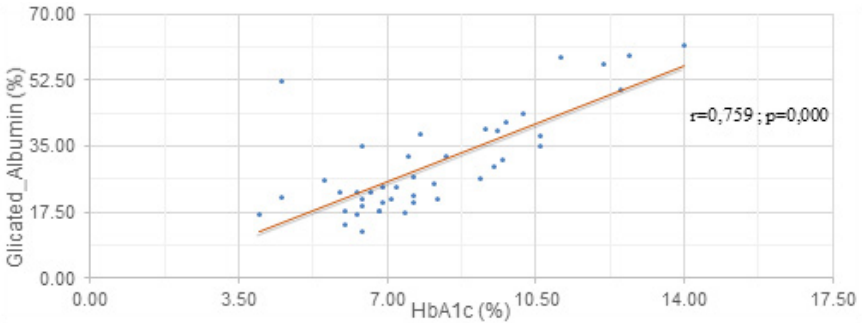

Figure 1. Correlation of HbA1c and GA (Pearson correlation)

DISCUSSION

Diabetes is a chronic metabolic disease that lasts a lifetime and results various morbid complications.[11] In the disease, there is interference in processing of blood glucose by the body, which causes damage to the kidneys (diabetic nephropathy).[11] DM patients who have terminal kidney failure must undergo renal replacement therapy in a form of dialysis (HD or peritoneal dialysis or kidney transplantation. Several factors increase complications and death during the HD, for example: old age and presence of micro and macrovascular diseases.[5] HbA1c examination has proven to be reliable as a prognostic marker in a general population of diabetics, but this may not be applicable in DM patients with complications of CKD. Synchronicity between HbA1c values with glucose concentrations in average patients with terminal kidney disease is still debated.[8] Some aspects of CKD have a significant impact on HbA1c concentrations, and their values may be falsely low or highly false. Until now, International guidelines for diabetes treatments in CKD have suggested that the HbA1c target for diabetics should be <7.0% regardless of the presence or absence of CKD.[12]

This study examined HD patients with type 2 DM by age of 35 to 76 years old, with a mean age of 57.16 years old (Table 1). The mean age of patients in this study is similar to a research of Kobayashi et al. who reported that the mean age of HD patients was 58.6 ± 7.4 years old.[11] A study by Tsuruta et al, also reported that the mean age of HD patients with DM was 66.3 ± 11.4 years old.[13] In addition, a study of Al-Maskari et al. reported that prevalence of DM patients with or without complications increased with their increasing age with average age of 53 years old.[14]

The glycemic control of the patients of this study was based on HbA1c levels ranging from 4 - 14% with an average value of 8 ± 2.3% (Table 1). The glycemic control based on GA levels ranged from 12.32 to 61.82% with an average value of 30.02 ± 13.3% (Table 1). Based on the glycemic control, it could be seen that the patients in this study showed that the condition of glycemic control was not good/not controlled. It could be seen that the mean values of glycemic control using HbA1c and GA showed higher values than what was recommended, namely HbA1c <7% and GA <16%.[6,10,15] When using glycemic control based on HbA1c markers, the highest value was 14 %, and based on GA was 61.82%, this means that false glycemic control was lower when using HbA1c as a glycemic control than when using GA. By using HbA1c, the increase of glycemic control was about 2-fold from the recommended value of <7%; meanwhile, when using GA, the glycemic control increased to about 3.86 times from the recommended value of <16%. This was reinforced by the Fisher test results in Table 3 showing glycemic control with HbA1c and GA that was significantly different (p = 0.028). Gan et al's study pointed out that there was no significant difference between HbA1c and GA in early-stage CKD, but in advanced CKD, GA was superior to HbA1c because HbA1c in these conditions became inaccurate to reflect glycemic control in DM patients with HD.[16] The patients in this study had an average HD length of 4.5 + 1.3 years old (Table 1), so it was likely that they had experienced advanced CKD or had terminal kidney disease that could be seen by the average eGFR of 11.3 + 2.1 mL/min/1.73m^2. Some issues that could contribute to the inaccuracy of HbA1c included erythrocyte life span, use of iron or erythropoietin therapy, uremia and the patient's need for repeated transfusions.[17] Iron therapy and/or use of erythropoietin could cause a rapid decrease in HbA1c levels without changes in actual glycemic status due to the increased ratio between young and old erythrocytes; as a result,the proportion of glycated hemoglobin could decrease.[18,19] In patients with CKD especially those undergoing HD, the age of erythrocytes could decrease significantly with a decrease of 20-50%.[20] Thus, the patients with CKD accompanied by a decrease in the age of erythrocytes would affect values or levels of HbA1c than what was expected in blood glucose control measurements.[20] Ningrum et al. studying patients with type 2 DM by age of 30 to 60 years old reported that a range of glycemic control

using HbA1c was 5.8 - 12.2% (9.09 ± 2.10%), and GA was from 12.29-35.43% (21.90 ± 5.92%).[21] The study of Kobayashi et al. reported that the mean age of HD patients was 58.6 ± 7.4 years old, HbA1c levels by 6.1 ± 0.7%, and GA levels by 20.8 ± 2.8%.[11] Compared to this study, the mean age of the patients was almost similar, and the HbA1c levels in this study were higher than the study of Kobayashi et al. Similarly, the GA levels in this study were also higher. The reason for this difference was probably because this study was conducted in different ethnicities and the methods used to conduct the HbA1c and GA examination. Besides, Kobayashi et al used peritoneal dialysis but not HD.[11] The results of this study indicated that HD patients with type 2 DM who used GA as glycemic control were superior.

In this study, both HbA1c and GA levels were not affected by age or gender (Table 2). The age limit of 50 years old used in this study was in accordance with a research conducted by Shamshirgaran et al. who used an age limit of <50 years old and over 50 years old to conduct a glycemic control analysis that showed results consistent with this study as there were no significant differences with p values = 0.111. The age of 50 years old was considered to represent age of middle age people and transition from young to old age.[22] The results of this study were also similar to a study conducted by Bador et al. showing significant differences in age, sex, or ethnicity amomg all patient groups.

Based on results of Pearson correlation test, HbA1c and GA showed values of r = 0.759 and p = 0.000 (Figure 1) indicating that there was a significant correlation between HbA1c and GA. The results of this study were in line with the study of Tsuruta et al. who obtained GA values of HD patients with DM that correlated with HbA1c values (r = 0.697, p <0.0001).[13] The results of Tsuruta et al.'s study demonstrated a significant correlation between pre-dialysis glucose, HbA1c values, GA values, and their daily glucose profiles in HD patients. The Tsuruta et al's study also showed that only GA levels were independently correlated with glucose. The life span of erythrocytes ranged from 120 days, so serum HbA1c levels could reflect blood glucose levels over the previous several months, while GA levels could be used as indicators of short-term glycemic control because metabolic albumin could change faster than the hemoglobin. Albumin has a life span of about 17 to 23 days.[13] Large blood glucose fluctuations could increase albumin glycation and oxidation reactions, followed by elevated levels of GA. Besides, hyperglycemia was reported to reduce erythrocyte survival. In DM patients with HD, many factors could influence HbA1c levels; therefore, GA levels could be a better indicator for glycemic control because HD patients had large fluctuations in glucose levels.[16]

The GA reflected the percentage of albumin duplicated regardless of total serum albumin concentration, although further studies on dialysis patients are still needed to strengthen the study results.[5] Low levels of the albumin in serum could be caused by impaired synthesis (malnutrition, liver dysfunction) or loss (ascites, missing proteins due to nephropathy or enteropathy) causing serious interference with intravascular oncotic pressure.[7] In dialysis therapy, the process that caused a decrease in serum albumin levels continued. Increased albumin metabolism (including exogenous expenditure) and changes in the volume of albumin distribution due to an increase in plasma volume mainly occur in peritoneal dialysis. In hemodialysis, it was said that hypoalbuminemia could occur mainly due to decreased albumin synthesis.[5,7] In certain cases, GA levels could be influenced by factors that affect the turnover of albumin. Most patients with advanced nephropathy are accompanied by obvious proteinuria; hence, GA levels can be affected. A study showed a significant decrease in GA values in DM patients with nephrotic syndrome, whereas it did not affect non-nephrotic patients.[11]

The clinical implication of this study was that the GA was better as a glycemic control compared to HbA1c in HD patients with DM so that clinicians should be more vigilant in choosing markers for glycemic control; therefore, they will make more

treatment that is appropriate. If HbA1c was still used for glycemic control in HD patients with DM, the glycemic control was likely to be obtained without showing actual conditions. The limitation of this study was that there was no drug monitoring during the erythropoietin use.

CONCLUSION

There was a significant correlation between HbA1c and GA with r = 0.759 and p = 0.000. GA was a better glycemic control for HD patients with DM.

CONFLICT OF INTEREST

There was no conflict of interest.

ACKNOWLEDGEMENT

The researcher would like to thank to the patients who participated in this study, the Director of the Hospital in East Jakarta and the Prodia Clinical Laboratory who gave permission and a place to conduct this study and assisted with laboratory examinations.

REFERENCES

1. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Diabetes Research and Clinical Practice. 2011;93(3):299–309.
2. International Diabetes Federation. IDF diabetes atlas. 7th ed. Brussels: International Diabetes Federation; 2015.p.50–3.
3. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: A report from an ADA consensus conference. Diabetes Care 2014;37(10):2864–83.
4. Selvin E, Sacks DB. Monitoring glycemic control in end-stage renal disease: What whould be measured? Clinical Chemistry. 2017;63(2):447–9.
5. Sany D, Elshahawy Y, Anwar W. Glycated albumin versus glycated hemoglobin as glycemic indicator in hemodialysis patients with diabetes mellitus: Variables that influence. Saudi Journal of Kidney Diseases and Transplantation. 2013;24(2):260–73.
6. Soelistijo SA, Novida H, Rudijanto A, Soewondo P, Suastika K, Manaf A. Konsensus pengelolaan dan pencegahan diabetes melitus tipe 2 di Indonesia. PB. PERKENI; 2015.
7. Parrinello CM, Selvin E. Beyond HbA1c and glucose: The role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Current Diabetes Reports. 2014;14(11):548.
8. Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker. Endocrine Journal. 2010;57(9):751–62.
9. Inaba M, Okuno S, Kumeda Y, Yamada S, Imanishi Y, Tabata T, et al. Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: Effect of anemia and erythropoietin injection. Journal of American Society of Nephrology. 2007;18(3):896–903.
10. American Diabetes Association. Glycemic targets. Diabetes Care. 2016;39(Suppl.1):S39–46.
11. Kobayashi H, Abe M, Yoshida Y, Suzuki H, Maruyama N, Okada K. Glycated albumin versus glycated hemoglobin as a glycemic indicator in diabetic patients on peritoneal dialysis. International Journal of Molecular Sciences. 2016;17(5):619-25.
12. Speeckaert M, Van Biesen W, Delanghe J, Slingerland R, Wiecek A, Heaf J, et al. Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? Nephrology Dialysis Transplantantion. 2014 ;29(12):2167–77.
13. Tsuruta Y, Ichikawa A, Kikuchi K, Echida Y, Onuki T, Nitta K. Glycated albumin is a better indicator of the glucose excursion than predialysis glucose and hemoglobin A1c in hemodialysis patients. Renal Replacement Therapy. 2016;2(3):1–5.
14. Al-Maskari F, El-Sadig M, Norman JN. The prevalence of macrovascular complications among diabetic patients in the United Arab Emirates. Cardiovascular Diabetology. 2007;6:24.
15. Bador KM, Kamaruddin SKA, Yazid NT.

Brief communication (Original). Correlation of glycated albumin with self blood glucose monitoring in diabetic patients on hemodialysis taking erythropoietin. Asian Biomedicine. 2014;8(3):387–92.
16. Gan T, Liu X, Xu G. Glycated albumin versus HbA1c in the evaluation of glycemic control in patients with diabetes and CKD. Kidney International Reports. 2018;3(3):542–54.
17. El Sayed ZH, Ismail SM, El-hagrasy HA. Glycated albumin as a predictor of glycemic state in type 2 diabetes mellitus with chronic kidney disease. International Journal of Diabetes Research. 2018;7(3):50–6.
18. Koga M, Murai J, Saito H, Kasayama S. Glycated albumin and glycated hemoglobin are influenced differently by endogenous insulin secretion in patients with type 2 diabetes. Diabetes Care. 2010;33(2):270–2.
19. El Okel A, El-Arbagy A, Yassein Y, Khodir S, Kasem HS. Effect of erythropoietin treatment on hemoglobin A1c levels in diabetic patients with chronic kidney disease. Journal of The Egyptian Society of Nephrology and Transplantation. 2019;19(3):86–94.
20. Ng JM, Cooke M, Bhandari S, Atkin SL, Kilpatrick ES. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. Diabetes Care. 2010;33(11):2310–3.
21. Ningrum VDA, Ikawati Z, Sadewa AH, Ikhsan MR. Kontrol glikemik dan prevalensi gagal ginjal kronik pada pasien diabetes melitus tipe 2 di puskesmas wilayah provinsi DIY tahun 2015. Jurnal Farmasi Klinik Indonesia. 2017;6(2):78–90.
22. Shamshirgaran SM, Mamaghanian A, Aliasgarzadeh A, Aiminisani N, Iranparvar-Alamdari M, Ataie J. Age differences in diabetes-related complications and glycemic control. BMC Endocrine Disorders. 2017;17(1):25.