The Proportion of Orthostatic Hypotension and Its Relationship with HbA1c Levels in Elderly Patients with Diabetes

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ABSTRAK

Tujuan: *mendapatkan proporsi hipotensi ortostatik pada pasien diabetes melitus (DM) usia lanjut dan hubungannya dengan kadar HbA1c.* ***Metode:*** *penelitian ini merupakan studi potong lintang terhadap 350 pasien DM usia ≥60 tahun yang berobat di poliklinik Geriatri dan Diabetes RS Cipto Mangunkusumo periode Januari-Maret 2016. Hipotensi ortostatik didefinisikan sebagai penurunan tekanan darah sistolik ≥20 mmHg dan atau tekanan diastolik ≥10 mmHg dalam 3 menit setelah perubahan posisi dari berbaring ke berdiri. Pemeriksaan kadar HbA1c menggunakan alat Nycocard dari Axis Shield. Uji chi square digunakan untuk analisis bivariat dan regresi logsitik digunakan untuk analisis multivariat terhadap variabel perancu.* ***Hasil:*** *proporsi hipotensi ortostatik sebesar 27,4% pada subjek diabetes melitus usia lanjut. Median HbA1c didapatkan lebih tinggi pada subjek dengan hipotensi ortostatik dibandingkan tanpa hipotensi ortostatik (7,6% vs 7,1%; p<0,05). Terdapat hubungan antara kadar HbA1c ≥7,35% dengan kejadian hipotensi ortostatik (OR 1,987, 95%IK 1,2-3,2). Lama DM merupakan variabel perancu dalam penelitian ini.* ***Kesimpulan:*** *hipotensi ortostatik banyak ditemukan pada subjek DM usia lanjut. Terdapat hubungan antara kejadian hipotensi ortostatik dengan peningkatan kadar HbA1c pada pasien diabetes melitus usia lanjut.*

Kata kunci: *diabetes melitus, HbA1c, hipotensi ortostatik, usia lanjut.*

ABSTRACT

Aim: *to obtain information on the proportion of orthostatic hypotension in elderly patients with diabetes and its relationship with HbA1c levels.* ***Methods:*** *this is a cross-sectional study on 350 patients with diabetes mellitus (DM) aged ≥60 years old who sought treatment at outpatient clinic of Geriatry and Diabetes Division at Cipto Mangunkusumo Hospital between January and March 2016. Orthostatic hypotension was defined as a decrease in systolic blood pressure ≥20 mmHg and/or diastolic pressure ≥10 mmHg within 3 minutes after changing position from lying to standing. HbA1c levels was measured using Nycocard from Axis Shield. Chi square test was used for bivariate analysis and logistic regression was used for multivariate analysis against confounding variables.* ***Results:*** *the proportion of orthostatic hypotension in elderly subjects with DM was 27.4%. Median of HbA1c levels was higher in subjects with than without orthostatic hypotension (7.6% vs. 7.1%; p<0.05). There was an association between HbA1c levels of ≥7.35% and the incidence of orthostatic hypotension (OR 1.987, 95% CI 1.2-3.2). The duration of having DM was a confounding variable.* ***Conclusion:*** *orthostatic hypotension is more common in elderly subjects with DM. There is an association between the incidence of orthostatic hypotension and increased HbA1c levels in elderly patients with diabetes mellitus.*

Keywords: *diabetes mellitus, elderly, HbA1c, orthostatic hypotension.*

INTRODUCTION

The number of elderly in Indonesia is increasing with the rising life expectancy. The increased number also escalates the number of chronic degenerative diseases, including diabetes mellitus (DM).[1] The prevalence of DM in elderly patients aged ≥65 years old is approximately 22-33%. DM in elderly is associated with increased DM complications, both acute and chronic.[2] One of DM complications is autonomic neuropathy. Elderly patients have the highest risk for having autonomic dysfunction due to aging process.[3] Orthostatic hypotension is one of the signs of severe autonomic neuropathy.[4] Orthostatic hypotension may occur due to reduced intravascular volume, baroreceptor reflex, inadequate sympathetic and cardiovascular responses which may lead to reduced cardiac output.[3,5] Orthostatic hypotension in elderly patients with DM is associated with increased risks of fall, syncope, cardiovascular events and death.[6,7]

The combination of aging process and DM increases the risk for developing orthostatic hypotension. Several studies have reported that the prevalence of orthostatic hypertension in elderly population with DM is approximately 28–30.5%.[8,9] There are many factors that affect the development of orthostatic hypotension in elderly patients with DM such as age, duration of DM, adequate control of blood sugar levels, hypertension and also other neurological diseases.[10,11] Orthostatic hypotension in diabetic patients has been often associated with poor glycemic control. Several studies have investigated the association between HbA1c levels and the incidence of orthostatic hypotension in diabetic patients. Study conducted by Wu et al[11] in Taiwan found that diabetic patients with uncontrolled HBA1c levels would have increased risk for orthostatic hypotension as much as 1.27 fold.

Another multicenter study in Japan has found a strong negative and significant correlation between increased HbA1c levels and reduced systolic blood pressure in diabetic patients with a correlation coefficient of 0.63.[10] However, a study by Bouhanick et al in France found that in diabetic patients aged more than 70 years old, there was no significant difference of mean HbA1c levels between subjects with orthostatic hypotension and those without orthostatic hypotension.[9]

The limited data on the proportion of orthostatic hypotension in elderly patients with diabetes has become the basis of our research. Previous studies on the association between orthostatic hypotension and HbA1c levels in diabetic patients are also still very limited and the results elicited many controversies. Moreover, by identifying the association between HbA1c levels and the incidence of orthostatic hypotension in elderly patients with DM in Indonesia, we expect that the metabolic control can be adequate, which results in reduced adverse events associated with orthostatic hypotension. This study is aimed to obtain information on the proportion of orthostatic hypotension in elderly patients with diabetes and its relationship with HbA1c levels.

METHODS

The study was conducted using cross-sectional design and consecutive sampling in diabetic patients aged ≥60 years who sought treatment at the outpatient clinic of geriatric and diabetic divisions at Cipto Mangunkusumo Hospital between January and March 2016. Patient who was unable standing for 5 minutes during blood pressure measurement, patients with parkinson diseases, arythmia, cirrhosis, fever, infections or dehydrations, patient with chronic kidney disease that underwent hemodialysis and patients with systolic blood pressure of <90 mmHg or diastolic blood pressure of <60 mmHg while lying down were excluded from the study.

We collected the data by using interview and reviewing medical records. We also measured the patients' blood pressure using Omron digital blood pressure measuring device HBP-1100 which had been calibrated. Orthostatic hypotension was defined as a decrease of systolic BP ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg in 3 minutes after changing of position from lying to standing. The measurement of HbA1c was conducted using Nycocard from Axis Shield at the Clinical Pathology Laboratory in Cipto Mangunkusumo Hospital.

The collected data was analyzed using SPSS version 17.0. The mean difference of HbA1c was analyzed using Mann-Whitney test. The cut-off point for HbA1c was determined using receiver operator curve, which measured the value of AUC (Area Under the Curve). Data of HbA1c levels was categorized according to the cut-off value and we subsequently tried to find its correlation with the incidence of orthostatic hypotension using chi-square test and incorporated the 95% confidence interval and p value. We conducted bivariate analysis with the confounding variable and found that the $p < 0.25$. It was then continued with multivariate analysis and logistic regression. Ethical clearance was given by the Committee for Medical Research Ethics in Faculty of Medicine, University of Indonesia (119/UN2.F1/ETIK/2015).

RESULTS

Of 350 subjects participating in our study, the majority was female (57.1%). Most subjects (42.9%) had experienced DM for more than 10 years and were obese according to the BMI category (42%). The median age was 69 years with a range of 60-90 years. Regarding the medication used for treating their diabetes, 65.1% subjects had taken oral hypoglycemic agent. The most common complications were hypertension, which reached 84.6% of all subjects. Median HbA1c levels was 7.2% of all subjects with a range of 4.5%-14.3%. Orthostatic hypotension was found in 27.4% cases of all subjects. Subject characteristics of subjects with and without orthostatic hypotension are presented in **Table 1**.

The median HbA1c levels in the diabetic elderly patients with orthostatic hypotension was 7.6% with a range between 5.3 and 14.1%. Median HbA1c levels in subjects without orthostatic hypotension was 7.1% with a range of 4.5-14.3%. Therefore, the analysis indicated that there was a significant difference regarding the HbA1c levels in diabetic elderly patients between those with orthostatic hypotension and without orthostatic hypotension (p=0.005).

HbA1c levels then were categorized according to the cut-off value using AUC, which was statistically recommended (7.35%). The AUC was 59.8% (95%CI: 53%-66.5%; p=0.005) with sensitivity and specificity of 58.3% and 58.7%, respectively. Bivariate analysis was performed on the confounding variables, which can be seen in **Table 2**.

Variables with $p < 0.25$ in bivariate analysis were subsequently included in the multivariate analysis. The changes on adjusted odds ratio in the HbA1c group for each additional confouncing

Table 1. Characteristics of subjects with and without orthostatic hypotension

Variables	With orthostatic hypotension (n=96)	Without orthostatic hypotension (n=254)
Sex (male), n (%)	44 (29.3)	106 (70.7)
Age (years), median (range)	68 (60-85)	70 (60-90)
Diabetes duration, n (%)		
- ≤5 years	22 (18.5)	97 (81.5)
- 6-10 years	20 (24.7)	61 (75.3)
- >10 years	54 (36)	96 (64)
HbA1c level, n (%)		
- <6.5%	18 (20.9)	68 (79.1)
- 6.5% - <7.5%	25 (22.5)	86 (77.5)
- 7.5% - <8.5%	21 (32.3)	44 (67.7)
- 8.5% - <10%	19 (30.6)	43 (69.4)
- ≥10%	13 (50)	13 (50)
Supine SBP (mmHg), median (range)	151 (110-223)	141 (85-194)
Supine DBP (mmHg), median (range)	75 (52-107)	71 (48-101)
Supine HR (beats/min), median (range)	78 (54-109)	74 (50-106)
Standing SBP (mmHg), median (range)		
- 1 min	126 (85-205)	139 (96-200)
- 3 min	133 (82-209)	141 (101-193)
Standing DBP (mmHg), median (range)		
- 1 min	70 (45-116)	75 (51-131)
- 3 min	72 (51-109)	76 (52-129)
Standing HR (beats/min), median (range)	83 (56-120)	78 (51-120)
Symptoms, n (%)		
- Dizziness (n=24)	6 (25)	18 (75)
- Lightheadedness (n=3)	2 (66.7)	1 (33.3)
- Weakness (n=2)	1 (50)	1 (50)
Fall in past year, n (%)	13 (27.7)	34 (72.3)

SBP: Sistolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate

Table 2. Bivariate analysis of HbA1c levels and confounding variables of subjects with orthostatic hypotension

Variables	P value	OR (95% CI)
HbA1c	0.004	1.987 (1.234 - 3.199)
Age	0.107	0.678 (0.422 - 1.089)
Diabetes therapy	0.028	1.730 (1.059 - 2.824)
Diabetes duration	0.002	2.116 (1.314 - 3.407)
Hypertension	0.788	1.095 (0.566 - 2.118)
Stroke	0.592	0.797 (0.348 - 1.828)
Chronic kidney disease	0.052	1.593 (0.994 - 2.555)

Table 3. Multivariate analysis of HbA1c levels and confounding variables in subjects with orthostatic hypotension

Variables	OR (95% CI)	% change OR
Crude OR	1.987 (1.2-3.2)	
Adjusted OR		
- Diabetes duration	1.713 (1.1-2.8)	13.7%
- Diabetes treatment	1.574 (0.9-2.7)	0.81%
- Age	1.514 (0.9-2.6)	3.81%
- Chronic kidney Disease	1.557 (0.9-2.6)	2.84%

variable were carried out gradually from the smallest p-values as can be seen in **Table 3**.

DISCUSSION

The cross-sectional study was conducted in 350 elderly patients with diabetes. About 57.1% of all subjects are female. The RISKESDAS (National Basic Health Research) in 2013 suggests that the prevalence of DM is higher in female compared to male patients (7.7% vs 5.6%).[12] It is because there is higher proportion of female patients among the elderly and a longer life expectancy in females compared to males.[1]

The median age was 69 years with a range of 60-90 years. The majority of age group that participated in our study was those aged 60-69 years old. There was no significant difference between age and orthostatic hypotension. Such results are similar to the findings demonstrated by Decoda study, which is a study of 11 cohort studies in Asia. The study found that DM prevalence in India increases with age. The peak incidence is found in subjects aged 60-69 years old and it is decreased after 70 years of age. In Japan and China, the highest prevalence of DM is found in 70-90 years age group. It may be due to the very high life expectancy rate in those countries.[13]

Most subjects with orthostatic hypotension have experienced diabetes for more than 10 years. Patients without orthostatic hypotension usually have shorter duration of DM, i.e. less than 5 years. Tsutsu et al found that the highest prevalence of orthostatic hypotension can be found in those with DM duration of more than 10 years.[10] Previous studies have demonstrated evidence that there is a correlation between the duration of hyperglycemia and the development of DM neuropathy and it can explain why patients with orthostatic hypotension tend to have a longer duration of DM.[14]

Subjects with orthostatic hypotension usually have higher mean systolic and diastolic blood pressure during supine position compared to those without orthostatic hypotension. The high levels of blood pressure while lying may have a correlation with reduced blood pressure during standing posture. Inelastic artery may cause a defect in baroreceptor reflex in the carotid and aorta to maintain blood pressure during orthostatic stress.[9]

The decrease of systolic and diastolic blood pressure in subject with orthostatic hypotension can be found larger in the first minute of the posture changing compared to the third minute. This phenomenon can be explained as there is a delay of cathecolamine release in subjects with orthostatic hypotension when they change their position.[15]

Subjects with orthostatic hypotension had higher mean heart rate during supine position compared to those without orthostatic hypotension. It may be caused by parasympathetic neuropathy.[16] The changes in position may cause inhibition of parasympathetic activity and increase the cardiovascular adrenergic response. Moreover, the acceleration of cardiovascular response is not adequate to maintain normal blood pressure when the subjects back to their standing position.[9,17]

Our study found that the proportion of orthostatic hypotension in elderly patients with diabetes was 27.4%. The proportion is higher compared to the findings from previous study,

which was conducted by Rahayu et al[18] The previous study found that the prevalence of orthostatic hypotension among elderly patients who are older than 60 years is 15.5%. The different result may be found since the study did not have specific subjects, i.e. patients with diabetes. Another study, which was conducted in Netherlands, found that the prevalence of orthostatic hypotension in elderly patients aged more than 70 years is 28%.[8] Many factors can affect the prevalence rate in the study, including sociodemographic status, study populations, the subjects' age, diagnosis criteria, the duration of DM, and whether the patients had an adequate control of blood glucose. Moreover, many patients that may have orthostatic hypotension may be excluded. Thus, the end prevalence of orthostatic hypotension may not illustrate the true proportion of those patients.

The median HbA1c levels in our study was 7.2% with a range of 4.5-14.3%. Our result is lower than two previous studies that were conducted in Indonesia, in which the mean HbA1c levels is 8.3% (SD 2.2) and 8.1%, respectively.[19] The difference can be explained as the subjects in our study were mainly diabetic elderly patients with a high proportion of chronic kidney disease, which may also affect the HbA1c levels.

The diabetic elderly subjects with orthostatic hypotension had median HbA1c levels, which was significantly higher compared to those without orthostatic hypotension. Two previous studies in Japan and China also found that HbA1c levels is significantly higher in diabetic subject with orthostatic hypotension compared to those without orthostatic hypotension.[10,17] Poor glycemic control as shown by high HbA1c levels actually can affect vascular elasticity and it can lead to reduced extravascular volume due to osmotic dieresis, which eventually induces orthostatic hypotension.[20]

The bivariate analysis demonstrated that there was a significant association between HbA1c levels and orthostatic hypotension (p=0.004). Diabetic elderly patients with HbA1c levels of more than 7.35% had 1.987 fold of greater risk to have orthostatic hypotension compared to those with HbA1c levels lower than 7.35% (CI 95%, 1.234-3.199). These findings are similar to the results found by Tsutsu et al[10] in Japan that found median HbA1c levels of 9.7% in cut-off value and they also found an independent association between HbA1c levels and orthostatic hypotension after an adjustment with many confounding variables ($p<0.025$); however, the study does not have specific target on elderly patients.

Poor glycemic control may modulate many biochemical pathway activities such as oxidative stress, aldose-reductase activity, polyol activity and reduced myo-inositol content that may cause decreased vasodilatation leading to diminishing blood flow in nerve fibers. There is also autonomic denervation that occurs simultaneously with endothelial dysfunction, reduced neuropeptide responses, volume depletion caused by nephropathy and osmotic dieresis, which may induce the development of orthostatic hypotension.[3,5,21-23]

Several confounding variables that may affect the association between HbA1c levels and orthostatic hypotension are age, insulin treatment, duration of diabetes, hypertension, stroke and chronic kidney disease.

The bivariate analysis showed that the age did not have any association with orthostatic hypotension (p=0.107; 95% CI 0.422-1.089). Wu et al found a correlation between age and orthostatic hypotension in their control group; however, they did not find similar correlation in subjects with type 2 diabetes. It may be caused by the high mortality rate in geriatric subjects with DM who had orthostatic hypotension.[11]

Insulin therapy had an association with the incidence of orthostatic hypotension (p=0.028; 95% CI 1.059-2.824). Tsusu et al[10] also found a significant correlation between diabetes treatment and orthostatic hypotension; however there were no significant difference of mean insulin doses between subjects with and without orthostatic hypotension. Insulin may decrease adrenergic response that may subsequently cause vasodilation and reduced chronotrophic response.[24]

Our study found that the DM duration of more than 10 years is an important confounding variable for HbA1c levels with the incidence of orthostatic hypotension. After performing an adjustment with the duration of DM, we found

adjusted OR for HbA1c was 1.713 (95% CI 1.0-2.8). A prospective cohort in Sweden also found a significant correlation between DM duration and the increased risk of orthostatic hypotension; particularly in type 2 DM patients with diastolic hypotension.[14] Prolonged hyperglycemia may reduce the number of nerve growth factor, which eventually causes damage to myelin sheath and nerve fibers.[22]

The duration of DM was also correlated with HbA1c levels. Verma et al[25] have also found a significant correlation between HbA1c levels and DM duration. It may be caused by increased insulin resistance, which is consistent with longer DM duration.[25]

Our study showed that the history of hypertension did not have a strong association with the incidence of orthostatic hypotension. Controlled blood pressure due to treatment using antihypertensive agents can reduce the incidence of orthostatic hypotension in subjects with hypertension.[26] In our study, although the proportion of hypertension was similar between subjects with and without orthostatic hypotension, but subjects with orthostatic hypotension has higher mean systolic and diastolic blood pressure compared to those without orthostatic hypotension. The high levels of blood pressure in supine position is an important predictor of the incidence of orthostatic hypotension.[9]

Our study also did not find any association between the incidence of stroke and orthostatic hypotension. Our findings are similar with the results of Cardiovascular Health Study that also found no significant association between stroke and orthostatic hypotension. It may be due to the high mortality rate of stroke in patients with orthostatic hypotension.[17]

Chronic kidney disease was not a confounding variable in our study. Subjects with chronic kidney disease stage 3 to 5 had lower HbA1c levels compared to those in the control group; particularly when the HbA1c levels was lower than 7.5%. It may be related with the shortened life cycle of red blood cells, uremic conditions, reduced erythropoietin (EPO) and Fe supplementation or transfusion.[27] Moreover, Aso et al also found that patients with orthostatic hypotension usually has lower kidney function.[28] Reduced glomerular filtration (non-dipper) due to autonomic neuropathy may cause kidney becomes more susceptible to hemodynamic changes.[16]

The advantage of our study is that it identifies the high proportion of orthostatic hypotension among elderly patients with diabetes in Cipto Mangunkusumo Hospital, Jakarta. The high proportion may illustrate the full extent of the problem among patients. Our study also found significant mean differences in diabetic elderly patients between those with and without orthostatic hypotension. These findings may be used as a guideline for better glycemic control. Moreover, our study has also considered many confounding variables; therefore the association between HbA1c levels and orthostatic hypotension can be considered as an independent association.

The limitation of our study is the design of study, which was cross sectional. Therefore, we could not determine whether HbA1c levels is a predisposing factors for the development of orthostatic hypotension. HbA1c levels can only be used to evaluate whether the patients has a good control on their diabetes in the last 3 months and it cannot illustrate the long-term glycemic control that may affect the progressiveness of autonomic neuropathy. Moreover, the data about DM duration, comorbidities and history of fall were obtained from medical interview and medical records instead of direct measurement; therefore, it may not illustrate the real condition of the patients.

CONCLUSION

Orthostatic hypotension is commonly found in elderly patients with diabetes at Cipto Mangunkusumo Hospital, Jakarta; therefore, blood pressure measurement should be performed both with patients in lying and standing position to detect orthostatic hypotension. It should be a routine measurement for all elderly patients with diabetes, especially those who have HbA1c levels higher than 7.35% and DM duration longer than 10 years.

There is an association between the incidence of orthostatic hypotension and increased HbA1c levels in elderly patients with diabetes. To confirm the cause and effect relationships, we recommend further prospective cohort studies,

which evaluate the serial HbA1c levels over particular period of time. Moreover, further population-based studies are also necessary so that the findings can be generalized for all elderly patients with diabetes in Indonesia.

REFERENCES

1. Manullang EV. Gambaran kesehatan lanjut usia di Indonesia. Pusat Data Informasi Kemenkes RI. 2013;1:1-18.
2. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diab care. 2012;35(12):2650-64.
3. Winkler AS, Bosman DR. Symptomatic postural hypotension in diabetes: aetiology and management. Pract Diab Int. 2003;20(6):219-25.
4. Spallone V, Ziegler D, Freeman R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diab Metabolism Res Rev. 2011;27(7):639-53.
5. Purewal TS, Watkins PJ. Postural hypotension in diabetic autonomic neuropathy: a review. Diab Med. 1995;12(3):192-200.
6. Azidah AK, Hasniza H, Zunaina E. Prevalence of falls and its associated factors among elderly diabetes in a tertiary center, Malaysia. Curr Gerontol Geriatrics Res. 2012;2012:539073.
7. Angelousi A, Girerd N, Benetos A, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. J Hyperten. 2014;32(8):1562-71.
8. van Hateren KJ, Kleefstra N, Blanker MH, et al. Orthostatic hypotension, diabetes, and falling in older patients: a cross-sectional study. Brit J General Pract. 2012;62(603):e696-702.
9. Bouhanick B, Meliani S, Doucet J, et al. Orthostatic hypotension is associated with more severe hypertension in elderly autonomous diabetic patients from the French Gerodiab study at inclusion. Annal de Cardiol et d'angeiol. 2014;63(3):176-82.
10. Tsutsu N, Nunoi K, Yokomizo Y, Kikuchi M, Fujishima M. Relationship between glycemic control and orthostatic hypotension in type 2 diabetes mellitus--a survey by the Fukuoka Diabetes Clinic Group. Diab Res Clin Pract. 1990;8(2):115-23.
11. Wu JS, Yang YC, Lu FH, Wu CH, Wang RH, Chang CJ. Population-based study on the prevalence and risk factors of orthostatic hypotension in subjects with pre-diabetes and diabetes. Diab Care. 2009;32(1):69-74.
12. Situasi dan Analisis Diabetes [Internet]. Pusat Data dan Informasi Kementrian Kesehatan Republik Indonesia. 2014 [cited 15 Mei 2016]. Available from: http://www.depkes.go.id/article/view/15021800007/situasi-dan-analisis-diabetes.html.
13. Qiao Q, Hu G, Tuomilehto J, et al. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diab Care. 2003;26(6):1770-80.
14. de Kanter M, Lilja B, Elmstahl S, Eriksson KF, Sundkvist G. A prospective study of orthostatic blood pressure in diabetic patients. Clin Autonomic Res. 1998;8(4):189-93.
15. Senard JM, Barbe P, Estan L, et al. Decreased high affinity state in platelet alpha 2-adrenoceptors from diabetic patients with orthostatic hypotension. J Clin Endocrinol Metabolism. 1990;71(2):311-7.
16. Kempler P, Tesfaye S, Chaturvedi N, et al. Autonomic neuropathy is associated with increased cardiovascular risk factors: the EURODIAB IDDM Complications Study. Diab Med. 2002;19(11):900-9.
17. Wu JS, Lu FH, Yang YC, Chang CJ. Postural hypotension and postural dizziness in patients with non-insulin-dependent diabetes. Arch Intern Med. 1999;159(12):1350-6.
18. Rahayu S. Prevalensi dan sebaran faktor risiko hipotensi ortostatik pada pasien usia lanjut di RS DR Cipto Mangunkusumo Jakarta. Jakarta: Universitas Indonesia; 2005.
19. Soewondo P. Current practice in the management of type 2 diabetes in Indonesia: Results from the International Diabetes Management Practices Study (IDMPS). J Indon Med Assoc. 2011;61:474-81.
20. Doelman CJ, Oude Elberink JN, Miedema K, Bilo HJ. Orthostatic hypotension in poorly regulated NIDDM. Diab Care. 1996;19(5):542.
21. Verrotti A, Prezioso G, Scattoni R, Chiarelli F. Autonomic neuropathy in diabetes mellitus. Frontiers Endocrinol. 2014;5.
22. Fleischer J. Diabetic autonomic imbalance and glycemic variability. J Diab Sci Tech. 2012;6(5):1207-15.
23. Iovino M, Triggiani V, Licchelli B, et al. Vasopressin release induced by hypothension is blunted in patients with diabetic autonomic neuropathy. Immunopharmacol Immunotoxicol. 2011;33(1):224-6.
24. Madden KM, Tedder G, Lockhart C, Meneilly GS. Euglycemic hyperinsulinemia alters the response to orthostatic stress in older adults with type 2 diabetes. Diab Care. 2008;31(11):2203-8.
25. Verma M, Paneri S, Badi P, Raman PG. Effect of increasing duration of diabetes mellitus type 2 on glycated hemoglobin and insulin sensitivity. Indian J Clin Biochem. 2006;21(1):142-6.
26. Di Stefano C, Milazzo V, Totaro S, et al. Orthostatic hypotension in a cohort of hypertensive patients referring to a hypertension clinic. J Human Hyperten. 2015;29(10):599-603.
27. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update. Am J Kidney Dis. 2012;60(5):850-86.
28. Aso Y, Wakabayashi S, Terasawa T, et al. Elevation of serum high molecular weight adiponectin in patients with type 2 diabetes and orthostatic hypotension: association with arterial stiffness and hypercoagulability. Diab Med. 2012;29(1):80-7.