www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2016; 5(9): 08-12

www.thepharmajournal.com
Received: 03-07-2016
Accepted: 04-08-2016

NV Altunina
O.O. Bogomolets National Medical University, Kyiv, Ukraine

VG Lizogub
O.O. Bogomolets National Medical University, Kyiv, Ukraine

AN Bondarchuk
O.O. Bogomolets National Medical University, Kyiv, Ukraine

Correspondence
NV Altunina
O.O. Bogomolets National Medical University, Kyiv, Ukraine

Changes of daily profile of blood pressure with application of alpha-lipoic acid and zinc sulfate in patients with type 2 diabetes mellitus who have had myocardial infarction

NV Altunina, VG Lizogub and AN Bondarchuk

Abstract
The article presents the dynamics of parameters of 24-hour ambulatory blood pressure monitoring of 49 postinfarction patients with type 2 diabetes mellitus (DM) under the influence of 4-month combined treatment of alpha-lipoic acid (ALA) with zinc (Zn) sulfate. Treatment showed a significant decreasing in systolic BP (SBP) and diastolic BP (DBP) morning rise (p<0, 05) and mean daily and nighttime DBP variability (p<0, 05). Besides, it is recorded a positive downward trend in the level of mean daily and night-time SBP and DBP, mean daytime DBP, SBP variability in all time intervals and the DBP daytime variability. After the applied treatment it was the redistribution of patients by type of BP daily profile with the decrease of the contribution of "night-peakers" – 12, 2% on SBP and 14, 3% on DBP. Thus, the 4-month use of ALA and Zn sulfate in the complex treatment of patients with type 2 DM who had myocardial infarction, causes a decrease in BP morning rise, daily and nighttime DBP variability and improves daily profiles of SBP and DBP.

Keywords: Daily blood pressure profile, type 2 diabetes mellitus, non-Q-myocardial infarction, alpha-lipoic acid, zinc sulfate

1. Introduction
Cardiovascular pathology is the main reason of death among patients with type 2 diabetes mellitus (DM). The important factor that increases cardiovascular morbidity and mortality in diabetic patients is the presence of high blood pressure (BP). The MRFIT study [1], which included about 5 thousand patients with DM, showed that arterial hypertension (AH) is associated with a 2-3-fold increase in the absolute risk of cardiovascular mortality in patients with type 2 DM compared with patients without diabetes. It is supposed that about 75% of deaths from cardiovascular complications in DM are connected with high BP [2]. Thus, the control of BP in type 2 DM may have decisive importance for improvement of prognosis of these patients. The prevalence of AH among patients with type 2 DM are significantly higher comparing with the general population [3-5]. Increase of BP in diabetic patients is caused by oxidative stress, endothelial dysfunction, insulin resistance, athero-inflammatory state. Since the efficiency of standard antihypertensive treatment under the condition of impaired glucose metabolism is lower and, regretfully, target BP is achieved only in 20-25% of all patients, it is important to considerate the pathophysiology of AH in type 2 DM [6, 7]. Taking into consideration the above, it is of interest to investigate the possibilities of recognized antioxidants with additional pleiotropic effects – alpha lipoic acid (ALA) and zinc (Zn) sulfate. Existing experimental [8-13] and clinical [14-19] data concerning the antihypertensive effects of these drugs by their individual use is controversial.
The purpose of the study is to investigate 24-hour ambulatory blood pressure monitoring (ABPM) data changes in patients with type 2 DM who have had non-Q-myocardial infarction (non-Q-MI) under the influence of ALA and Zn sulfate.

2. Materials and methods
49 patients were examined (32 men and 17 women, mean age 60,97 ± 1,59 years) with type 2 DM who have had non-Q-MI. The patients' baseline characteristics are summarized in Table 1.

Table 1: Baseline characteristics of the studied patients (M±m).

Characteristics		Studied patients (n=49)
Age, M±m years		60,97±1,59
Sex: (n, %)	Male	32 (65,3%)
	Female	17 (34,7%)
Time after non-Q-MI, M±m years		5,01±0,49
DM duration, M±m years		8,96±0,61
HbA1c, %		8,23±0,26
HOMA-IR		7,29±0,78
Grade 1-2 hypertension (n, %)		37 (75,5%)
Office SBP, M±m mm Hg		142,13±2,15
Office DBP, M±m mm Hg		88,02±2,01

SBP – systolic BP, DBP – diastolic BP.

This study was approved by the Ethics Committee of the O.O. Bogomolets National Medical University. Patients signed an informed consent form before inclusion.

Patients were included in the study if they met the following criteria: 1) type 2 DM in the stages of compensation / subcompensation treated with oral antidiabetic drugs; 2) history of non-Q-MI; 3) signed informed consent for participation in the study.

Patients were excluded from the study according to the following criteria: 1) the patient has type 1 DM; 2) DM decompensation; 3) congenital and acquired heart defects; 4) atrial fibrillation / flutter; 5) secondary AH; 6) heart failure (NYHA class III-IV); 7) liver and kidney diseases.

At the time of the study, the patients received basic therapy: ACE inhibitor, β-blocker, statin, antiaggregant, oral hypoglycemic therapy. For the basic treatment of patients it was added ALA 600mg/day and Zn sulphate 248mg/day (correspond to 90mg Zn ions). The duration of treatment and monitoring of patients was 4 months.

All participants before taking ALA with Zn sulfate and at the end of the treatment underwent ABPM with a portable automatic device "VAT41-2" (Ukraine, 2010). ABPM was conducted ambulatory in the free movement regime of the patient.

SBP, DBP and heart rate (HR) were measured every 15 minutes during the day (7a.m. to 10p.m.) and every 30 minutes at night (10p.m. to 7a.m.). With the help of results processing program it was analyzed the following parameters: mean daily SBP ($SBP_{24\text{-}h}$), daytime SBP (SBP_d), nighttime SBP (SBP_n); daily DBP ($DBP_{24\text{-}h}$), daytime DBP (DBP_d), nighttime DBP (DBP_n); daily HR ($HR_{24\text{-}h}$), daytime HR (HR_d) and nighttime HR (HR_n). BP variability (BPV) for a given time interval was estimated by standard deviations from the respective mean BP separately for daily, day and night periods (respectively $SBPV_{24\text{-}h}$, $DBPV_{24\text{-}h}$, $SBPV_d$, $DBPV_d$, $SBPV_n$, $DBPV_n$).

The proportion of increased BP was evaluated by the time index (TI) of hypertension, which was defined as the percentage of BP measurements exceeding the threshold BP values for each of the periods of the day. The value of the morning rise in BP (MR SBP, MR DBP) was analyzed. MR was evaluated as the difference between the maximum and minimum value of BP in the period from 4a.m. to 10a.m.

The degree of night-time reduction in BP compared with daytime was determined by the value of the daily index (DI). DI SBP and DI DBP were calculated using the formulas: DI SBP = (SBP_d-SBP_n) / SBP_d *100%, DI DBP = (DBP_d-DBP_n) / DBP_d *100%. The patients were defined as „dippers" (DI = 10-20%), „non-dippers"(DI = 0-10%) and „night-peakers" (DI has a negative value, night-time BP levels higher than daytime).

Statistical processing of the study results was conducted using parametric methods. The accuracy of differences in comparing mean values before and after treatment was determined using Student's *t*-test. Value of $p<0,05$ was considered to be significant. The value of studied parameters are presented as M±m, where m – arithmetic mean value, m – standard error. Statistical analysis was performed by Statistics Package for Social Science (SPSS version 13.0, SPSS Inc., USA).

3. Results

The use of ALA and Zn sulfate for 4 months in patients with type 2 DM who had non-Q-MI, causes a decrease in SBP and DBP morning rise ($p<0,05$), mean daily and nighttime DBP variability ($p<0,05$).

The character of changes of the main parameters of ABPM in the examined patients on the background of the applied treatment is presented in table 2.

Table 2: ABPM parameters in the studied patients before and after treatment (M±m).

ABPM parameters		Studied patients (n=49)	
		1	2
Mean daily parameters	SBP, mm Hg	133,71±2,18	130,90±1,75
	SBPV, mm Hg	16,93±0,63	15,56±0,50
	TI SBP, %	47,62±4,57	42,61±4,38
	DI SBP, %	3,82±1,19	5,01±0,79
	MR SBP, mm Hg	52,6±2,77	44,20±3,14*
	DBP, mm Hg	79,76±1,64	76,26±1,42
	DBPV, mm Hg	13,96±0,52	12,42±0,46*
	TI DBP, %	30,03±4,44	23,65±4,49
	DI DBP, %	5,50±1,23	7,03±0,85
	MR DBP, mm Hg	46,28±3,01	37,00±2,79*
	HR/min	70,19±1,53	69,01±1,53
Mean daytime parameters	SBP, mm Hg	135,33±2,33	132,92±1,70
	SBPV, mm Hg	16,36±0,66	15,48±0,54
	TI SBP, %	37,32±5,13	33,15±4,11
	DBP, mm Hg	81,35±1,77	78,50±1,59
	DBPV, mm Hg	13,74±0,63	12,49±0,56
	TI DBP, %	27,72±4,80	20,91±4,32
	HR/min	72,45±1,64	71,02±1,72
Mean nighttime parameters	SBP, mm Hg	129,92±2,19	126,29±1,98
	SBPV, mm Hg	15,83±0,93	14,54±0,76
	TI SBP, %	65,59±5,52	59,75±6,05
	DBP, mm Hg	76,66±1,55	72,86±1,33
	DBPV, mm Hg	12,49±0,56	10,98±0,42*
	TI DBP, %	34,65±4,84	27,40±4,98
	HR/min	64,49±1,55	63,41±1,30

1 - before treatment, 2 - after 4 months of treatment; * – $p<0,05$ compared with data before treatment.

In addition to the above changes, it is also recorded a positive downward trend in the level of mean daily and nighttime SBP ($p<0,2$) and DBP ($p<0,1$), the mean daytime DBP ($p<0,2$), variability of the SBP in all the time intervals – $SBPV_{24\text{-}h}$ ($p<0,1$), $SBPV_d$ ($p<0,2$) and $SBPV_n$ ($p<0,1$), and the daytime variability of DBP ($p<0,2$). Furthermore, it was noted the decrease of the time load of DBP – TI $DBP_{24\text{-}h}$, TI DBP_d and TI DBP_n ($p<0,2$). Dynamics in DBP parameters affected the degree of its night reduction, raising DI DBP ($p<0,2$).

Despite the fact that DI SBP and DI DBP in the treatment by ALA with Zn sulfate have not reached significant changes, under the influence of therapy there was a redistribution of patients by type of diurnal profile of SBP and DBP. Thus, by the value of DI SBP before treatment 4 patients (8,2%) had normal levels of night decrease SBP – "dippers", 35 (71,4%) were characterized by lack of nocturnal decline of SBP – "non-dippers" and 10 patients (20,4%) with nocturnal hypertension

were related to "night-peakers". After treatment it was observed an increase in "dippers" and "non-dippers" by 6,1% (p>0,2) and the reduction of "night-peakers" by 12,2% (p<0,1) (Figure 1).

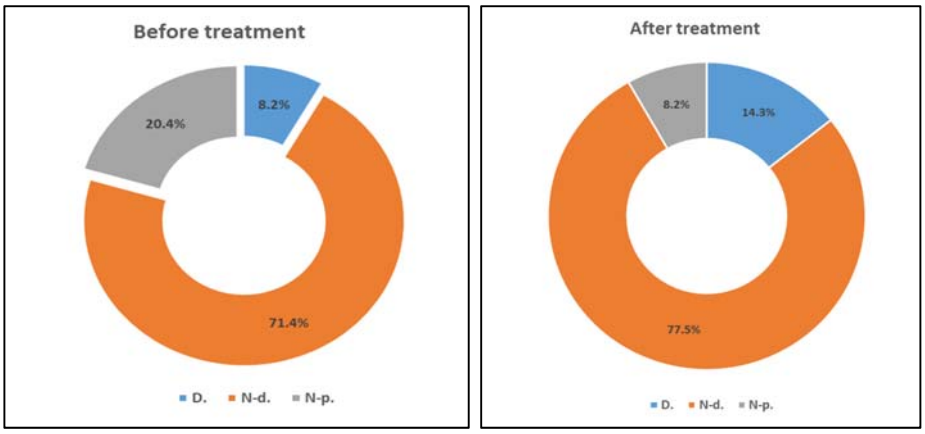

Fig 1: The distribution of patients by type of diurnal profile of the SBP – "dippers", N-d – "non-dippers", N-p – "night-peakers".

By the value of DI DBP among patients before treatment "non-dippers" prevailed – 28 persons (57, 1%), 12 patients (24,5%) belonged to the type "dippers", and 9 patients (18,4%) to "night-peakers". After applied treatment it was observed an increase in "dippers" by 12,2% (p<0,2), reduction of "night-peakers" – 14,3% (p<0,05), with almost unchanged number of "non-dippers" (Figure 2).

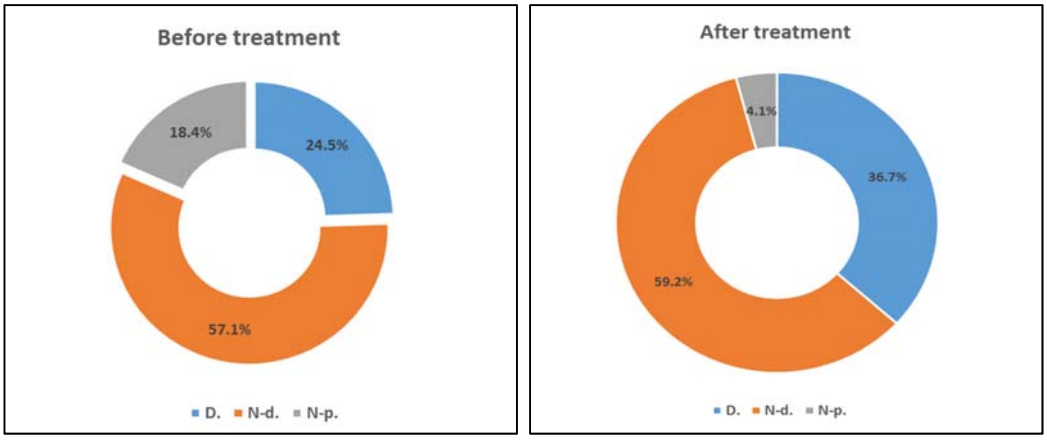

Fig 2: The distribution of patients by type of diurnal profile of the DBP: D – "dippers", N-d – "non-dippers", N-p – "night-peakers".

4. Discussion

So, according to the study, it is defined that 4-month application of ALA and Zn sulfate as an additional complex to basic treatment of patients with type 2 DM who had non-Q-MI, determines the decrease in MR SBP and MR DBP, mean daily and nighttime DBP variability and has a positive effect on diurnal profiles of SBP and DBP. The level and degree of loading by DBP at all time periods, the level of mean daily and nighttime SBP and its variability in our study had only a tendency to decrease.

Literature data analysis has shown the absence of similar experimental and clinical studies, therefore, we have analyzed existing information regarding the effect of ALA and Zn on the BP parameters with their separate application.

Some experimental studies have demonstrated the antihypertensive potential of ALA in diabetic rats [8] and various models of hypertensive rats, including spontaneously hypertensive rats [20], uninephrectomized deoxycorticosterone acetate-salt hypertensive rats [9], renovascular hypertensive rats [10] fructose-loaded [21] and salt-loaded rats [22-24]. In other works it was shown that the use of ALA prevents the development of dexamethasone-induced[25] and glucose-induced[26] hypertension in rats.

In human studies the use of ALA as a hypotensive agent presented conflicting results showing improvement or no effect [14-17, 27]. So, Rahman ST. and co-invest. [15] showed that adding of 600mg ALA up to 40mg quinapril for 8 weeks in diabetic patients with stage I hypertension significantly enhances the positive effects on endothelial function and proteinuria, but it doesn't have additional influence on the BP. In the work of Huang YD. [27] it wasn't also obtained the effect of ALA in a dose 1200mg/day used for 8 weeks on BP parameters in patients with obesity. In the ISLAND study [14] it was compared the effect of irbesartan 150 mg/day and ALA 300 mg/day on endothelial dysfunction in patients with metabolic syndrome. After a 4-week treatment it was defined a significant increase in endothelium-dependent vasodilation, however there was no significant hypotensive effect of ALA. The data of the above studies coincides with the results of our work. In our study, it was not obtained significant effect of the combination of ALA with Zn sulfate on mean BP values in all time intervals, although it was observed a decrease in the magnitude of the morning rise in BP, but this parameter was not analyzed in presented works. In contrast to the results of the presented

researches, in McMackin CJ. And co-invest. Work [17] it's shown that the combined use of 400 mg of ALA per day and acetyl-L-carnitine at a dose of 1000 mg per day for 8 weeks in patients with CHD significantly reduces BP in the subgroup of patients with hypertension and metabolic syndrome. The results of N. Noori and co-invest. [16] Study also indicate a decrease in BP under the effect of the combined intake of 800mg of ALA and 80 mg of pyridoxine for 12 weeks in patients with diabetic nephropathy.

Presented clinical studies don't help to assess the therapeutic effect of ALA against BP, because the cohort of examined patients had various nosology, different doses and duration of treatment were used, in most studies patients received combined therapy, although experimental evidence base demonstrate absolute antihypertensive potential of this substance.

As for Zn, the results of a small base of existing studies are contradictory. For example, in the Muhammad SA. And co-invest. [11] Work it's shown that the application of Zn in salt-loaded hypertensive rats causes a decrease in SBP by 7, 73%, Adeniyi OS. And co-invest. [28] Indicate the prevention of development of hypertension in salt-loaded rats when adding Zn. In another study [12] it is found that taking of indapamide in spontaneously hypertensive rats significantly reduced serum concentration of Zn and copper, and their addition to the treatment not only restores mineral homeostasis, but also leads to a decrease in SBP and DBP. While Yanagisawa H. and co-invest. [13] Demonstrated that excessive intake of Zn by rats' leads to increase of BP and stimulates oxidative stress.

In clinical study of Farvid MS. and co-invest. [29] Using vitamin-mineral complexes in patients with type 2 DM, that included 30mg of Zn, magnesium, vitamins C and E for 3 months, recorded a decrease in BP, however the separate application of minerals didn't lead to significant changes in BP. It was not obtained significant effect of 30mg Zn on the BP parameters in diabetic patients in the study of Parham M. [18]. In our work there were no significant changes in BP that also coincides with the above studies. Another work [19] with the use of 660мг Zn in patients with type 2 DM for 6 weeks in contrast to the presented study indicates a significant decrease in BP.

Thus, the analysis of works concerning the antihypertensive effect of Zn, show dose-dependent of this effect. A small experimental and clinical base, contradictory results, use of Zn in combination with other drugs don't help to clearly evaluate the possibility of Zn on lowering BP in its separate application. Our clinical study improves understanding of the impact of the combination of ALA with Zn sulfate on the BP parameters in patients with type 2 DM who had non-Q-MI. The use of ABPM helped to define that in the absence of effect on BP conventional parameters, changes in MR, variability and diurnal profile of BP are taking place, which is significant in the prognosis of such patients. Therefore, applied combination has impact on BP, which can have additional increase of effect of basic therapy in patients with type 2 DM with prior MI.

5. Conclusion

The use of ALA and Zn sulfate for 4 months in patients with type 2 DM who had non-Q-MI, causes a decrease in BP morning rise, daily and nighttime DBP variability and improves daily profiles of SBP and DBP.

6. References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D. for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors, and 12year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993; 16:434-444.
2. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. Hypertension. 2001; 37:1053-1059.
3. Sowers JR. Diabetes mellitus and vascular disease. Hypertension. 2013; 61:943-947.
4. Nibouche WN, Biad A. Arterial hypertension at the time of diagnosis of type 2 diabetes in adults. Ann Cardiol Angeiol (Paris). 2016; 65(3):152-158.
5. Ruilope LM. SEVITENSION Study Investigators Fixed-Combination Olmesartan/Amlodipine Was Superior to Perindopril + Amlodipine in Reducing Central Systolic Blood Pressure in Hypertensive Patients With Diabetes. J Clin Hypertens (Greenwich). 2016; 18(6):528-535.
6. Brown MJ, Castaigne A, de Leeuw PW. Influence of diabetes and type of hypertension on response to antihypertensive treatment. Hypertension. 2000; 35:1038-1042.
7. Rajzer M, Kawecka-Jaszcz K, Wojciechowska W. Antihypertensive treatment for patients with hypertension and diabetes type II-current clinical research. Przegl Lek. 2003; 60(2):111-115.
8. Kocak G, Aktan F, Canbolat O. Alpha-lipoic acid treatment ameliorates metabolic parameters, blood pressure, vascular reactivity and morphology of vessels already damaged by streptozotocin-diabetes. Diabetes Nutr Metab. 2000; 13(6):308-318.
9. Takaoka M, Kobayashi Y, Yuba M, Ohkita M, Matsumura Y. Effects of alpha-lipoic acid on deoxycorticosterone acetate-salt-induced hypertension in rats. Eur J Pharmacol. 2001; 424:121-129.
10. Oueiroz TM, Guimaraes DD, Mendes-Junior LG, Braga VA. α-lipoic acid reduces hypertension and increases baroreflex sensitivity in renovascular hypertensive rats. Molecules. 2012; 17(11):13357-13367.
11. Muhammad SA, Bilbis LS, Saidu Y, Adamu Y. Effect of Antioxidant Mineral Elements Supplementation in the Treatment of Hypertension in Albino Rats. Oxid Med Cell Longev. 2012; 2012:134723.
12. Suliburska J, Bogdanski P, Jakubowski H. The influence of selected antihypertensive drugs on zinc, copper, and iron status in spontaneously hypertensive rats. Eur J Pharmacol. 2014; 738:326-331.
13. Yanagisawa H, Miyazaki T, Nodera M, Miyajima Y, Suzuki T, Kido T *et al*. Zinc-Excess Intake Causes the Deterioration of Renal Function Accompanied by an Elevation in Systemic Blood Pressure Primarily Through Superoxide Radical-Induced Oxidative Stress. Int J Toxicol. 2014; 33(4):288-296.
14. Sola S, Mir MQ, Cheema FA, Khan-Merchant N, Menon RG, Parthasarathy S *et al*. Irbesartan and lipoic acid improve endothelial function and reduce markers of inflammation in the metabolic syndrome: results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study. Circulation. 2005; 111(3):343-348.
15. Rahman ST, Merchant N, Haque T, Wahi J, Bhaheetharan S, Ferdinand KC *et al*. The impact of lipoic acid on endothelial function and proteinuria in quinapril-treated diabetic patients with stage I hypertension: results from the QUALITY study. J Cardiovasc Pharmacol Ther. 2012; 17(2):139-145.
16. Noori N, Tabibi H, Hosseinpanah F, Hedayati M, Nafar M. Effects of combined lipoic acid and pyridoxine on

albuminuria, advanced glycation end-products, and blood pressure in diabetic nephropathy. Int J Vitam Nutr Res. 2013; 83(2):77-85.
17. McMackin CJ, Widlansky ME, Hamburg NM, Huang AL, Weller S, Holbrook M *et al*. Effect of combined treatment with alpha-Lipoic acid and acetyl-L-carnitine on vascular function and blood pressure in patients with coronary artery disease. J Clin Hypertens (Greenwich). 2007; 9(4):249-255.
18. Parham M, Amini M, Aminorroaya A, Heidarian E. Effect of Zinc Supplementation on Microalbuminuria in Patients With Type 2 Diabetes: A Double Blind, Randomized, Placebo-Controlled, Cross-Over Trial. Rev Diabet Stud. 2008; 5(2):102-109.
19. Afkhami-Ardekani M, Karimi M, Mohammadi SM, Nourani F. Effect of zinc sulfate supplementation on lipid and glucose in type 2 diabetic patients. Pak J Nutr. 2008; 7:550-553.
20. Vasdev S, Ford CA, Parai S, Longerich L, Gadag V. Dietary alpha-lipoic acid supplementation lowers blood pressure in spontaneously hypertensive rats. J Hypertens. 2000; 18:567-573.
21. Thirunavukkarasu V, Anitha Nandhini AT, Anuradha CV. Lipoic acid attenuates hypertension and improves insulin sensitivity, kallikrein activity and nitrite levels in high fructose-fed rats. J Comp Physiol B. 2004; 174(8):587-592.
22. Su Q, Liu JJ, Cui W. Alpha lipoic acid supplementation attenuates reactive oxygen species in hypothalamic paraventricular nucleus and sympathoexcitation in high salt-induced hypertension. Toxicol Lett. 2016; 241:152-158.
23. Vasdev S, Gill V, Longerich L, Parai S, Gadag V. Salt-induced hypertension in WKY rats: prevention by alpha-lipoic acid supplementation. Mol Cell Biochem. 2003; 254:319-326.
24. Vasdev S, Gill V, Parai S, Gadag V. Dietary lipoic acid supplementation attenuates hypertension in Dahl salt sensitive rats. Mol Cell Biochem. 2005; 275:135-141.
25. Ong SL, Vohra H, Zhang Y, Sutton M, Whitworth JA. The effect of alpha-lipoic acid on mitochondrial superoxide and glucocorticoid-induced hypertension. Oxid Med Cell Longev. 2013; 2013:517045.
26. Midaoui AE, Elimadi A, Wu L, Haddad PS, de Champlain J. Lipoic acid prevents hypertension, hyperglycemia, and the increase in heart mitochondrial superoxide production. Am J Hypertens. 2003; 16(3):173-179.
27. Huang YD, Li N, Zhang WG. The effect of oral alpha-lipoic acid in overweight/obese individuals on brachial-ankle pulse wave velocity and supine blood pressure: a randomized, crossover, double-blind, placebo-controlled trial. Zhonghua Liu Xing Bing Xue Za Zhi. 2011; 32(3):290-296.
28. Adeniyi OS, Fasanmade AA. Effect of dietary zinc supplementation on salt induced hypertension in rats. International Journal of Pharmacology. 2006; 2(5):485-491.
29. Farvid MS, Jalali M, Siassi F, Hosseini M. Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. Diabetes Care. 2005; 28:2458-2464.