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

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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 (р < 0.05) and mean daily and nighttime DBP variability (р < 0.05). Besides, it is recorded a positive downward trend in the level of mean daily and nighttime 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 consider 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.
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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: daily SBP (SBPV24-h), daytime SBP (SBPd), nighttime SBP (SBPn); daily DBP (DBPV24-h), daytime DBP (DBPd), nighttime DBP (DBPn); daily HR (HR24-h), daytime HR (HRd) and nighttime HR (HRn).

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 SBPV24-h, DBPV24-h, SBPVd, DBPVd, SBPn, DBPn).

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 value of the morning rise in BP (MR SBPV24-h, MR DBPV24-h, MR SBPVn, MR DBPVn).

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 – SBPV24-h (p<0.1), SBPVd (p<0.2) and SBPn (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 DBPV24-h, TI DBPVd and TI DBPn (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 and various models of hypertensive rats, including spontaneously hypertensive rats, uninephrectomized deoxycorticosterone acetate-salt hypertensive rats, renovascular hypertensive rats, fructose-loaded and salt-loaded rats. In other works it was shown that the use of ALA prevents the development of dexamethasone-induced and glucose-induced hypertension in rats.

In human studies the use of ALA as a hypotensive agent presented conflicting results showing improvement or no effect. Rahman ST. and co-invest. 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. 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 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. [11] 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%, Adeniy OS. And co-invest. [20] Indicate the prevention of development of hypertension in salt-loaded rats when adding Zn. In another study [15] it was 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. [20] 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 660mg 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
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