**PATHOGENETIC ADVANCES OF FOSINOPRIL SODIUM WITH HYDROCHLOROTHIAZIDE IN OBESE HYPERTENSIVE PATIENTS**

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**Introduction**

Essential hypertension (EH) stays the important public challenge, because of leading positions in morbidity and mortality in not only Ukraine, but also worldwide. This number is predicted to increase 1.5 billion by 2025. Unfortunately half of that population is unaware of present hypertension [20].

Numerous clinical studies have established the relationship of high blood pressure with increasing body weight. In particular, in the INTERSALT study, carried out in 52 population groups, showed direct correlation between body mass index (BMI) and elevated blood pressure [21]. In Hypertension Control Program was found that 50% of surveyed middle-aged overweight have hypertension (EH), and 2/3 cases of the hypertension are associated with obesity [27]. Framingham study showed that 78% of men and 65% of women has hypertension and are obese [14]. Data confirmed by Swedish Obesity Study [28] where 44-51% of individuals with obesity have essential hypertension. Consequently, increasing in body weight is a potential risk factor for essential hypertension.

Finally, the term "obesity induced hypertension" appears. Obesity-associated hypertension is a multicomponent process, and the pathogenesis includes increasing in circulating blood volume, vasoconstriction, hyperreactivity of sympathetic and renin-angiotensin-aldosterone system (RAAS), prediabetes, dyslipidemia and other metabolic disorders. Investigations of the last decade showed that one of the early phases of the pathogenesis of this comorbid pathology is the development of endothelial dysfunction (ED). Elevated levels of angiotensin secreted by the adipocytes, is an important link between visceral obesity and ED, as proved by the correlation of waist - to - hips ratio with the level of mRNA angiotensinogen in visceral and subcutaneous adipose tissue. The subsequent increasing of angiotensin II tissue level stimulates the secretion of superoxide that is known as leading - factor in the etiology of ED. Currently, leading role of the endothelium and nitric oxide in the pathogenesis of cardiovascular complications of hypertension is proved [24, 18, 19].

The leading role in reducing endothelium-dependent vasodilation belongs to the intracellular oxidative stress (OS) as free radical oxidation dramatically reduces the production of NO by endothelial cells [6,1]. Endothelial dysfunction and OS are becoming the new therapeutic targets in the treatment of hypertensive patients. It should be noted that the analyses of pharmacological properties of antihypertensive drugs pay little attention to this aspect. According to some researchers, OS can be a promotor of proinflammatory cytokines system activation. Among the pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) deserves particular attention in context of hypertension [1,2,7,16,17,29]. Thus, Zahorska-Markiewiez [30] was found in blood of patients with essential hypertension increased content of C-reactive protein (CRP) and TNF-α. It hemodynamic stress caused by hypertension, is stimulus of increased release into the blood of proinflammatory cytokines, including TNF-α [10,15] which, in turn, can modulate the structure and function of the cardiovascular system.

The most important predisposal for the maximum reduction in cardiovascular risk in hypertension is achieving the target BP, which may be a problem in presence of overweight and obesity. In many cases there is a need in combination of two antihypertensive drugs that should be metabolically neutral [8,25].

Thus, the scientific justification of treatment regimens in hypertensive patients with overweight and obesity, the study of the antioxidant efficacy of combined antihypertensive therapy is extremely relevant and important for today’s practical healthcare. Despite the large number of antihypertensive drugs and the scientific study of the principles of treatment of patients with hypertension, it would be a mistake to assume that the problem is completely solved.

**Purpose**

To improve antihypertensive therapy on the basis of studying the antioxidant properties of an angiotensin-converting enzyme (ACE) inhibitor (fosinopril sodium) and a diuretic (hydrochlorothiazide), their impact on endothelial dysfunction and pro-inflammatory cytokines activity in hypertensive patients with overweight and obesity.

**Materials and methods**

A combination of an angiotensin-converting enzyme (ACE) inhibitor and diuretic (D) (fosinopril sodium 20 mg/day and hydrochlorothiazide 12.5 mg/day) was prescribed to 54 patients with essential hypertension of II stage, 1-3 grades, 30 to 65 years old (mean age – 54,54 ± 0.91 years), who previously have not been receiving regular antihypertensive therapy. The control group included 10 healthy subjects matched for age and sex.

The fasting blood was taken for research the day after the patient's admission to hospital, in 12-18 hours after eating. In a part of this group (22 persons) the study was conducted after 2 weeks of treatment on the background of antihypertensive therapy and 8 weeks after the start of treatment. Blood sampling was performed from the cubital vein. Other patients preferred different from fosinopril therapy because of financial reasons. All patients were similar in terms of physical activity, did not take any nitro-containing drugs, and did not eat foods rich in nitrates and nitrites that might affect nitric oxide system.

European Society of Hypertension (ESH) / European Society of Cardiology (ESC) (2013) were used for verification of the diagnosis and estimation of the hypertension grade. Exclusion criteria were: secondary hypertension, associated inflammatory and endocrine disorders as well as other conditions that could have an impact on the activity of oxidative processes. Thus 8 patients diagnosed with essential hypertension of 1 degree, 21 cases of 2 degree in 25 patients of 3 degree.

In addition to the standard examination protocol, anthropometric measurements (height, weight, waist and hips circumference) had been taken with the calculation of body mass index (BMI), waist to hips ratio (W/H) in order to determine the presence of excess body weight and degree of obesity as well as type of fat distribution.

Surveyed patients had overweight or obesity 1, 2 and 3 degrees. 20 patients were overweight and obesity has 34 patients: obesity of 1 degree was observed in 15 patients, 2nd degree – in 13 and 3rd degree – in 6 patients.

The endothelial functional on the background of combined therapy was studied (n = 22) by evaluating the activity of endothelial and inducible NO-synthase. Determining the state of pro-oxidant and antioxidant systems in the dynamics of treatment in this group of patients was based on the analysis of 8-isoprostane level, superoxide dismutase (SOD), and catalase activity. According to the current data, 8-isoprostane (8-IP) is considered one of the most specific markers allowing to assess the level of free radicals production with a sufficient degree of accuracy, reliability and reproducibility of the results. 8-IP is a product of metabolism in peroxidation of arachidonic acid which is isomerical to prostaglandin F2α [9].

Immune activation during therapy with fosinopril sodium and hydrochlorothiazid was assessed by evaluating the serum levels of TNF-α and its type I soluble receptor (sTNF-αRI) in all subjects. These parameters were used as a criteria for treatment efficacy in hypertensive patients with overweight and obesity.

The activity of NO-synthases (NOS), SOD, and catalase were determined by biochemical method. The contents of serum 8-iso-PgF2α (8-isoprostane), TNF-alpha and its type I soluble receptor (sTNF-αRI) were determined in all subjects using the «8-isoprostane ELISA» (Usbiological, USA), «ProCon TNFα» (Protein contour, Russian Federation) and «sTNF-RI EASIA» (BioSource Europe SA, Belgium) ELISA kits, respectively.

Statistical analysis of the study results was performed using Statsoft Inc. Statistica for Windows. The obtained results are presented as mean value (Mean) ± standard deviation (SD). t-test was used. P level less than 0,05 was considered as significant.

**Results**

Initial data before treatment is presented in table 1. Significant increasing of the i-NOS activity, pro-inflammatory cytokines (TNF-α, sTNF-RI) levels, as well as markers of oxidative stress - 8-iso-PgF2α was found during investigation. In contrast, activity of e-NOS and SOD were decreased in the serum of patients with essential hypertension that are associated obesity. There were no significant differences in catalase activity, compared with the control group.

Table 1

**Levels of TNF-α, sTNF-αRI, 8-isoprostane, activity of i-NOS, e-NOS,**

**SOD and catalase in hypertensive patients with obesity vs control group**

|  |  |  |
| --- | --- | --- |
| Parameter | Control group | Patients |
| TNF-α, pg/ml | 13.23 ± 3.40 | 78.24 ± 23,67\* |
| sTNF-αRI, ng/ml | 1.20 ± 0.60 | 2.25 ± 0.21\* |
| 8-isoprostan , ng/ml | 1.41 ± 0.25 | 20.20 ± 11.97\* |
| i-NOS, pmol / (min. х mg of protein) | 0.208 ± 0.089 | 0.566 ± 0.13\* |
| e-NOS, pmol / (min. х mg of protein) | 0.782 ± 0.045 | 0.707 ± 0,14\*\* |
| SOD, μcatal/l | 0.54 ± 0.05 | 0.48 ± 0.11\*\* |
| Catalase, μcatal/l | 3.388 ± 0.39 | 3.66 ± 1.2\*\* |

Note: \* - p < 0.05 vs control group; \*\*- p > 0.05 vs control group.

The correlation analysis that is presented in table 2 shows interrelations of cardiohemodinamic parameters with nitric oxide pool and oxidative stress data. So, significant correlation between obesity, immune inflammation and oxidative stress was found in observed cases. Also, there is interrelations of TNF-α with level of arterial pressure.

As it was mentioned, effectiveness of the treatment was evaluated after 2 and 8 weeks from the beginning of the treatment. During of treatment the patients had been noting the improvement of general feeling, the reduction of intensity and frequency of headaches, dizziness, pain in the heart region, fatigue, and increase in the exercise tolerance. All patients who had been receiving this treatment were discharged from the hospital in satisfactory general condition. After 2 weeks of treatment 3 patients were excluded because of the coughing, that is connected with seasonal allergy. Also, 6 patients discontinued observation because of migration. 6 patients with essential hypertension and severe obesity starting metformin, knowing its pleiotropic effects, patients were excluded from observation too. The side effects of the treatment weren’t observed.

Table 2

**Correlation matrix endothelial function and oxidative stress parameters with arterial pressure, heart rate and BMI in hypertensive patients with obesity**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | e-NOS | i-NOS | TNF-α, pg/ml | sTNF-αRI, ng/ml | SOD, μcatal/l | Catalase, μcatal/l | 8-isoprostan ng/ml |
| BMI, kg/m2 | r=-0,08р>0,05 | r=0,35\*р<0,05 | r=0,31\*р<0,05 | r=0,17р>0,05 | r=0,02р>0,05 | r=0,08р>0,05 | r=0,08р>0,05 |
| SAT | r=-0,02р>0,05 | r=-0,13р>0,05 | r=0,41\*р<0,05 | r=0,51\*р<0,05 | r=0,06р>0,05 | r=0,08р>0,05 | r=0,42\*р<0,05 |
| DAT | r=-0,04р>0,05 | r=-0,18р>0,05 | r=0,47\*р<0,05 | r=-0,58\*р<0,05 | r=0,10р>0,05 | r=0,16р>0,05 | r=0,12р>0,05 |
| Heart rate | r=0,05р>0,05 | r=-0,11р>0,05 | r=0,52\*р<0,05 | r=0,46\*р<0,05 | r=0,06р>0,05 | r=0,03р>0,05 | r=0,15р>0,05 |

Note: \* - p < 0.05

In the group of patients treated with fosinopril and hydrochlorothiazid, a reduction in the mean values of office systolic blood pressure by 47.6 mmHg and office diastolic blood pressure by 30.6 mmHg was observed during the hospital treatment period. The average mean blood pressure level has been decreased by 36.3 mmHg, pulse blood pressure – by 17.5mm Hg, which corresponded to 26.43%, 28.55%, 27.63%, and 23.95% reduction, respectively, compared with the levels before the onset of treatment p < 0.05 for all parameters.

The dynamics of mean values of the assessed parameters during antihypertensive therapy is presented in table 3.

The NOS isoforms ratio was changed during the treatment with fosinopril sodium / hydrochlorothiazid In the group of patients with hypertension. The activity of i-NOS was significantly reduced by 9.72% and 13.5% (0.474 ± 0.07 vs 0.548 ± 0.11 vs the group prior to treatment) after the 2 weeks of treatment and after 8 weeks of treatment, respectively, p < 0.05. The activity of e-NOS, in contrast, was significant increased by 4.4% and 10.3% (0.741 ± 0.16 vs 0.672 ± 0.12 compared to the level before treatment) after the 2 weeks and after 8 weeks of therapy, p < 0.05.

Table 3

**Endothelial functional state and oxidative stress dynamics during the course of combined therapy with fosinopril sodium and hydrochlorothiazid in hypertensive patients with obesity**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Before treatment(n=22) | After 2 weeks of treatment (n=22) | After 8 weeks of treatment (n=10) |
| 8-isoprostan, ng/ml (n=10) | 20.20 ± 11.97 |  12.12 ± 5.37\* | 10.16 ± 7.61\* |
| i-NOS, pmol / (min. х mg of protein) | 0.566 ± 0.13 | 0.511 ± 0.11\* | 0.474 ± 0,07\* |
| e-NOS, pmol / (min. х mg of protein | 0.707 ± 0.14 | 0.738 ± 0.15\* | 0.741 ± 0.16\* |
| SOD, μcatal/l | 0.485 ± 0.11 | 0.570 ± 0.11\* | 0.572 ± 0.14\*\* |
| Catalase, μcatal/l | 3.66 ± 1.2 | 4.76 ± 1.04\* | 4.7 ± 1.21\* |

Note:\* - p < 0.05 vs levels before treatment ; \*\*- p > 0.05 vs levels before treatment

During of treatment in hypertensive patients with overweight and obesity using a combination of fosinopril sodium and hydrochlorothiazid, we have also observed a change in the SOD and catalase activity. The obtained data indicates that the SOD activity in the period of hospital treatment was significantly increased by 17.5% (р < 0.05) and by 9.7% after 8 weeks of treatment (0.572 ± 0.14 vs 0.521 ± 0.14) compared to a group of patients before treatment, p > 0.05. A significant increase in the catalase activity was also prominent both during the hospital treatment period by 30% and 8 weeks from the start of treatment – by 20.5% (4.7 ± 1.21 vs 3.9 ± 1.02, p < 0.05).

Analysing the level of 8-isoprostane as the main marker of oxidative stress, a decrease of its serum level by 40% (12.12 ± 5.37 vs 20.20 ± 11.97, p < 0.05) has been observed during 2 weeks of treatment in a hospital. After 8 weeks of treatment, 8-isoprostane levels had been decreased by 49.7% (down to 10.16 ± 7.61) compared to baseline and 1.98 times, respectively, was below. These facts testify to the beneficial effects of the studied scheme of antihypertensive therapy on the level of 8-isoprostane.

Analysis of the pro-inflammatory cytokines activity has shown that 8 weeks treatment with a fosinopril sodium / hydrochlorothiazid led to 48.11% decrease of mean TNF-α levels by 37.64 pg/ml (40.60 ± 15.8 vs 78.24 ± 23.67, p < 0.05) compared to baseline prior to treatment. sTNF-αRI showed the opposite trend, increasing its mean levels on 0.13ng/ml (5.47%) (2.38 ± 0.19 vs 2.25 ± 0.21) during the course of treatment. A significant decrease of the ratio TNF-α/ sTNF-αRI by 17.72 (51%) (17.05 vs 34.77) indicates a preferential increase in the level of sTNF-αRI, along with a reduction of TNF-α. Since the sTNF-αRI is a natural antagonist of TNF-α, a decrease in this ratio shows the suppression of autoimmune and apoptotic activity in patients as a result of treatment.

**Discussion**

Changes in the nitric oxide system showed activation of inducible synthase with the development of oxidative stress. Thus, obtained results of the study confirm the endothelial dysfunction as a leading mechanism of the pathogenesis in essential hypertension with obesity, where increased activity of iNO-synthase and a decreased activity of eNO-synthase are found [11]. Immune activation that is mediated by proinflammatory cytokines, like tumor necrosis factor-α has an important role in the development of endothelial dysfunction.

We observed changes in NOS activity under the influence of fosinopril sodium and hydrochlorothiazid. This drug combination improves the activity of SOD, catalase, and 8-isoprostane level.

From the above it can be concluded that the treatment of hypertensive patients with overweight and obesity with angiotensin-converting enzyme (ACE) inhibitor (fosinopril sodium) and diuretic (hydrochlorothiazid) leads to positive dynamics of NO pool increase throughout the treatment period, indicating the restoration of vasodilatory capacity.

So, the changes observed during the course of the above scheme of combined antihypertensive therapy may indicate the improvement of the functional state of endothelium.

The results obtained in the course of treatment with fosinopril sodium (20mg) combined with hydrochlorothiazid (12.5mg) can be explained by their mechanism of action.

Fosinopril is the only angiotensin-converting enzyme (ACE) inhibitor that retains the phosphinic acid residue in its chemical formula. Fosinopril - an ester that is hydrolyzed in the body by the action of esterases in the active communication of fosinoprilat [3,13]. Fosinopril due to its specific connection phosphinate group of ACE prevents conversion of angiotensin I to angiotensin II, resulting in vasopressor activity and aldosterone secretion reduced [4,12].

Also, fosinopril is the only phosphinate-containing ACE inhibitor marketed. Fosinopril is de-esterified by the liver or gastrointestinal mucosa and is converted to its active form, fosinoprilat. Fosinoprilat competitively binds to ACE, preventing ACE from binding to and converting angiotensin I to angiotensin II. Inhibiting the production of AII lowers peripheral vascular resistance, decreases afterload, and decreases blood pressure, thus helping to alleviate the negative effects of AII on cardiac performance.

Thus, on the basis of the above, can explain the rapid (during the period of treatment in hospital) and good result (40%) in reducing the level of 8-isoprostane (factor of construction prostaglandin F2α,), as a marker of OS in hypertensive patients with overweight and obesity.

The second mechanism of action of ACE-inhibitors on endothelial function is their ability to prevent the splitting of bradykinin [22]. The ACE is identical to the kinase II enzyme, which causes the conversion of bradykinin to an inactive state. Bradykinin is a potent stimulator for the release of endothelium-dependent relaxing factors such as nitric oxide, endothelium hyperpolarization factor and prostacyclin (PGI2).

The advantage of fosinopril is the balanced double way of isolation - slightly more than half of the total volume of the drug (54%) is excreted from the body by renal excretion with urine, the rest (46%) by hepatic degradation of active metabolites with their sequential release through the gastrointestinal tract.

It is important to note that the decrease in renal filtration increases proportionally hepatic route of excretion of the drug, and on the contrary, in liver disease - increase the contribution of renal excretion. Actually, this pharmacokinetic feature of fosinopril is the basis of the important clinical recommendations: as in renal and hepatic insufficiency additional correction doses of fosinopril is not usually required [3,5].

Unlike other ACE inhibitors that are primarily excreted by the kidneys, fosinopril is eliminated from the body by both renal (54%) and hepatic (46%) pathways. This characteristic of fosinopril makes the drug a safer choice than other ACE inhibitors for heart failure patients with impaired kidney function resulting from poor perfusion as fosinopril can still be eliminated by the liver, preventing accumulation of the drug in the body.

Hydrochlorothiazide is a benzothiadiazinium (thiazide) diuretic with diuretic, natriuretic and antihypertensive effects. The hypotensive action of the last one is based on the blockade of the sodium and chlorine transportation through the luminal membrane of the initial segment of the distal part of the twisted tubules, where up to 5% of the filtered sodium is normally reabsorbed. As a consequence of this, the volume of plasma decreases (unfortunately, together with potassium ions) and extracellular fluid, cardiac output decreases and reduced blood pressure. However, prolonged use of hydrochlorothiazide is accompanied by compensatory hyperreneinemia, which is aimed at storing a reduced volume of plasma and extracellular fluid, and can lead to hypokalemia. It is known that one of the components for the synthesis of angiotensin II is a renin which is excessively produced by the body in prolonged use of hydrochlorothiazide. The higher the concentration of renin is the stronger hypotensive effect of angiotensin-converting enzyme (ACE) inhibitor.

Thus, prolonged use of hydrochlorothiazide, due to hyperreninemia, forms the ideal conditions for realizing the maximum hypotensive effect of i-ACE. Moreover, reducing the synthesis of AT II, i-ACE "involuntarily" reduces the production of aldosterone, drive to the retention of potassium ions and the elimination of hypokalemia, provoked by hydrochlorothiazide. The combination of the fosinopril sodium and hydrochlorothiazide is a unique situation, when the negative effects of one drug appear to be a source for strengthening and prolongation of the hypotensive effect of another drug. [4,5,23]. Thiazide diuretics led to an increase in neuronal NO synthase in the “maculae densa” and e-NOS in the renal vessels in experimental model of DOCA salt hypertension in rats caused by administration of deoxycorticosterone and sodium chloride.[26].

Thus, the assessment of endothelial function and pro-inflammatory cytokines activity allows to optimize the scheme of differentiated prescription of therapy in hypertensive patients.

**Conclusion**

A positive result in the treatment of overweight and obese hypertensive patients using the combination of antihypertensive drugs (fosinopril sodium 20mg and hydrochlorothiazid 12.5mg) is associated with improving of endothelial function that was displayed in enhancement of endothelial NO-synthase activity on 10.3% and decreasing of inducible NO-synthase activity on 13.5% after 8 weeks of therapy.

Using of combination of fosinopril and hydrochlorothiazid leads to reducing of oxidative stress according to decreasing of 8-isoprostane levels on 49.7% as well as superoxide dismutase and catalase activity increasing compared to baseline. Significant SOD and catalase activity increasing was found on 30% and on 17.5% during 2 weeks treatment period and forward increasing on 20.5% and 9.7% after 8 weeks of treatment respectively.

Therefore, we speculate that fosinopril sodium with hydrochlorothiazid has positive influence on the endothelial function besides reducing the autoimmune activation level, which is manifested in the reduction of TNF-α ratio to its type I soluble receptor.

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**РЕЗЮМЕ**

**ПАТОГЕНЕТИЧЕСКОЕ ОБОСНОВАНИЕ ВЫБОРА ФОЗИНОПРИЛА НАТРИЯ В СОЧЕТАНИИ С ГИДРОХЛОРТИАЗИДОМ У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ С ОЖИРЕНИЕМ**

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Цель исследования: усовершенствование комбинированной антигипертензивной терапии на основании изучения антиоксидантных свойств ингибитора ангиотензинпревращающего фермента (і-АПФ) фозиноприла натрия в комбинации с диуретиком (Д) гидрохлортиазидом и их влияния на уровень провоспалительных цитокинов у больных АГ с избыточной массой тела и ожирением.

В условиях стационара 54 пациентам гипертонической болезни (ГБ) в возрасте от 30 до 65 лет была назначена комбинация фозиноприл натрия 20 мг/сут с гидрохлортиазидом 12,5 мг/сут. В контрольную группу вошли 10 практически здоровых лиц, сопоставимых по возрасту и полу.

В ходе комбинированной антигипертензивной терапии было установлено достоверное снижение активности i-NOS, уменьшении соотношения ФНО-α к его растворимому рецептору I типа (рФНО-αRI) и 8-iso-PgF2α у обследуемых пациентов. Показатели активности e-NOS, СОД и каталазы напротив, увеличиваются в сыворотке крови пациентов с ГБ и сопутствующим ожирением. Положительный результат связан с улучшением функционального состояния эндотелия и значительным уменьшением уровня аутоиммунной активации на фоне снижения напряжения оксидативного стресса.

**Ключевые слова:** гипертоническая болезнь, ожирение, эндотелиальная и индуцибельная NO-синтаза, фактора некроза опухолей-α и его растворимый рецептор I типа, 8-изопростан, СОД, каталаза, фозиноприл натрия, гидрохлортиазид.

**SUMМARY**

**PATHOGENETIC ADVANCES OF FOSINOPRIL SODIUM WITH HYDROCHLOROTHIAZIDE IN OBESE HYPERTENSIVE PATIENTS**

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Purpose **-** to improve antihypertensive therapy on the basis of studying the antioxidant properties of an angiotensin-converting enzyme (ACE) inhibitor (fosinopril sodium) and a diuretic (hydrochlorothiazide), their impact on endothelial dysfunction and pro-inflammatory cytokines activity in hypertensive patients with overweight and obesity.

A combination of fosinopril sodium 20 mg/day and hydrochlorothiazid 12.5 mg/day was prescribed to 54 patients with essential hypertension of 1-3 grades, 30 to 65 years old . The control group included 10 healthy subjects matched for age and sex.

During the course of combined antihypertensive therapy we observed a significant decrease of i-NOS activity, reduce of TNF-α type I of its soluble receptor (sTNF-αRI), and 8-iso-PgF2α in the patients. Activity of e-NOS, superoxide dismutase and catalase, in contrast, were increased in patients with hypertension and concomitant obesity.

Thus, the improvement of endothelial function, a significant decrease autoimmune activation due to lower tension of oxidative stress in the examined patients optimizes use of a combination of fosinopril sodium and hydrochlorothiazid for differentiated therapy in hypertensive patients with obesity.

**Key words:** endothelial and inducible NO-synthase, tumor necrosis factor-alpha and its soluble receptor type I, 8-isoprostane, superoxide dismutase, catalase, fosinopril sodium, hydrochlorothiazid.

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