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Arterial hypertension, cardiovascular remodeling and plasma level of osteopontin in patients with end-stage kidney disease on hemodialysis

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Key words: *End-Stage Renal Disease, Hemodialysis, Hypertension, Osteopontin, Candesartan.*

Aim. Large population-based studies acknowledge that patients with chronic kidney disease have a high risk of cardiovascular diseases regardless of etiology, especially in its late stages. The aim of this study was to investigate the features of arterial hypertension, cardiovascular remodeling and plasma level of osteopontin in dynamics of candesartan therapy, as well as to identify the relationships between studied parameters in patients with chronic kidney disease treated by hemodialysis.

Methods and results. 50 patients were performed ambulatory blood pressure monitoring, the plasma level of osteopontin was determined by ELISA method, standard echocardiography and ultrasonography of common carotid after treatment of candesartan during 12 weeks.

Conclusion. The results indicate that the use of candesartan cilexetil in hemodialysis populations promotes regression of left ventricular hypertrophy and vascular remodeling indices, has antihypertensive effect.

Артеріальна гіпертензія, кардіоваскулярне ремоделювання та плазмовий рівень остеопонтину в пацієнтів із кінцевою стадією хронічної хвороби нирок на гемодіалізі

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Масштабні популяційні дослідження свідчать, що пацієнти з термінальною нирковою недостатністю мають високий ризик розвитку серцево-судинної патології. Мета роботи полягала в дослідженні особливостей артеріальної гіпертензії, кардіоваскулярного ремоделювання та плазмового рівня остеопонтину в динаміці терапії кандесартаном цилексетилом, а також виявлення взаємозв'язків між цими показниками в пацієнтів на програмному гемодіалізі. 50 хворим виконали добове моніторування артеріального тиску, ехокардіографію, допплерографію сонних артерій, імуноферментне визначення плазмового рівня остеопонтину до та після 12-тижневого лікування кандесартаном. Результати свідчать, що лікування кандесартаном сприяє регресу гіпертрофії лівого шлуночка та показників судинного ремоделювання, препарат має антигіпертензивний ефект, а також знижує концентрацію остеопонтину.

Ключові слова*: кінцева стадія хронічної хвороби нирок, гемодіаліз, артеріальна гіпертензія, остеопонтин, кандесартан.*

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Артериальная гипертензия, кардиоваскулярное ремоделирование и плазменный уровень остеопонтина у пациентов с конечной стадией хронической болезни почек на гемодиализе

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Масштабные популяционные исследования свидетельствуют, что пациенты с терминальной почечной недостаточностью имеют высокий риск развития сердечно-сосудистой патологии. Целью исследования стало изучение особенностей артериальной гипертензии, кардиоваскулярного ремоделирования и плазменного уровня остеопонтина под влиянием терапии кандесартаном цилексетилом, установление взаимосвязей между изучаемыми показателями у пациентов на программном гемодиализе. 50 больным проведено суточное мониторирование артериального давления, эхокардиография, допплерография сонных артерий, иммуноферментное определение плазменного уровня остеопонтина до и после 12-недельного лечения кандесартаном. Полученные данные свидетельствуют, что прием кандесартана способствует регрессу гипертрофии левого желудочка и показателей сосудистого ремоделирования, препарат обладает антигипертензивным эффектом, а также снижает концентрацию остеопонтина.

Ключевые слова: *конечная стадия хронической болезни почек, гемодиализ, артериальная гипертензия, остеопонтин, кандесартан.*

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Large population-based studies acknowledge that patients with chronic kidney disease (CKD) have high risk of cardiovascular (CV) diseases regardless of etiology, especially in its late stages. Deceleration of glomerular filtration on every 10 mL/min increases cardiovascular risk and risk of death from any causes up to 20 %, that reaches the maximum level in patients on renal replacement therapy [2,11]. Lesion of cardiovascular system in subjects suffering from CKD occurs in different pathogenic mechanisms simultaneously. One of the main factors of development the CV remodeling in dialysis patients is arterial hypertension (AH). It occurs as a result of volume overload, anemia and existing arteriovenous fistula [3]. Further the number of investigators pay a special attention to bone mineral violations in the development of the CV remodeling, specifically to high level of phosphate and vascular calcification (VC) [5,18]. The extracellular phosphate mechanism of action is induction of the osteoblastic differentiation factors. One of this factors is osteopontin (OP) [10]. As pleotropic cytokine this major noncollagenous bone matrix protein is expressed in mineralized tissue and synthesized by fibroblasts, osteoblasts, smooth muscle and endothelial cells [6, 23]. OP regulation is not completely investigated yet. But there are results of the protein activity stimulation due to activity of proinflammatory cytokines, angiotensin II [12]. Literature data indicate the expression of OP in hypertrophied myocardium [1]. This cytokine is believed to cause smooth muscle cells proliferation and elastic membrane degradation, thus to trigger processes of vascular remodeling. The negative role of OP in the development of diastolic dysfunction in patients

with essential hypertension was proved by Nakayama [et al.] [19]. Achieving target values of blood pressure (BP) in dialysis patients often have difficulties on the one hand due to the threat of the intra-dialysis hypotension, and on the other – there is the need to normalize BP as the primary objective in the way of preventing cardiovascular complications. The importance of this fact was confirmed in meta-analysis of 8 large studies (1679 hemodialysis patients), they shows that the normalization of BP was associated with reduced risk of cardiovascular events and mortality, as well as reduced risk of death from all causes [14].

In the treatment of hemodialysis patients, angiotensin receptor blockers II (ARBs) have several advantages, due to the efficiency, safety, improvement of survival rates, that have been demonstrated in several large-scale studies [15]. The effect of ARBs to the level of OP is not studied yet. Thus, Kurata M. et al. showed the ability of valsartan to reduce plasma levels of OP during treatment patients with arterial hypertension [16]. It reduction of the expression of OP mRNA was showed experimentally on rats according to the action of candesartan by Hatanka Y. et al. [13].

The significant role belongs to OP level in processes of bone and mineral disorders, it is expected of OP possible participation in the development of VC during the treatment of hemodialysis patients. A single focus of these processes that ultimately lead to a negative outcome in patients on renal replacement therapy, the interest is presented in the study of the plasma levels of OP, the development of approaches for its quantitative assessment and feasibility study of the pharmacological effect on the level of this marker.

The **aim** of this study was to investigate the features of the OP, AH, CV plasma level remodeling in dynamics of candesartan therapy, as well as to identify the relationships between studied parameters in patients with chronic kidney disease treated by hemodialysis.

Material and methods

The main study group included 50 patients (24 female, 26 male), average age 49,1±11,4 years, average dialysis experience 100,0 ± 58,12 months, with prior arterial hypertension 116,4±43,7 months, who received renal replacement therapy by hemodialysis in Municipal Institution «City Hospital № 7» Zaporozhye Region. Criteria for inclusion to the study were: duration of renal replacement therapy ≥ 3 months; age 18 - 70 years; weekly dialysis time at least 12 hours; index of hemodialysis adequacy for eKt/v ≥ 1,2; C-reactive protein ≤ 5 mg/L; agreement to participate in the study. Exclusion criteria were: diabetes mellitus; myocardial infarction; symptomatic stable manifest angina; heart failure NYHA III-IV; acute infectious processes of different etiology, that were diagnosed within last 3 months; oncological diseases. Control group included 20 healthy volunteers (12 – women, 8 – men), average age 48,2±12,2 years.

In all included patients level of hemoglobin, albumin, total cholesterol, body mass index (BMI) were determined. Before treatment and after 12 weeks of treatment with candesartan, patients were examined in the following scope: level of OP was determined by ELISA method using kits «EnzoLifeSciences» (USA) and enzyme immunoassay analyzer SIRIO S (Italy). Standard echocardiography and ultrasonography of common carotid arteries were performed on My Lab 50X «ESAOTE» (Italy). Also myocardial mass of myocardium (MM) by Devereux was calculated [7] with the measurement of left ventricle mass index (LVMI). Left ventricular hypertrophy was defined as LVMI ≥ 134 g/m² in men and ≥ 110 g/m² in women. Diameter of common carotid arteries (D CCA), the resistivity index (RI), pulsativity index (PI), and the thickness intima-media complex (cIMT) were evaluated. Ambulatory blood pressure monitoring (ABPM) in the peri-dialysis period using apparatus of the digital automatic blood pressure monitor registration «CardioTens» (Hungary) was performed in all patients. In this case cuff was put on hand free from arteriovenous fistula. AH has been validated according to the NKF-KDOQI [20] and ESH / ESC [8] recommendations. All patients intook candesartan cilexetil per os in average dose 17,35±6,2 mg.

Research results were processed by parametric and non-parametric statistical methods such as t-test for selection of unrelated variants and Mann-Whitney method. The difference was considered as reliable by P<0,05. The data was presented as mean (M) ± standard deviation (SD). Assessment of the relationship between pairs of independent features, expressed in a quantitative scale was performed using Pearson's rank correlation coefficient (r) or Spearman's (R), depending on the nature of the variables distribution. Digital data obtained in result of research were processed on a personal computer using software applications: Microsoft Excel 2007, Statistica 7.0 and the standard version of SPSS 16.0 (USA).

Results and discussion

Analysis of baseline data showed the mean hemoglobin level of main group of patients 100,3 ± 18,41 g/l, albumin level 41,49 ± 4,22 g/l, total cholesterol level 4,97 ± 0,94 mmol/l, BMI 23,7 ± 4,82 kg/m².

Changes in 24-hour blood pressure monitoring after 12 weeks of treatment with candesartan are showed in *table 1*.

Table 1

Parameters of the ABPM in dynamics of treatment by candesartan (M±SD)

Parameter, unit of measurement	Before treatment, (n=50)	After treatment, (n=50)
mSBP, mmHg	134,14±18,75	120,22±11,83*
mDBP, mmHg	74,15±14,33	72,79±12,75
mPBP, mmHg	59,67±13,98	49,28±10,82*
*P<0,05		

It was noted the significant decrease of mean systolic blood pressure (mSBP) and mean pulse blood pressure (mPBP) after 12-weeks of treatment.

Changes of the cardiac remodeling parameters after treatment with candesartan cilexetil are showed in *table 2*.

Table 2

Parameters of cardiovascular remodeling in dynamics of treatment with candesartan (M±SD)

Parameter, unit of measurement	Before treatment, (n=50)	After treatment, (n=50)
LVMI, g/m²	169,39±27,81	152,57±14,00*
D ACC, мм	6,13±0,49	6,11±0,51
RI, y.e.	0,65±0,05	0,52±0,02*
PI, y.e.	1,41±0,27	1,55±0,21
cIMT, mm	1,11±0,31	0,88±0,22*
*P<0,05		

After 12 weeks of treatment, significant decrease of LVMI from 169,39 ± 67,81 g/m^2 to 152,57 ± 54,00 g/m^2 (9,9%) was observed. As for the parameters of vascular remodeling, the indices of RI decreased significantly from 0,65 ± 0,05 relative value units to 0,52 ± 0,02 relative value units (20 %) after treatment. cIMT decreased from 1,11±0,31 to 0,88±0,22. PI increase was not significant.

In group of patients on program hemodialysis level of OP was significantly higher compared with the control (246,23±50,31 ng/ml vs 64,1 ± 22,31 ng/ml). The candesartan treatment was accompanied with decreased levels of OP to 200,68 ± 40,92 ng / ml (on 18.5%) (*table 3*).

Table 3

Plasma level of osteopontin in dynamics of treatment by candesartan (M±SD)

Parameter, unit of measurement	Control group, (n=20)	Before treatment, (n=56)	After treatment, (n=56)	P
Osteopontin, ng/ml	64,1±22,31	246,23±50,31	200,68±40,92	$P_{1-2} < 0,001$ $P_{1-3} < 0,001$ $P_{2-3} < 0,05$

Correlation analysis demonstrated a positive correlation between plasma level of OP and cIMT (r = 0,33, p = 0,02), between level of OP and mSBP (r = 0,2, p = 0,024), between OP and LVMI (r = 0,23, p = 0,005). After treatment with candesartan, due to OP level decrease and improvement of CV remodeling and blood pressure indices, this positive correlation has been preserved, although of the weak strength (r = 0,2, p = 0,02; r = 0,21, p = 0,03; r = 0,22, p = 0,006 respectively). Negative correlation of average strength between total cholesterol level and OP (r = -0,24, p = 0,006) was found. Obtained data allow suggesting plasma OP level as a marker of CV remodeling in patients who are treated by hemodialysis.

There was not found any correlation between the OP and age, gender, duration of AH, dialysis experience, albumin, hemoglobin level in these patients. Positive correlation was determined between the level of OP and body weight index (r = 0,25, p = 0,001).

Despite some particular success in the treatment of AH in hemodialysis patients, questions of cardiovascular remodeling are remaining still an unsolvable problem, that leads to negative consequences. Medications use for reduce activity of renin-angiotensin system is probably the only one tool in the treatment of these patients. Angiotensin receptor type I blockers have several advantages, that confirmed by the literature data [4, 9]. Our study revealed regression of LVH and its significant decrease. Regarding to the effect of ARBs on the plasma levels of OP, scientific sources give quite contradictory data.

The study EUTOPIA showed that ARBs olmesartan has the ability to reduce plasma levels of OP. Authors attributed this fact to possible inflammatory marker [17]. In this case, despite the fact that the level of C-reactive protein is within the reference ranges for all patients who had increased levels of OP, in comparison with the control group. That may indicate non-inflammatory nature of this marker. Concerning the relationship between the level of OP and vascular remodeling, it should be noted that some researchers have found any [17], other researchers have found these links [21]. Clearly, the role of OP in processes of CV remodeling needs further clarification. Study of the OP role in the development of cardiovascular calcification in patients on hemodialysis seems to be rather challenging.

Conclusions

1. Plasma levels of OP are significantly higher in the hemodialysis patients compared to the control group (246, 23 ± 50,31 vs 64,1 ± 21,31 ng/ml).

2. Candesartan treatment was associated with significant reduction of the mSBP, mDBP, mPBP, decreasing plasma OP by 18,5%, decreasing LVMI by 9,9%, reducing RI by 20%.

3. It was found positive correlations between plasma levels of OP and cIMT, mSBP, LVMI, that were measured after treatment with candesartan.

It is interesting to study the role of OP in the development of vascular calcification in hemodialysis patients, the study of long-term effects of therapy with candesartan on cardiovascular calcification in patients with chronic kidney disease.

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