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ENDOTHELIAL FUNCTION OF VESSELS IN PATIENTS WITH CHRONIC KIDNEY DISEASE COMBINED WITH SUBCLINICAL HYPOTHYROIDISM UNDER THE INFLUENCE OF COMBINED ANTIHYPERTENSIVE THERAPY

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Ключові слова: *хронічна хвороба нирок, артеріальна гіпертензія, субклінічний гіпотиреоз, комбінована антигіпертензивна терапія, ендотелій-залежна вазодилятація*
Ключевые слова: *хроническая болезнь почек, артериальная гипертензия, субклинический гипотиреоз, комбинированная антигипертензивная терапия, эндотелий-зависимая вазодилатация*

Abstract. Endothelial function of vessels in patients with chronic kidney disease combined with subclinical hypothyroidism under the influence of combined antihypertensive therapy. Garmish I.P. *The aim of the study: to evaluate the endothelial function of the vessels under the influence of combined antihypertensive therapy (valsartan 160 mg / amlodipine 5 mg vs valsartan 160 mg / hydrochlorothiazide 12,5 mg) in patients with CKD and subclinical hypothyroidism. 80 patients with CKD I-II stages and AH 1 and 2 degrees were examined. According to TSH level patients were divided into 2 groups. Than patients with SH were separated into 2 subgroups: 1a – patients that received valsartan 160mg/ amlodipine 5 mg and 1b - patients that received valsartan 160mg/ hydrochlorothiazide 12,5 mg). More often violation of brachial artery flow-mediated dilation was found among the main group. The use of two-component antihypertensive therapy based on valsartan 160 mg and amlodipine 5 mg or valsartan 160 mg and hydrochlorothiazide 12,5 mg ensured the achievement of target blood pressure levels in 83,3% and 84% of patients, respectively. The more significant improvement of brachial artery flow-mediated dilation was observed in patients that received fixed combination valsartan 160 mg/amlodipine 5 mg.*

Реферат. Ендотеліальна функція судин у хворих на хронічну хворобу нирок у поєднанні з субклінічним гіпотиреозом під впливом комбінованої антигіпертензивної терапії. Гарміш І.П. *Мета дослідження: оцінити ендотеліальну функцію судин під впливом комбінованої антигіпертензивної терапії (валсартан 160 мг / амлодипін 5 мг проти валсартану 160 мг / гідрохлортіазид 12,5 мг) у пацієнтів з ХХН і субклінічним гіпотиреозом. Досліджували 80 пацієнтів з ХХН I-II стадії та АГ 1 і 2 ступеня. Згідно з рівнем ТТГ пацієнти були розподілені на 2 групи. Потім пацієнти з субклінічним гіпотиреозом були розподілені на 2 підгрупи: 1а - пацієнти, які отримували валсартан 160 мг / амлодипін 5 мг та 1b - пацієнти, які отримували валсартан 160 мг / гідрохлортіазид 12,5 мг. найчастіше порушення ендотелій-залежної вазодилятації було виявлено серед основної групи. Використання двокомпонентної антигіпертензивної терапії на основі валсартану 160 мг і амлодипіну 5 мг або валсартану 160 мг і гідрохлортіазиду 12,5 мг забезпечувало досягнення цільового рівня артеріального тиску у 83,3% і 84% пацієнтів відповідно. Більш значне поліпшення ендотелій-залежної вазодилятації спостерігалося в пацієнтів, які отримували фіксовану комбінацію валсартан 160 мг / амлодипін 5 мг.*

The relationship between elevated blood pressure (BP) and chronic kidney disease (CKD) is known for many years. On the one hand, CKD is the most common cause of symptomatic arterial hypertension, on the other hand, increased BP, despite its etiology, leads to a decrease in the functional capacity of the kidneys [1, 2]. Today, the frequency of arterial hypertension (AH) among patients with CKD I-II stages is 40%, but with reduced glomerular filtration rate (GFR) up to 60 ml/min / 1,73 m^2, this number is sharply increasing and at the terminal stage of CKD is over 90% [3]. It is well-known that mortality of nephrological patients is formed mainly due to cardiovascular events. Therefore, in modern medicine, the tactics of treating patients with CKD is based on: 1) the treatment of the kidney itself, if

possible; 2) reduction of cardiovascular risk, first of all it is the control of BP [4]. At the same time, today, more and more attention is paid to the states with a combination of two or more diseases. These conditions are called comorbidity (simultaneous damage to two organs or body systems or two diseases), poly-, multimorbidity (≥3 diseases), concomitant pathology, or associated diseases.

Thus, GFR decreasing is associated with a higher incidence of clinical and subclinical hypothyroidism (SH). SH is a proven lethality predictor among patients in dialysis, and a risk factor for nephropathy and cardiovascular events in patients with type 2 diabetes [5, 6]. SH is also considered as a potential predictor of the development of complications and increased mortality in patients with CKD. Traditionally it is believed that with hypothyroidism, hypertension is noted with a predominant increase in diastolic blood pressure (DBP) [5, 7]. However, recently there were results of researches, according to which the cause of hypertension in patients with hypothyroidism is heterogeneous: with an increase in the age of patients increases the percentage of patients with hypertension of mixed genesis, which leads to progressive increase in BP [8]. Thus, AH, CKD and SH contribute to the mutual aggravation of each of these diseases, the rapid development and progression of lesions of the target organs, and also substantially complicate the implementation of effective and safe antihypertensive therapy [3, 4]. ESH / ESC, taking into account the results of the ACCOMPLISH study, prefer the calcium channel blocker (CCB) as the second level of antihypertensive therapy. In this study, the same ACE inhibitor was compared with a diuretic or calcium antagonist - the combination of ACE inhibitor diuretics was less effective in reducing of cardiovascular events than the combination of calcium antagonist, although BP in both groups did not differ. In the KDIGO recommendations 2012, preference is given to thiazide and thiazide-like diuresis (Clinical Practice Guideline for management of Blood Pressure in Chronic Kidney Disease). It should be noted that in existing studies where AH was studied in hypothyroidism, it was CCB that more effectively influenced on the BP level. However, a small number of studies on the characteristics of the course and treatment of hypertension in patients with reduced function of the kidneys in combination with SH does not give an unambiguous answer, which combination of antihypertensive drugs will be more effective for these patients.

The aim of the study: to evaluate the endothelial function of the vessels under the influence of combined antihypertensive therapy (valsartan 160 mg / amlodipine 5 mg vs valsartan 160 mg / hydrochlorothiazide 12.5 mg) in patients with CKD and subclinical hypothyroidism.

MATERIALS AND METHODS

The study included 80 patients. The mean age of patients was 54.2±7.5 years, 49 men and 31 women. Criteria for inclusion: arterial hypertension 1-2th degree; CKD I-II stages (GFR>60 ml/min / 1.73 m^2); presence of SH (TSH level>4.3 mE / l); signed informed consent of the patient. The study was conducted in accordance with the requirements of the Helsinki Declaration and after approval of the local ethics commission of the medical institution. The diagnosis of SH was established after consultation of the endocrinologist based on the levels of TSH and free T4. AH was diagnosed according to the Order of the Ministry of Health of Ukraine N 384 of 24.05.2012 and recommendations ESH/ESC (2013) on treatment of hypertension. The diagnosis of CKD was established according to the Order of the Ministry of Health of Ukraine N 593 dated 12.12.2014. Exclusion criteria: GFR<60 ml/min /1.73 m^2; TSH level >10 mU/l; type 1 diabetes and type 2 diabetes insulin-dependent; body mass index >40 kg/m^2; hemodynamically significant cardiovascular diseases, arrhythmias and heart disease requiring medical or surgical treatment, acute myocardial infarction and acute cerebrovascular accident in up to 6 months; resistant arterial hypertension; severe decompensated heart failure of the III-IV functional class.

All patients were divided into 2 groups: the main group (n=55) – patients with CKD and subclinical hypothyroidism and the comparison group (n=25) – patients with preserved thyroid function and CKD. At the second stage, patients of the main group were divided into 2 subgroups, depending on the antihypertensive therapy:

• 1a subgroup (n=30) – patients with CKD in combination with SH who received a fixed combination of valsartan 160 mg / amlodipine 5 mg

• 1b subgroup (n=25) – Patients with CKD in combination with SH who received a fixed combination of valsartan 160 mg / hydrochlorothiazide 12.5 mg (Tab. 1).

The office measurement of BP was performed 4 times: at the beginning of the study, in 10 days, in 1 month and 3 months. Brachial artery flow-mediated dilation was measured at the beginning of the study, and after 3 months. Investigation of the functional state of the endothelium by calculation of endothelium dependent vasodilatation was carried out according to the method described by D. Celermajer [9]. With an increase in arterial diameter of 10% and above, the functional state of the endothelium was

considered to be preserved. The level of GFR was calculated using the formula CKD-EPI (2011) [9].

The statistical analysis was conducted using Microsoft Excel 2010 (Microsoft), STATISTICA for Windows 6.0 (StatSoft Inc., USA). The reliability of the differences was determined using Student's parametric t-criterion and Wilcoxon's non-parametric criterion.

Table 1

Characteristics of researched groups (Me [25; 75%])

Indicators	Main group (n=55)		Comparison group (n=25)
	1a subgroup (n=30)	1б subgroup (n=25)	
Sex: male/female, n (%)	18 (60%)/12 (40%)	15 (60%)/10 (40%)	16 (64%)/9(36%)
Age, years (Me [25%; 75%])	55,21 [37; 65]	54,35 [36; 68]	54,79 [34; 67]
Blood pressure (AT), mm Hg			
Systolic (Me [25%; 75%])	160,1 [144; 180]	159,7 [143; 180]	153,4 [142; 179]
Diastolic (Me [25%; 75%])	96,3 [86; 100]	95,9 [87; 112]	91,2 [85; 109]
Heart rate per minute (Me [25%; 75%])	74,65 [64; 98]	72,42 [66; 95]	78,6 [71; 94]
GFR, ml/min/1,73 m^2 (Me [25%; 75%])	68,9 [64; 91]	71,1 [65; 92]	72,2 [69; 94]
TSH level, mU/L (Me [25%; 75%])	7,29* [4,62; 9,26]	7,98* [4,54; 9,89]	2,18* [0,95; 3,86]

N o t e . * p<0,001 - the reliability of differences between groups.

RESULTS AND DISCUSSION

At the beginning of the study, a violation of the functional status of the endothelium of vessels was established among 52 (94,6%) patients with CKD in combination with subclinical hypothyroidism and among 18 (72%) patients with CKD and euthyroidism. In patients with CKD in combination with SH, inverse relationship was established between the level of TSH and the functional state of the vascular endothelium (r = -0,674; p <0,001) (Fig. 1).

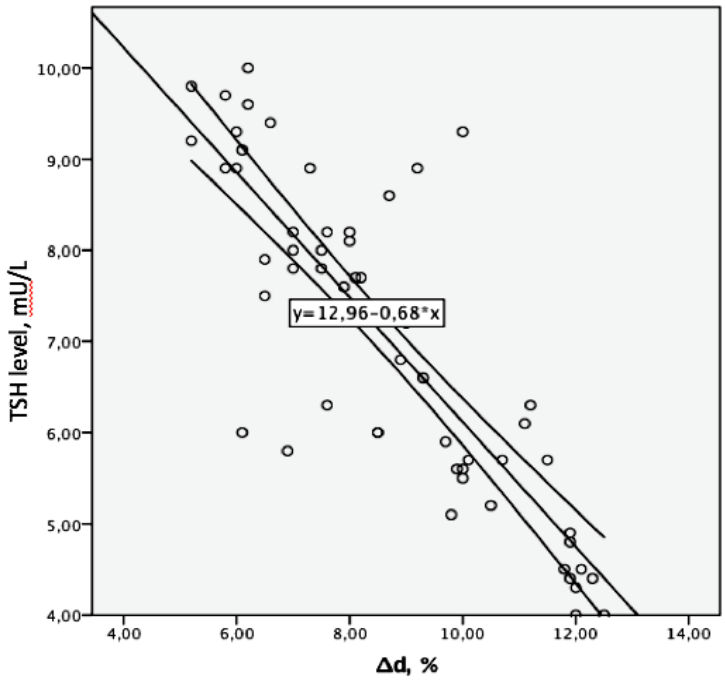
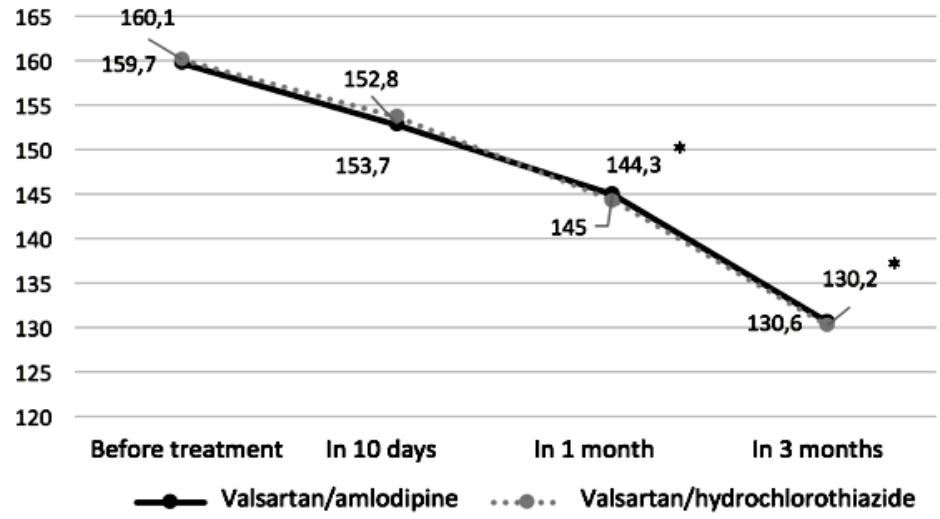


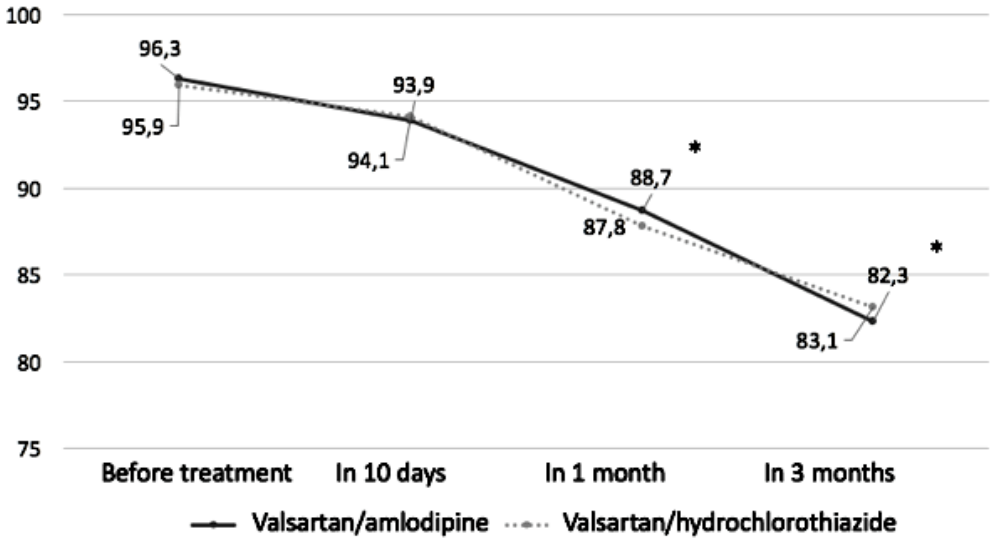
Fig. 1. Correlation between the level of TSH and the functional state of the endothelium of vessels in patients with CKD in combination with SH

Target BP levels after 3 months of observation were achieved in 25 (83.3%) patients of 1a subgroup and 21 (84%) patients of 1b subgroup. The doses of amlodipine up to 10 mg and hydrochlorothiazide 25 mg per day, respectively, were increased for five patients of 1a subgroup and four patients of 1b subgroup that did not reach the target BP. Already in 10 days a positive dynamic in the direction of lowering blood pressure in both subgroups was observed. But a statistically significant reduction of blood pressure was recorded only from the first month of combined antihypertensive therapy. At the end of the study, the systolic blood pressure (SBP) in 1a subgroup decreased by 22.9%, diastolic blood pressure (DBP) decreased by 14.5%; among patients of 1b subgroup SBP decreased by 18.2%, and DBP by 13.3% (p <0,01) (Fig. 2, 3).



N o t e . * p <0,01 - reliability of differences within subgroups

Fig. 2. Dynamics of office SBP in patients with CKD and subclinical hypothyroidism during antihypertensive therapy



N o t e . * p <0,01 - reliability of differences within subgroups

Fig. 3. Dynamics of office DBP in patients with CKD and subclinical hypothyroidism during antihypertensive therapy

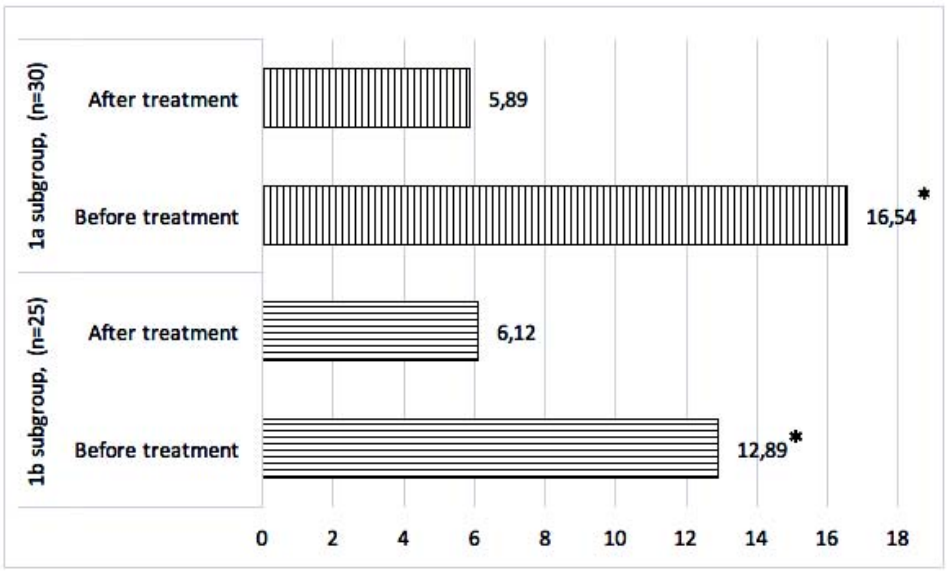
In the beginning of the study violation of brachial artery flow-mediated dilation was detected in 27 (90%) patients in the 1a subgroup and in 23 (92%) patients in 1b subgroup. A reliable improvement of the functional state of the endothelium was noted in both subgroups (Tab. 2).

Table 2

Functional state of the endothelium of vessels of patients of both subgroups on the background of treatment

	1a subgroup (n=30)			1б subgroup (n=25)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
Patients with violation of brachial artery flow-mediated dilation, n (%)	28 (93,3%)	6 (20%)	<0,01	24 (96%)	8 (32%)	<0,05
Patients with normal violation of brachial artery flow-mediated dilation, n (%)	2(6,7%)	24 (80%)	<0,001	1 (4%)	17 (68%)	<0,01

However, a more pronounced increase in the diameter of the brachial artery was observed among the subgroup of patients receiving, a fixed combination of valsartan 160 mg and amlodipine 5 mg as antihypertensive therapy. In this subgroup, the brachial artery flow-mediated dilation index increased by 2.8 times, and in the other subgroup – by 2.1 times (Fig. 4).



N o t e . * p <0,05 - the reliability of the differences between subgroups.

Fig. 4. Dynamics of the functional state of the endothelium in patients with CKD and subclinical hypothyroidism in the context of multi-component antihypertensive therapy

CONCLUSIONS

1. In patients with chronic kidney disease combined with subclinical hypothyroidism, there is a more pronounced impairment of the endothelial function of the blood vessels compared with those with thyroid preservation.

2. The use of two-component antihypertensive therapy based on valsartan 160 mg and amlodipine 5 mg or valsartan 160 mg and hydrochlorothiazide 12,5 mg ensured the achievement of target blood pressure levels in 83.3% and 84% of patients, respectively.

3. Two-component antihypertensive therapy based on valsartan 160 mg and amlodipine 5 mg significantly affects the functional state of the endothelium in patients with chronic kidney disease in combination with subclinical hypothyroidism compared with two-component antihypertensive therapy based on valsartan 160 mg and hydrochlorothiazide 12,5 mg.

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