

METABOLIC PATTERN, CHOLECALCIFEROL, PARATHYROID HORMONE AND IONIZED CALCIUM VALUES IN PATIENTS WITH ARTERIAL HYPERTENSION AND CHRONIC KIDNEY DISEASE

B. A. Lytvyn, L. P. Sydorчук

Bukovinian State Medical University, Chernivtsi, Ukraine

Key words:

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E-mail:
dr.bogdan@ukr.net

Arterial Hypertension (AH), Diabetes Mellitus along with other metabolic disorders are among the leading causes of kidney damage worldwide.

Objective – to investigate the metabolic pattern, cholecalciferol and ionized calcium blood values in patients with essential AH (EAH) and chronic kidney disease (CKD) depending on gender.

Material and methods. 100 EAH patients and 60 practically healthy individuals participated in the study. All participant underwent a complex of clinical and laboratory examinations. Metabolism was analyzed by the lipid profile (total cholesterol (TC), high-, low density lipoproteins (HDL-C, LDL-C), atherogenity index (AI), triacylglycerols (TG)), blood glucose, creatinine, cystatin-C, bilirubin, cholecalciferol, ionized calcium, parathyroid hormone (PTH) and albuminuria values. Body mass index (BMI), waist circumference (WC), hip circumference (HC) and waist to hip ratio (WHR) were also determined.

Results. The CKD appearance in EAH patients is accompanied by a higher blood pressure (BP) values (systolic BP – 5.98 % ($p=0.012$), diastolic BP – 5.57 % ($p=0.007$)), mainly in women – 6.34 % ($p=0.008$) and 5.81 % ($p=0.013$), respectively; a higher bilirubin blood concentration – 27.79 % ($p=0.007$), creatinine and cystatin-C regardless of gender (stronger in men) – by 21.76-26.67 % ($p<0.001$), glucose (significantly in men) – 33.49 % ($p=0.035$), with a lower level of ionized Ca^{2+} ($p=0.05$), HDL-C – 16.81 % ($p=0.02$), which cause an increase of the AI (reliably in men) – 35.36 % ($p=0.027$); higher BMI – 24.67 % ($p=0.003$) and WC – 14.97 % ($p=0.023$) in men. Also, in EAH patients with CKD, more massive albuminuria is observed in general – 32.45 % ($p=0.02$), reliably only in women – 44.20 % ($p=0.004$). Changes in the vitamin D metabolites concentration and PTH were not associated with CKD in EAH patients in our study.

Conclusion. A proatherogenic pattern, hyperglycemia, excess body weight/or obesity (mainly in men), albuminuria and hemodynamic disorders (mainly in women) generally form metabolic changes in EAH patients with CKD.

Ключові слова:

артеріальна гіпертензія,
хронічна хвороба нирок,
альбумінурія, вітамін
D, паратгормон,
цистатин-С, ліпіди, ХС
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МЕТАБОЛІЧНИЙ ПАТЕРН, РІВНІ ХОЛЕКАЛЬЦИФЕРОЛУ, ПАРАТГОРМОНУ ТА ІОНІЗОВАНОГО КАЛЬЦІЮ У ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ І ХРОНІЧНУ ХВОРОБУ НИРОК

Б. А. Литвин, Л. П. Сидорчук

Буковинський державний медичний університет, м. Чернівці, Україна

Артеріальна гіпертензія (АГ), цукровий діабет поряд з іншими метаболічними розладами є одними з провідних причин ураження нирок у світі.

Мета роботи – дослідити метаболічний патерн, рівні холекальциферолу, паратгормону та іонізованого кальцію у хворих на есенційну артеріальну гіпертензію (ЕАГ) і хронічну хворобу нирок (ХХН) з урахуванням статі.

Матеріали і методи. У дослідженні взяли участь 100 хворих на ЕАГ і 60 практично здорових осіб групи контролю, які пройшли комплекс клінічно-лабораторних обстежень. Метаболізм аналізували за ліпідним профілем (загальним холестеролом (ЗХС), ліпопротеїнами високої і низької щільностей (ХС ЛПВЩ, ХС ЛПНЩ), коефіцієнтом атерогенності (КА), триацилгліцерилами (ТГ)), вмістом у крові глюкози, креатиніну, цистатину-С, білірубину, холекальциферолу, іонізованого кальцію, паратгормону (ПТГ) та альбумінурії. Також визначали індекс маси тіла (ІМТ), обвід талії (ОТ), стегон (ОС), їх співвідношення (ОТ/ОС).

Результати. Поява ХХН у хворих на ЕАГ супроводжується вищим рівнем артеріального тиску (АТ) (систоличного АТ – на 5,98 % ($p=0,012$), діастолічного АТ – на 5,57 % ($p=0,007$)), переважно у жінок – на 6,34 % ($p=0,008$) і 5,81 % ($p=0,013$) відповідно; вищою концентрацією у крові білірубину – на 27,79 % ($p=0,007$), креатиніну та цистатину-С незалежно від статі (суттєвіше у чоловіків) – на 21,76-26,67 % ($p<0,001$), глюкози (вірогідно у чоловіків) – на 33,49 % ($p=0,035$), за нижчого рівня іонізованого Ca^{2+} ($p=0,05$), ХС ЛПВЩ – на 16,81 % ($p=0,02$), що зумовило збільшення

коєфіцієнту атерогенності (вірогідно у чоловіків) – 35,36 % ($p=0,027$); більшим ІМТ – на 24,67 % ($p=0,003$) і ОТ – на 14,97 % ($p=0,023$) у чоловіків. Також при ХХН у хворих на ЕАГ спостерігається масивніша альбумінурія загалом – на 32,45 % ($p=0,02$), достовірно тільки у жінок – на 44,20 % ($p=0,004$). Зміни концентрації сумарних метаболітів вітаміну D і паратгормону не асоціюють із ХХН у пацієнтів із ЕАГ у нашому дослідженні.

Висновок. Проатерогенний патерн, гіперглікемія, надмірна маса тіла /чи ожиріння (переважно у чоловіків), альбумінурія і гемодинамічні розлади (переважно у жінок) формують загалом зміни метаболізму при ХХН у хворих на ЕАГ.

Introduction

Arterial Hypertension (AH) is a primary risk factor for cardiovascular disease and global mortality. There is a close interrelation between AH and chronic kidney disease (CKD), as hypertension can lead to declining renal function, while progressive CKD can exacerbate hypertension [3, 4, 14]. The pathophysiology of AH in CKD is intricate and involves multiple factors, such as a decreased number of functioning nephrons, sodium retention, volume expansion, activation of the sympathetic nervous system, hormonal influences like the renin-angiotensin-aldosterone system upregulation, and endothelial dysfunction [7, 12].

Blood pressure (BP) variability in the chronic kidney disease (CKD) population is significant and requires close monitoring for appropriate management. With accumulating evidence, the diagnosis and management of AH in CKD and vice versa have been evolving over the last decade. The Kidney Disease: Improving Global Outcomes (KDIGO) Organization in 2024 upgraded Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [8].

Diabetes Mellitus (DM), other metabolic disorders in addition to AH are among the leading causes of kidney damage worldwide. Essential AH (EAH) and diabetes account for 63 % of all CKD cases [8]. In the American population, CKD is registered in 23 % of hypertensive patients [22], in the Italian population – in 42 % likewise [9]. Thus, the problem of early diagnosis of genetic, cardiometabolic, and immunological causes of CKD development in EAH patients in the cardiovascular diseases' continuum is on cutting edge and requires further investigation.

Objective

To investigate the metabolic pattern, cholecalciferol, parathyroid hormone and ionized calcium blood values in patients with EAH and CKD depending on gender.

Research material and methods

The EAH patients were selected in accordance with the guidelines and recommendations of the National Ukrainian and European Societies of Cardiology and Hypertension (ESC, ESH 2018, 2023) [1, 12].

The research protocol was approved by the Bioethics commission at the Bukovinian State Medical University. 100 patients with Hypertension-mediated organ damage (IInd stage), 1st-3rd degrees of arterial blood pressure (BP) elevation, moderate, high, or very high cardiovascular risk were screened and selected for the study. The patients age ranged from 45 to 70 years (59.87 ± 7.98 years on average), 21.0 % of them were men, 79.0 % were women. The control group consisted

of 60 practically healthy people (22 men (36.67 %), 38 women (63.33 %)), aged 44.39 ± 5.92 years ($p < 0.001$). The groups did not differ by sex. All participants signed an informed consent to participate in the study.

Comprehensive examination included: anthropometric (body mass index, (BMI), waist and hip circumference (WC, HC), waist-to-hip ratio (WHR)), general clinical, laboratory (general blood and urine tests, urine protein, fasting plasma glucose, serum creatinine, cystatin-C, bilirubin, lipid spectrum), instrumental (12-lead ECG, Echocardiogram, office BP, ultrasound of the kidneys), as well as consultations of an ophthalmologist and a neurologist, if necessary. Besides, the level of ionized calcium was determined in all patients by the potentiometric method using the blood electrolyte analyzer SINO 005 (Sinnowa, China). The lipid panel was studied using colorimetry after serum content of total cholesterol (TC), triacylglycerols (TG) and high-density lipoprotein cholesterol (HDL-C). Serum low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald equation, atherogenicity index (AI) – according to Klimov's equation [5, 10, 18, 19, 21].

The parathyroid hormone (PTH) and cholecalciferol (the total metabolites of 25(OH) vitamin D) blood concentration were determined by the immunochemiluminescence method according to the manufacturer's instructions using the device «MAGLUMI 1000 Plus» («SNIBE», China) [20].

CKD was diagnosed in 43 EAH patients according to the US National Kidney Association recommendations (KDIGO 2024) [8]. Glomerular filtration rate (GFR) was calculated using the CKD-EPI equation based on cystatin-C and creatinine serum values (depending on gender). There were 35 women (44.30 %) and 8 men (38.10 %) among EAH patients with CKD. A decrease in GFR was defined as ≤ 60 ml/min/1.73m², for ≥ 3 months with or without other signs of kidney damage, according to the KDIGO recommendations (2024) [8].

The statistical analysis was carried out by the variational statistics methods using the Statistica v.7.0 software (StatSoft Inc., USA). The differences between groups for independent samples were verified using the unpaired Student's t-test (if the data distribution were close to normal according to the Kolmogorov-Smirnov tests and the Shapiro-Wilk W-test), or the Wilcoxon-Mann-Whitney U-test (for an uneven data distribution). Differences were considered significant at $p < 0.05$.

Results and Discussion

In EAH patients with CKD ($GFR \leq 60$ ml/min/1.73m²) higher systolic and diastolic BP (SBP, DBP) were

established – 5.98 % ($p_1=0.012$) and 5.57 % ($p_1=0.007$), mostly in women: SBP–6.34 % ($p_1=0.008$), DBP–5.81 % ($p_1=0.013$), respectively (Tab.1). Some anthropometric parameters also prevailed in EAH patients with CKD, over those without CKD, but only in men: for BMI – 24.67 % ($p_1=0.003$), for WC – 14.97 % ($p_1=0.023$). Most

anthropometric data in men with CKD exceed those in women with CKD. SBP and DBP in practically healthy subjects of control group, in contrast to patients, are higher in men than in women – 3.76 % ($p_w=0.036$) and 6.58 % ($p_w=0.035$), as well as WC and WHR – 21.96 % and 20.51 % ($p_w<0.001$).

Table 1
Some clinical and anthropometric parameters depending on glomerular filtration rate according to Cystatin-C and gender

Parameters		Control group, n=60	Patients (study group), n=100	
			GFR ≤60 ml/min/1.73m ² , n=43	GFR >60 ml/min/1.73m ² , n=57
BMI, kg/m ²	W	25.18±1.15	30.96±1.45 $p<0.001$	31.45±1.38 $p<0.001$
	M	27.02±0.83	35.58±1.43 $p<0.001$; $p_w=0.028$	28.54±0.66 $p_1=0.003$; $p_w=0.01$
SBP, mm Hg		116,33±2,36	158.97±4.48 $p<0.001$	150.0±3.57 $p<0.001$; $p_1=0.012$
DBP, mm Hg		76,0±2,58	98.12±2.80 $p<0.001$	92.94±1.89 $p<0.001$; $p_1=0.007$
WC, cm	W	78.79±2.93	98.17±2.40 $p<0.001$	100.67±2.97 $p<0.001$
	M	96.09±2.24 $P_w<0.001$	115.50±4.41 $p=0.007$; $p_w=0.002$	100.46±2.60 $p_1=0.023$
WHR, yo	W	0.78±0.02	0.88±0.01 $p<0.001$	0.90±0.02 $p<0.001$
	M	0.94±0.02 $p_w<0.001$	1.0±0.02 $P_w<0.001$	0.97±0.02 $p_w=0.004$

Note. P – probability of data differences with the control group; P_1 – probability of differences with patients whose GFR ≤60 ml/min/1.73m²; P_w – probability of differences between women and men within each subgroup according to a particular indicator; BMI – body mass index; SBP, DBP – systolic, diastolic blood pressure; WC – waist circumference; WHR – Waist-to Hip Ratio; W – women; M – men

EAH patients with CKD have a higher blood creatinine and Cystatin-C values, regardless of gender, more in men – 21.76-26.67 % ($p_1<0.001$), as well as more massive albuminuria in general – 32.45 % ($p=0.02$), but reliably only in women – 44.20 % ($p=0.004$).

The glucose blood concentration is higher in EAH patients with CKD (GFR ≤60 ml/min/1.73m²) than

without CKD, but only in men – 33.49 % ($p_1=0.035$), and the content of HDL-C on the contrary is lower – 16.81 % ($p_1=0.02$), which led to an increase in AI in general 13.29 % ($p_1=0.055$), significantly in men – 35.36 % ($p_1=0.027$). Most parameters of lipid-carbohydrate metabolism in patients deviated from reference values and those in controls (glucose, TG in women, AI and HDL-C) (Tab. 2).

Table 2
Parameters of lipids metabolism and glucose level depending on glomerular filtration rate according to Cystatin-C and gender

Parameters		Control group, n=60	Patients after GFR value, n=100	
			≤60 ml/min/1.73m ² , n=43	>60 ml/min/1.73m ² , n=57
Blood glucose, mmol/l	W	5.0±0.17	7.45±0.85 $p=0.005$	7.47±0.82 $p=0.002$
	M	5.28±0.13	8.65±0.84 $p<0.001$	6.48±0.45 $p=0.017$; $p_1=0.035$
Total cholesterol, mmol/l		5.55±0.22	5.63±0.32	5.64±0.29
Triacylglycerols, mmol/l		1.64±0.17	2.19±0.25 $p=0.019$	1.87±0.23
LDL-C, mmol/l		3.95±0.22	4.18±0.29	4.17±0.26
HDL-C, mmol/l	W	1.53±0.07	1.28±0.07 $p=0.014$	1.31±0.06 $p=0.005$
	M	1.24±0.09 $p_w=0.043$	0.99±0.05 $p=0.024$; $p_w=0.009$	1.19±0.06 $p_1=0.02$
AI, U		3.18±0.36	3.92±0.38 $p=0.04$	3.46±0.23 $p_1=0.055$

Note. P – probability of data differences with the control group; P_1 – probability of differences with patients whose GFR ≤60 ml/min/1.73m²; P_w – probability of differences between women and men within each subgroup according to a particular indicator; W – women; M – men; AI – atherogenicity index

The cholecalciferol concentration in EAH patients is lower than in the control group, regardless of GFR values, but reliably only in women – 11.76 % ($p=0.022$) and 10.0 % ($P=0.048$) with higher PTH content mainly in women – 24.61-30.64 % ($p≤0.046-0.022$). The level of ionized calcium (Ca²⁺) in EAH patients with CKD (GFR ≤60 ml/min/1.73m²) is generally marginally lower than in those without CKD ($p=0.05$) (Tab. 3).

The kidney performs numerous functions, including excretory, endocrine, and metabolic roles. GFR is a key indicator of excretory function and is widely accepted as the best overall measure of kidney function. GFR

typically decreases following extensive structural damage to the kidneys, and most other kidney functions decline in parallel with GFR in CKD. Metabolic disorders are pathological conditions where multiple risk factors for CKD, such as obesity, hypertension, hyperglycemia and dyslipidemia (characterized by high triglycerides and low HDL-C), coexist in individuals [2, 15, 25]. The incidence of metabolic disorders is on the rise as well as the prevalence of CKD has shown a steady annual increase in recent years. This trend poses a serious threat to life and health, imposes economic burdens on society and families, and diminishes the quality of life for those affected [8, 16].

Table 3

Parameters of metabolic-hormonal activity and ionized calcium depending on glomerular filtration rate according to Cystatin-C and gender

Parameters	Control group, n=60	Patients (study group), n=100	
		GFR ≤60 ml/min/1.73m ² , n=43	GFR >60 ml/min/1.73m ² , n=57
Total metabolites of vitamin D, ng/ml	23.86±1.26	21.69±1.43 p=0.048	21.35±1.25 p=0.022
Parathyroid hormone, pg/ml	57.76±3.48	72.58±7.64 p=0.025	75.46±8.77 p=0.022
Ionized calcium, mmol/l	1.16±0.01	1.16±0.009	1.18±0.007 p=0.052 p _i =0.05

Note. P – probability of data differences with the control group; P_i – probability of differences with patients whose GFR ≤60 ml/min/1.73m²

Xiao H. et al. proved that metabolic syndrome as its single or combined components are independently associated with CKD in populations of Southern China aged 40 years and older, in both non-diabetic and non-obese subjects [23]. In our study the EAH and CKD comorbidity also associate with metabolic and electrolyte changes: higher blood level of bilirubin, creatinine and Cystatin-C (more in men) – 21.76-26.67 %, atherogenicity index – 35.36 %, with lower ionized Ca²⁺ and HDL-C – 16.81 %.

Non-communicable diseases and conditions such as hypertension [11], diabetes [4] or insulin resistance [17], obesity [6] and dyslipidemia [13] are also risk factors for CKD [24]. In our study EAH patients with CKD had higher SBP and DBP (significantly in women) – 6.34 % and 5.81 % and higher BMI 24.67 %, WC – 14.97 % and glucose – 33.49 % as well, than those without CKD.

There are numerous kidney disorders that may manifest with tubular dysfunction rather than only a decrease in GFR. These conditions primarily lead to symptoms such as polyuria, albuminuria, and/or electrolyte imbalances, and they may or may not progress to reduced GFR or chronic kidney failure. Therefore, relying solely on GFR for diagnosing CKD would not be sufficient. It is crucial to recognize and utilize various markers that reflect different aspects of kidney function to obtain a comprehensive diagnosis. Therefore, in our research we rely upon not exclusively on GFR in diagnosing CKD, but use albuminuria level and electrolyte imbalance as well.

Thus, understanding the linkage between metabolic disorders and CKD, as well as implementing effective intervention measures to control them, will help alleviate the burden that chronic diseases affect medical resources worldwide.

Conclusions

1. In patients with essential arterial hypertension (EAH), the onset of chronic kidney disease (CKD) is accompanied by a higher level of blood pressure, mainly in women – 6.34 % and 5.81 %; higher BMI – 24.67 % and WC – 14.97 % in men; higher blood concentration of bilirubin – 27.79 %, creatinine and Cystatin-C regardless of gender (stronger in men) – 21.76-26.67 %, glucose (more in men) – 33.49 %, with lower level of ionized Ca²⁺, HDL cholesterol – 16.81 %, higher atherogenicity index (reliably in men) – 35.36 %.

2. The presence of CKD in EAH patients is characterized by more massive albuminuria in general – 32.45 %, but reliably only in women – 44.20 %.

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Prospects for further research

We see the prospects for further research in the study of metabolic changes in EAH patients taking into account salt sensitivity / salt resistance and genetic factors.

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Відомості про авторів:

Литвин Б. А. – аспірант кафедри сімейної медицини, Буковинський державний медичний університет, м. Чернівці, Україна.

E-mail: dr.bogdan@ukr.net

Сидорчук Л. П. – доктор медичних наук, професор, завідувач кафедри сімейної медицини, Буковинський державний медичний університет, м. Чернівці, Україна.

E-mail: lsydorchuk@ukr.net

ORCID ID: <https://orcid.org/0000-0001-9279-9531>

Information about the authors:

Lytvyn B. A. – Post-graduate, Department of Family Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine.

E-mail: dr.bogdan@ukr.net

Sydorchuk L. P. – Doctor of Science, Professor, Head of the Department of Family Medicine, Bukovinian State Medical University, Chernivtsi, Ukraine.

E-mail: lsydorchuk@ukr.net

ORCID ID: <https://orcid.org/0000-0001-9279-9531>

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