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ABSTRACT

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ALPHA-ADDUCIN 1 (ADD1) GENE, CLINICAL-DEMOGRAPHIC AND METABOLIC PREDICTORS OF ARTERIAL HYPERTENSION AND CHRONIC KIDNEY DISEASE IN WESTERN UKRAINE POPULATION

Introduction. Chronic kidney disease (CKD) is a global public health problem affecting about 10% of the population worldwide. Nowadays, the genetic predisposition to CKD development in patients with arterial hypertension (AH) is studied insufficiently. Therefore, the search for early CKD predictors due to hypertension is on the cutting edge of contemporary medicine. **Objectives**: to evaluate the risk of essential AH (EAH) and CKD in the population of Western Ukraine (North Bukovina) based on some demographic, clinical, and anthropometric data, gender, and alfa adducin 1 gene (ADD1; rs4961).

Materials and methods. 100 patients with EAH and 60 practically healthy (control group) participated in the study. All participants underwent clinical and laboratory examinations. Among the risk factors, a burdened anamnesis of cardiovascular disease (CVD), type 2 diabetes mellitus (DM2), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), body mass index (BMI) in men (M) and women (W) were studied. CKD was defined by glomerular filtration rate (GFR) according to the CKD-EPI equation, taking into account creatinine (cr) and cystatin-C (cys) blood levels (KDIGO, 2024). ADD1 (rs4961) gene polymorphism genotyping was performed by real-time PCR.

The results. The risk of EAH is 4 times higher with CVD burdened (95% CI: 1.15-13.88; p=0.027), 8.5 times higher – in the smokers who are carriers of the GG-genotype of the ADD1 gene (rs4961) (OR=8.67; 95% CI: 1.04–72.32; p=0.02), almost 2.5 times higher – with hypercystatinemia-C (≥1.1 mg/l) in T-allele carriers (rs4961), but the difference is significant only in women – by 4.67 times (95% CI: 1.19–18.33; p=0.033). The GG-genotype of the ADD1 gene (rs4961)

increases the CKD risk in EAH men by 2.67 times (95% CI: 1.0–7.34; p=0.047). The EAH risk increases regardless of ADD1 gene polymorphic variants (somewhat stronger in patients with mutated T-allele) in subjects with obesity – by 3.37 and 12 times (95% CI: 1.23–9.24; p=0.014 and 95% CI: 2.24–64.29; p=0.001), in subjects with increased WC (W >88 cm, M >102 cm) – by 4.14 and 45 times (95% CI: 1.49–11.48; p=0.006 and 95% CI: 7.34–275.8; p<0.001), in subjects with increased BMI (≥25.0 kg/m^2) and WHR (>0.85 U) – but only in women – by 5.78–9.90 and 30.33–60.67 times (95% CI: 1.12–56.96; p≤0.029–0.008 and 95% CI: 5.58–659.3; p<0.001), respectively.

Conclusions. The risk of EAH in the Western Ukraine population increases with burdened CVD heredity, smoking, hypercystatinemia-C in T-allele carriers of the ADD1 gene (rs4961), BMI, WC, and WHR elevation. The GG-genotype of the ADD1 gene increases the CKD risk in hypertensive men.

Keywords: chronic kidney disease, arterial hypertension, glomerular filtration rate, gene *ADD1* (rs4961), risks, anthropometria, obesity, heredity.

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РЕЗЮМЕ

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ГЕН АЛЬФА-АДДУЦИНУ 1 (ADD1), КЛІНІЧНО-ДЕМОГРАФІЧНІ І МЕТАБОЛІЧНІ ПРЕДИКТОРИ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ І ХРОНІЧНОЇ ХВОРОБИ НИРОК У МЕШКАНЦІВ ЗАХІДНОЇ УКРАЇНИ

Актуальність. Хронічна хвороба нирок (ХХН) є глобальною проблемою громадської охорони здоров'я, яка охоплює близько 10% населення планети. На сьогодні, недостатньо дослідженою є генетична схильність до розвитку ХХН у хворих на артеріальну гіпертензію (АГ). Тому пошук ранніх предикторів ХХН за АГ є актуальним завданням сучасної медицини. Мета роботи: дослідити ризик есенційної артеріальної гіпертензії (ЕАГ) і ХХН у популяції мешканців західної України (Буковина) з урахуванням окремих демографічних, клінічних та антропометричних параметрів, статі та гена альфа-аддуцину 1 (ADD1; rs4961).

Матеріали і методи. У дослідженні прийняло участь 100 хворих на ЕАГ і 60 практично здорових групи контролю, яким виконали комплекс клінічно-лабораторних обстежень. Серед чинників ризику досліджували обтяжений анамнез за серцево-судинними захворюваннями (ССЗ), наявність цукрового діабету 2 типу (ЦД2), обвід талії (ОТ), обвід стегон (ОТ), співвідношення ОТ/ОС, індекс маси тіла (ІМТ) у чоловіків (Ч) і жінок (Ж). ХХН встановлювали за швидкістю клубочкової фільтрації (ШКФ) за формулою CKD-EPI з урахуванням рівнів креатиніну (кр) і цистатину-С (цис) крові (KDIGO, 2024). Ген ADD1 (rs4961) вивчали методом ПЛР в режимі реального часу.

Результати. Ризик ЕАГ зростає за обтяженої спадковості за ССЗ – у 4 рази (95% CI: 1,15–13,88; p=0,027), у курців носіїв *GG*-генотипу гена *ADD1* (rs4961) – у понад 8,5 разів (OR=8,67; 95% CI: 1,04–72,32; p=0,02), за гіперцистатинемії-С (≥1,1мг/л) у носіїв *T*-алеля гена *ADD1* (rs4961) – майже у 2,5 рази, але вірогідно тільки

у жінок – у 4,67 разу (OR 95% CI: 1,19–18,33; p=0,033). *GG*-генотип гена *ADD1* підвищує ризик ХХН (за ШКФцис) у хворих на ЕАГ чоловіків у 2,67 разу (OR 95% CI: 1,0–7,34; p=0,047). Ризик ЕАГ підвищується незалежно від поліморфних варіантів гена *ADD1* (rs4961) (дещо сильніше у осіб із мутаційним *T*-алелем) за ожиріння у 3,37 і 12 разів (95% CI: 1,23–9,24; p=0,014 і 95% CI: 2,24–64,29; p=0,001), за збільшення ОТ (Ж >88 см, Ч >102 см) – у 4,14 і 45 разів (95% CI: 1,49–11,48; p=0,006 і 95% CI: 7,34–275,8; p<0,001), за зростання ІМТ ≥25,0 кг/м^2 і ОТ/ОС >0,85 уо, але тільки у жінок – у 5,78–9,90 і 30,33–60,67 разу (95% CI: 1,12–56,96; p≤0,029–0,008 і 95% CI: 5,58–659,3; p<0,001) відповідно.

Висновки. Ризик ЕАГ у популяції західної України зростає за обтяженої ССЗ спадковості, куріння, гіперцистатинемії-С у носіїв *T*-алеля гена *ADD1* (rs4961), за збільшення ІМТ, ОТ та ОТ/ОС. *GG*-генотип гена *ADD1* підвищує ризик ХХН у хворих на ЕАГ чоловіків.

Ключові слова: хронічна хвороба нирок, артеріальна гіпертензія, швидкість клубочкової фільтрації, ген *ADD1* (rs4961), ризики, антропометрія, ожиріння, спадковість.

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ABBREVIATIONS: alfa adducin 1 gene (ADD1), blood pressure (BP), body mass index (BMI), cardiovascular disease (CVD), chronic kidney disease (CKD), creatinine (cr), cystatin-C (cys), diabetes mellitus type 2 (DM2), diastolic blood pressure (DBP), essential arterial hypertension (EAH), glomerular filtration rate (GFR), hip circumference (HC), obesity (OB), systolic blood pressure (SBP), waist circumference (WC), waist-to-hip ratio (WHR)

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem affecting about 10% of the population worldwide [1, 2]. The medical, social, and economic burden of CKD (in terms of prevalence, morbidity, mortality, diagnostic, and treatment costs) is steadily increasing, especially in low- and middle-income countries, which are least equipped to deal with its consequences. In 2024, The Lancet Global Health published the updated Global Atlas of Kidney Health of the International Society of Nephrology (2024), which assesses differences in kidney disease and treatment in almost 200 countries worldwide with different economic levels [3]. Due to the numerous risk factors such as obesity (OB), hypertension, and diabetes mellitus (DM), the number of patients with CKD is also increasing [4]. Today, there are about 850 million people with CKD worldwide [5].

CKD is more common in the elderly, women, racial minorities, and people with hypertension, OB, and DM. Although mortality in patients with end-stage kidney disease (ESKD) has decreased, the Global Burden of Disease (GBD) studies have shown that CKD has become the leading cause of death worldwide and has generally increased over the past 2 decades. Besides, the genetic predisposition of CKD development or its underlying mechanisms has not been sufficiently studied. Therefore, it is important to search for early stable markers of CKD in the EAH population and prognostic predictors of its course severity, which will determine the metabolome, proteome, and epigenomic structures activity [6, 7]. One of the possible candidate genes for hypertension and CKD development through volume-dependent mechanisms is the alpha-adducin 1 (ADD1) gene, which encodes the corresponding protein adducin subunit alpha-1, which is responsible for the intracellular sodium and potassium ions transport in the body [8]. Therefore, we decided to investigate the association of the 1378G>T polymorphism of the ADD1 gene (rs4961) with EAH and CKD onset.

Objectives. To evaluate the risk of EAH and CKD in the population of Western Ukraine (North Bukovina) based on some demographic, clinical, and anthropometric data, gender, and ADD1 gene marker (rs4961).

MATERIALS AND METHODS

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) [9, 10]. The

research protocol was approved by the Bioethics Committee at the Bukovinian State Medical University (Protocol №2 from 19.10.2023). One hundred 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. Inclusion and exclusion criteria are listed in the former publication [11–13]. The patients' age ranged from 45 to 70 years (59.87±7.98 years on average); 21.0% of them were men, and 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.

The comprehensive examination included general clinical tests, anthropometric (waist and hip circumference (WC, HC), waist-to-hip ratio (WHR)), body mass index (BMI), laboratory tests (general blood and urine tests, urine protein, fasting plasma glucose, serum creatinine, cystatin-C, bilirubin, lipid spectrum), instrumental (12-lead ECG, Echocardiogram, office blood pressure (BP), ultrasound of the kidneys), as well as consultations of an ophthalmologist and a neurologist, if necessary.

Obesity was identified by a BMI increase of ≥30 kg/m^2, a BMI of ≤24.9 kg/m2 was considered normal, and a BMI of 25–29.9 kg/m2 was considered overweight [9, 10].

WC was considered as increased for men (M) >102 cm, for women (W) >88 cm; WHR increased in W >0.85 U, in M >0.95 U. All examined participants had objective signs of Hypertension-mediated organ damage (EAH IInd stage) [9]. Compensated DM type 2 (T2DM) was found in 29% of EAH patients.

CKD was diagnosed in 43 EAH patients according to the US National Kidney Association recommendations (KDIGO 2024) [1]. Glomerular filtration rate (GFR) was estimated (eGFR) using the CKD-EPI equation based on cystatin-C (cys) and creatinine (cr) 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) [1].

The SNP polymorphism of the ADD1 gene (378G>T, rs4961) was studied by real-time qualitative polymerase chain reaction (PCR). A genetic study was conducted for EAH 72 patients and 48 subjects of the control group. Lymphocyte DNA was isolated and purified from EDTA-stabilized peripheral venous blood lymphocytes according to the manufacturer's instructions (Thermo Fisher Scientific, USA). Amplification and genotyping were performed on a CFX96 Touch™ device (Bio-Rad Laboratories, Inc., USA) using specific complementary TaqMan probes. The CFX96 software recorded the melting temperature of the TaqMan probes, taking into account the Fam and Hex fluorescent labels.

Statistical processing was performed using the StatSoft Statistica v.7.0 software (StatSoft Inc., USA). Compliance of the genotype distribution with the Hardy-Weinberg equilibrium in the examined population was checked using the χ^2 test. Potential risk factors were determined by clinical epidemiology methods (multivariate logistic regression model) using relative risk (RR), odds ratio (OR), and 95% confidence interval [95% CI] based on the χ^2 criterion. Differences were considered significant at $p<0.05$.

RESULTS

The ADD1 gene genotypes distribution of the 1378G>T polymorphism (Gly460Trp, rs4961) did not differ between groups: GG-, GT- and TT-genotypes were found among patients – in 69.44% (50), 29.17% (21) and 1, 39% (1) of cases, in the control group – in 54.17% (26), 39.58% (19) and 6.25% (3) of people, respectively (χ^2=4.04; df=2; p=0.133). Binary logistic regression did not confirm the inheritance of EAH according to any model, except for the low probability of EAH in T-allele carriers within the additive model marginally [OR=0.52; 95% CI: 0.26–1.0; p=0.05] with the lowest Akaike index (AKI=14.81).

Reliable differences in the distribution of patients according to the EAH severity (BP ≥160/≥100 mm Hg), GFR according to creatinine (GFRcr ≤60 ml/min/1.73m^2) and cystatin-C (GFRcys ≤60 ml/min/1.73m^2) based on the 1378G>T polymorphism of the ADD1 gene (rs4961) were not established (Table 1).

The age of participants did not differ within each group, taking into account the allelic status of the ADD1 gene (Table 2). Women dominate over men quantitatively: among patients – 2.42 times (χ^2=25.0; $p<0.001$), in the control group – 1.67 times (χ^2=6.0; p=0.014). T2DM, BMI increase ≥25.0 kg/m^2 in men, eGFR decrease (≤60 ml/min/1.73 m^2) did not depend on ADD1 gene polymorphism (rs4961) and did not affect the EAH risk in the examined population.

In EAH patients burdened hereditary anamnesis for cardiovascular diseases (CVD) was registered more often than in control group, but significantly only in GG genotype carriers by 22.77% (χ^2=3.69; p=0.045); obesity and WC increased (W >88 cm, M >102 cm) also occurred more often in EAH patients: in GG genotype carriers – by 29.23% (χ^2=5.85; p=0.016) and 31.85% (χ^2=7.86; p=0.005), in the T-allele patients – by 45.46%

Table 1 – Glomerular filtration rate and arterial hypertension severity depending on the ADD1 gene 1378G>T polymorphism (rs4961)

Показники		**Gene genotypes *ADD1*, n=72 (%)**		χ^2	**p**
		GT-, *TT*-genotypes, n=22	*GG*-genotype, n=50		
BP, mm Hg	<160/<100	11 (50.0)	29 (58.0)	0.4	0.527
	≥160/≥100	11 (50.0)	21 (42.0)		
GFRcr, ml/min/1.73m^2	>60	13 (59.09)	35 (70.0)	0.82	0.365
	≤60	9 (40.91)	15 (30.0)		
GFRcys, ml/min/1.73m^2	>60	12 (54.55)	25 (50.0)	0.13	0.718
	≤60	10 (45.45)	25 (50.0)		

Note. BP – blood pressure; GFRcr, GFRcys – glomerular filtration rate after CKD-EPI equation according to Creatinine (cr), Cystatin-C (cys)

Table 2 – Some demographic, clinical and anthropometric data of the examined depending on the 1378G>T polymorphism of the ADD1 gene (rs4961)

Parameters			**Control, n=48 (%)**		**Patients, n=72**	
			GG-genotype, n=26	**GT-, TT-genotype, n=22**	**GG- genotype, n=50**	**GT-, TT-genotype, n=22**
Age, years			43.61±5.47	41.33±5.66	57.03±6.05 P<0.001	58.93±4.80 P<0.001
Sex, n (%)		W	16 (61.54)	14 (63.64)	35 (70.0)	16 (72.73)
		M	10 (38.46)	8 (36.36)	15 (30.0)	6 (27.27)
Smokers, n (%)			0	4 (18.18)	10 (20.0)	5 (22.73)
Burdened heredity for CVD, n (%)			18 (69.23)	17 (77.27)	46.0 (92.0)	19.0 (86.36)
T2DM, n (%)			0	0	19 (38.0)	10 (45.45)
Obesity, n (%)			8 (30.77)	2 (9.09)	30 (60.0)	12 (54.55)
WC, n (%)		↑	12 (46.15)	2 (9.09)	39 (78.0)	18 (81.82)
		N	14 (53.85)	20 (90.91)	11 (22.0)	4 (18.18)
WHR, n (%)	W	↑	2 (12.5)	0	29 (82.86)	13 (81.25)
		N	14 (87.5)	14 (100.0)	6 (17.14)	3 (18.75)
	M	↑	2 (20.0)	2 (25.0)	8 (53.33)	3 (50.0)
		N	8 (80.0)	6 (75.0)	7 (46.67)	3 (50.0)
BMI, n (%)	W	↑(≥25.0)	10 (62.5)	6 (42.86)	33 (94.29)	13 (81.25)
		N (<25.0)	6 (37.5)	8 (57.14)	2 (5.71)	3 (18.75)
	M	↑(≥25.0)	6 (60.0)	8 (100.0)	14 (93.33)	6 (100.0)
		N (<25.0)	4 (40.0)	0	1 (6.67)	0
BMI, n (%)		↑(≥25.0)	16 (61.54)	14 (63.64)	47 (94.0)	19 (86.36)
		N (<25.0)	10 (38.46)	8 (36.36)	3 (6.0)	3 (13.64)

Note. W – women; M – men; CVD – cardio-vascular disease; T2DM – type 2 diabetes mellitus; WC – waist circumference; WHR – waist-to-hip ratio; BMI – body mass index; P – probability of differences with corresponding genotypes of the control group

(χ^2=10.48; p=0.001) and 72.73% (χ^2=23.47; p<0.001) respectively. Similarly, the WHR prevailed, but reliably only in women: in GG-genotype carriers – by 70.39% (χ^2=22.80; p<0.001), in T-allele subjects, it occurred in 81.25% (χ^2=20.07; p<0.001).

Epidemiological analysis confirmed an EAH risk increase almost twice for the GG-genotype (rs4961) (OR=1.92; 95% CI: 0.90–4.10; p=0.066), burdened heredity for CVD – 4 times (OR=4.0; 95% CI: 1.15–13.88; p=0.027) and in GG genotype smokers – more than 8.5 times (OR=8.67; 95% CI: 1.04–72.32; p=0.02), respectively (Table 3). The risk of EAH increases regardless of polymorphic variants of the ADD1 (rs4961) gene, somewhat stronger in the mutated T-allele owners: for OB 3.37 and 12 times (95% CI: 1.23–9.24; p=0.014 and 95% CI: 2.24–64.29; p=0.001), for WC increase – 4.14 and 45 times (95% CI: 1.49–11.48; p=0.006 and 95% CI: 7.34–275.8; p<0.001), for BMI increase (≥25.0 kg/m^2) and WHR (>0.85 U), but only in women – 5.78–9.90 and 30.33–60.67 times (95% CI: 1.12–56.96; p≤0.029–0.008 and 95% CI: 5.58–659.3; p<0.001), respectively. The GG-genotype of the ADD1 gene increases the risk of CKD in men with EAH 2.67 times (OR 95% CI: 1.0–7.34; p=0.047).

Table 3 – Some clinical, anthropometric and demographic predictors of arterial hypertension in the examined population depending on the 1378G>T polymorphism of the ADD1 gene (rs4961)

Independent variables			***GG*-genotype of *ADD1* gene**			***T*-allele of *ADD1* gene**		
			OR	**OR 95% CI**	**p**	**OR**	**OR 95% CI**	**p**
Genotype			1.92	0.90–4.10	0.066	0.52	0.24–1.11	0.089
Sex	W		1.91	0.75-4.85	0.169	1.52	0.42-5.47	0.517
	M		0.69	0.25-1.85	0.458	0.66	0.18-2.36	0,373
Burdened heredity for CVD			4.0	1.15–13.88	0.027	2.94	0.50–17.14	0.206
SBP/DBP ≥160/100 mm Hg			0.72	0.26–1.98	0.354	1.38	0.50–3.78	0.527
Smoking			8.67	1.04–72.32	0.02	1.32	0.30–5.77	0.50
T2DM			0.73	0.27–2.03	0.554	1.36	0.49–1.75	0.367
Obesity			3.37	1.23–9.24	0.014	12.0	2.24–64.29	0.001
BMI, kg/m^2	W	≥25.0	9.90	1.72–56.96	0.008	5.78	1.12–29.85	0.029
		<25.0	0.1	0.02–0.58		0.17	0.03–0.89	
	M	≥25.0	9.33	0.85–101.9	0.064	–	–	1.0
		<25.0	0.11	0.01–1.17		–	–	
WHR, U	W	>0.85	33.83	6.04–189.5	<0.001	60.67	5.58–659.3	<0.001
	M	>0.95	4.57	0.72–29.13	0.105	3.0	0.21–28.84	0.343
WC, cm	W	>88	4.14	1.49–11.48	0.006	45.0	7.34–275.8	<0.001
	M	>102						
GFRcys, ≤60 ml/min/1.73 m^2			1.20	0.44–3.28	0.718	0.83	0.30–2.28	0.461
GFRcr, ≤60 ml/min/1.73 m^2			0.62	0.22–1.76	0.261	1.62	0.57–4.58	0.365

Note. OR – odds ratio; 95% CI – 95% confidence intervals; W – women; M – men; CVD – cardio-vascular disease; SBP / DBP – systolic / diastolic blood preasure; T2DM – type 2 diabetes mellitus; BMI – body mass index; WHR – waist-to hip ratio; WC – waist circumference; GFRcys/GFRcr – glomerular filtration rate for cystatin-C/creatinine

DISCUSSION

Adducin is a heterodimeric protein of the cell cytoskeleton containing a- and b-subunits, promotes the attachment of spectrin protein to actin, binds to calmodulin, is a substrate for protein kinases A and C, and also regulates the activity of (Na+, K+)-ATPase. Some recent studies confirm the α-adducin gene involvement in the development of EAH [14, 15]. Jin H et al. [8], in a meta-analysis, confirmed the rs4961 (ADD1) as a genetic marker of EAH in an Asian population of more than 40,000 participations.

Li YY [16] performed a meta-analysis of the ADD1 gene (rs4961) association with EAH in 10,960 Chinese people of four ethnic groups: Han, Kazakh, Mongolian,

and She. 18 studies with 5087 EAH patients and 4183 controls were included in the Han subgroup. Three studies with 636 EAH patients and 462 controls were included in the Kazakh subgroup. The Mongolian subgroup was represented by only one study with 100 EAH patients and 50 controls; similarly, only one study with 116 EAH patients and 326 controls was available for the She subgroup. A total of 23 separate studies involving 5939 EH patients and 5021 controls were retrieved and analyzed. The author established a reliable linkage of the rs4961 ADD1 gene with EAH in the recessive model (OR:1.40; 95% CI: 1.16–1.70, P=0.0005) and the allelic model as well (OR:1.12; 95% CI: 1.04–1.20; P=0.002), in the absence of such in the dominant (p>0.05). But the models significance was confirmed only for the Chinese Han ethnic group, not for the rest of the ethnic minorities.

Zhang Y et al. [17] also obtained similar results among the Han (n=410) but not the Mongolian (n=423) population in Inner Mongolia Area. RS4961-T carrier of the ADD1 gene was associated with a 1.63-fold higher EAH risk than G allele carriers females in the Han population, whereas the rs4961-G carrier (GG + GT) was 0.59-fold lower than the TT carrier in the dominant model.

On the contrary, Morrison AC et al. [18] proved that the ADD1 460W allele was not associated significantly with the prevalence of peripheral arterial disease (PAD) or incidence of coronary heart disease (CHD). However, when the researchers selected only hypertensive patients, the following relationship was confirmed: for PAD (OR: 2.61, 95% CI: 1.27–5.37, P=0.01) and CHD (HRR: 2.30, 95% CI: 1.20–4.42, P=0.01). In our research, we did not establish a direct linkage between the ADD1 gene (rs4961) and the EAH development in the examined population (Western Ukraine – North Bukovyna). However, after adjustment for multiple additional risk factors, we found an EAH risk elevation in the presence of obesity 3.37 and 12-fold (higher in the mutated T-allele carriers), by WC increase – 4.14 and 45 times, by BMI increase (≥25,0 kg/m^2) and WHR but only in women (>0.85 U) – 5.78–9.90 and 30.33–60.67 times, respectively.

Bianchi G. et al. [19] analyzed the association of ADD1, ADD2, ADD3 genes on three different chromosomes with impact on hypertension and related disorders in mice and humans and obtained controversial results in different studies: 12 of 16 studies found that ADD1 (rs4961) polymorphism alone or in combination with ACE (I/D) gene positively associates with stroke or coronary heart disease or renal or vascular dysfunctions; 4 out of 5 studies showed a selective beneficial effect of diuretics in mutated ADD1 carriers. Gupta S et al. [20] proved that the T allele of the ADD1 gene may be considered as the risk factor for the development of diabetes in hypertensive patients. In our studies, T2DM was not associated with ADD1 gene (rs4961) polymorphism in EAH patients. However, obesity increased the risk of EAH more strongly in the T-allele carriers. However, the recent studies' analysis related to anthropometric, clinical, and metabolic parameters, as well as ADD1 (rs4961) genetic factors, showed their contradictions and inconclusiveness. The inconsistency of the results obtained in different populations confirms the need for further research in this direction.

In Ukraine, the epidemiology of the ADD1 gene was studied only in the hypertensive population of Sumy region (n=120) and 112 healthy volunteers [21], so there was a need to expand and supplement the research in Western Ukraine (North Bukovina), as well as to study previously unknown mechanisms of CKD development in EAH patients depending on ADD1 gene polymorphism (rs4961).

CONCLUSIONS

The risk of EAH is 4 times higher with CVD burdened (95% CI: 1.15–13.88; p=0.027), 8.5 times higher – in the smokers who are carriers of the GG-genotype of the ADD1 gene (rs4961) (OR=8.67; 95% CI: 1.04–72.32; p=0.02), almost 2.5 times higher – with hypercystatinemia-C (≥1.1 mg/l) in T-allele carriers (rs4961), but the difference is significant only in women – by 4.67 times (95% CI: 1.19–18.33; p=0.033). The GG-genotype of the ADD1 gene (rs4961) increases the CKD risk in EAH men by 2.67 times (95% CI: 1.0–7.34; p=0.047).

The EAH risk increases regardless of ADD1 gene polymorphic variants (somewhat stronger in patients with mutated T-allele) in subjects with obesity – by 3.37 and 12 times (95% CI: 1.23–9.24; p=0.014 and 95% CI: 2.24–64.29; p=0.001), in subjects with increased WC (W >88 cm, M >102 cm) – by 4.14 and 45 times (95% CI: 1.49–11.48; p=0.006 and 95% CI: 7.34–275.8; p<0.001), in subjects with increased BMI (≥25.0 kg/m^2) and WHR (>0.85 U) – but only in women – by 5.78–9.90 and 30.33–60.67 times (95% CI: 1.12–56.96; p≤0.029–0.008 and 95% CI: 5.58–659.3; p<0.001), respectively.

PROSPECTS FOR FUTURE RESEARCH

We contemplate studying the EAH risk in the Western Ukraine population based on salt sensitivity/salt resistance and ADD1 gene (rs4961) polymorphisms.

AUTHOR CONTRIBUTIONS

Sydorchuk LP – contributed to the study conception and design, data extraction and analysis, the drafting of the manuscript, and final critical revision and approval.

Lytvyn BA – data extraction contributed to the interpretation and analysis of the descriptive data, critical revision, and final approval.

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CONFLICT OF INTEREST

The authors declare the absence of any conflicts of interest or personal financial interest that might be perceived as prejudicing the impartiality of the research reported.

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