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Original Research

Metabolic and hormonal prognostic markers of essential arterial hypertension considering the genes polymorphism AGTR1 (rs5186) and VDR (rs2228570)

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Abstract

Background and aims: Essential arterial hypertension (EAH) is the most common global non-communicable disease. **Material and method:** 100 subjects with EAH and target-organ damaging (2nd stage), moderate, high, very high cardiovascular risk was involved in the case-control study. The control group consisted of 60 healthy individuals of relevant gender and age. All recruited subjects were tested for serum levels of fasting glucose, ionized calcium, parathyroid hormone, *25-hydroxyvitamin D.* AGTR1 gene genotyping was performed for 72 patients and 48 healthy individuals, VDR gene – for 100 patients and 60 healthy subjects. **Results:** EAH associates with increased parathormone (>65.0 pg/ml) by 16.04% in *C*-allele carriers of *AGTR1* gene (rs5186) and decreased 25-hydroxyvitamin D (<30 ng/ml) regardless of the genotypes *AGTR1* (rs5186) and *VDR* (rs2228570) genes. Reduced serum level of *25-hydroxyvitamin D* escalates the risk of EAH almost threefold, fasting hyperglycemia leads to growth of EAH risk almost 15 times. Changes in parathormone, ionized calcium concentration, as well as *VDR* gene do not influence the risk of EAH in the examined. **Conclusions:** Low level of *25-hydroxyvitamin D,* fasting hyperglycemia increases the EAH risk regardless *AGTR1* (rs5186) *and VDR* (rs2228570) genes' alleles. *C*-allele of *AGTR1* gene is a prognostic marker of EAH in the observed population.

Keywords: prognostic marker, risk factor, essential arterial hypertension, AGTR1 (rs5186), VDR (rs2228570).

Background and aims

Nowadays, essential arterial hypertension (EAH) remains the most common global non-communicable disease, regardless of the country's income and its citizens [1, 2]. The number of adults with hypertension in the world increased from 594 million in 1975 to 1.13 billion in 2015, mostly in low- and middle-income countries [3]. More than 50% of patients with hypertension have additional cardiovascular risk (CVR) factors [4]. The most common are diabetes (15–20%), dyslipidemia (elevated LDL cholesterol and triglycerides – 30%), overweight and obesity (40%), hyperuricemia (25%) and metabolic syndrome (40%), as well as harmful habits (smoking, excessive alcohol

consumption, sedentary lifestyle, etc.) [5]. The presence of one or more additional CVR factors increases proportionally the risk of ischemic, cerebrovascular, and renal diseases in patients with EAH [1, 6]. Other risk factors: age (>65 years), sex (men>women), heart rate (>80 beats/min), high pulse pressure in the elderly (≥60 mm Hg), weight gain, diabetes, high levels of LDL cholesterol, triglycerides, hyperuricemia, family history of cardiovascular diseases (CVD) including hypertension, early menopause, smoking, psychosocial or socio-economic factors, also contribute to the CVR. According to the Global Burden of Disease Survey in 195 countries, the prevalence of obesity in 2015 was 12% among adults [7]. With increasing BMI, the prevalence of hypertension, diabetes, and dyslipidemia increases linearly [5]. Therefore, hypertension began to be considered one of the types of metabolic disorders [8].

Despite numerous researches of EAH predictors, changes in metabolic and hormonal parameters, that determine the activity of the metabolome and proteome in the human body in combination with its lifestyle and epigenetic structures, are still insufficiently studied.

The aim of this study is to establish the role of metabolic and hormonal prognostic markers of EAH depending on 1166A>C polymorphism of the AGTR1 gene (rs5186) and A/G polymorphism of the VDR gene (rs2228570).

Material and method

Study design and patients

The study was conducted according to the World Medical Declaration of Helsinki on the Ethical Principles of Medical Research involving human subjects. The diagnosis of EAH was established as reported by the current Ukrainian (Order of 24.05.2012 № 384) and European recommendations (ESC, ESH 2018) [9, 1]. After screening for inclusion and exclusion criteria 100 subjects were involved in the case-control study. Among them, 70.84% females, 29.16% males, the mean age was 57.86±7.81 yo.

Inclusion criteria. The study included patients with EAH and hypertensive-mediated organs damaging (2nd stage), moderate, high, or very high CVR (according to ESC recommendation Guidelines 2018); aged 40–70 years. Exclusion criteria have been described in our former publications [10–14]: we excluded patients with EAH stage III, with chronic heart failure of the functional class higher than II (NYHA III–IV); secondary arterial hypertension; type I diabetes mellitus, sub- and decompensated type 2 diabetes mellitus (with damage of the target organs); malignant or uncontrolled EAH; sub- and decompensated liver diseases (level of aspartate aminotransferase, alanine aminotransferase three times higher than the normal); bronchial asthma, chronic obstructive pulmonary disease stage III–IV; exacerbation of infectious diseases; mental disorders; oncological diseases; taking oral corticosteroids or contraceptives; pregnancy, or lactation.

The control group consisted of 60 practically healthy individuals: 62.5% women, 37.5% men, the average age was 46.37±6.77 yo. They were not relatives of the patients and without reliable differences of gender distribution and mean age with the study group (p>0.05).

Laboratory, anthropometric and clinical data collection

All recruited patients were observed by general physicians, cardiologists. Patients were tested for serum level of fasting glucose (enzymatic method, "CORMAY", Poland), ionized calcium (Ca^{2+}) (potentiometry, "SINNOWA", China), parathyroid hormone (PTH) and 25-*hydroxyvitamin* D (Vit D) (immune luminescent test "MAGLUMI", "SNIB", China), as well as genetic testing (qualitative real-time polymerase chain reaction (qRT-PCR, PCR)) for the detection of AGTR1 (rs5186) and VDR (rs2228570) gene polymorphism was done. AGTR1 gene genotyping was performed for 72 patients and 48 healthy individuals and VDR gene – for 100 patients and 60 healthy subjects.

Vacutainer tubes containing K2-EDTA were used to collect the venous blood of the examined. Extraction of DNA from the nuclei of the lymphocytes of patients was performed

according to the instructions Thermo Scientific GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific, USA), as it was described in our former publications [19–21, 23]. Alleles discrimination of AGTR1 (rs5186) and VDR (rs2228570) genes polymorphisms, obtained by RT-PCR system CFX96 Touch (Bio-Rad, USA), was analyzed by licensed computer Software Bio-Rad Real Time (Microsoft, USA).

Statistical analysis

Statistical analysis was performed using StatSoft Statistica v. 7.0 (USA) software. Pearson's criterion (χ^2) was used for the genotype distribution comparison. Analysis of qualitative data (categorical variables), risk of pathology development was assessed by a binary logistic regression model using relative risk (RelR); risk ratio (RR) was estimated by odds ratio (OR) with 95% confidence interval [95% CI] using a chi-square test (χ^2) (df=1). Quantitative data was calculated using a Student's t-test (two-tail distribution and equal variances between the two samples) based on the triplicate values for each gene genotype. The Wilcoxon-Mann-Whitney U-test was applied in case of uneven data distribution (according to W-Shapiro-Wilk or Kolmogorov-Smirnov test results). Differences were regarded as significant at p values <0.05.

Results

Genotypes distribution of AGTR1 (rs5186) gene polymorphism showed that in the group of EAH patients the relative frequency of AA-genotype was 61.11%, AC-genotype – 36.11%, CC-genotype – 2.78%, whereas only AA- and AC-genotypes carriers were observed in the healthy group, 70.83% (p>0.05) and 29.17%, respectively (p>0.05). Genotypes distribution of VDR (rs2228570) gene polymorphism in EAH patients showed that GG-, AG- and AA-genotypes occurred in 27%, 50%, and 23% of cases, while in the control group with a frequency of 23.33%, 46.67%, and 30% of cases, respectively (p>0.05). The distribution of genotypes corresponded to Hardy-Weinberg equilibrium and did not differ from the populations of the European race.

The relative frequency of carbohydrate and 25-hydroxyvitamin D metabolism disorders, changes in serum level of PTH and ionized calcium in EAH patients depending on polymorphic variants of AGTR1 (1166A>C) and VDR (A/G) genes are shown in Tables 1 and 2. No significant difference in frequency of the occurrence of metabolic and hormonal disorders in carriers of AA- and AC- + CC-genotypes of AGTR1 gene (rs5186), as well as in AA- and AG- + GG-genotypes carriers of VDR gene (rs2228570) was established.

No reliable changes in mineral metabolism values depending on the AGTR1 A/C

Table 1. Metabolic and hormonal disorders in hypertensive patients depending on AGTR1 (rs5186) gene polymorphic variants.

Values	AGTR1 (rs5186) gene polymorphic variants, n=72 (%)		OR [95% CI]	χ^2 p
	AA-genotype	AC-, CC-genotypes		
Decrease of Vit D concentration (<30 ng/ml), n (%)	40 (90.91)	26 (92.86)	1.30 [0.22–7.62]	χ^2<1.0 p>0.05
Increase of parathormone concentration (>65.0 pg/ml), n (%)	12 (27.27)	9 (32.14)	1.26 [0.45–3.55]	χ^2<1.0 p>0.05
Decrease of ionized Ca^{2+} concentration (≤1.12 mmol/l), n (%)	3 (6.82)	3 (10.71)	1.64 [0.31–8.76]	χ^2<1.0 p>0.05
Fasting hyperglycemia (>6.1 mmol/l), n (%)	19 (43.18)	13 (46.43)	1.14 [0.44–2.96]	χ^2<1.0 p>0.05

Notes: Vit D: total serum 25-*hydroxyvitamin* D (D2 + D3 metabolites); OR: odds ratio; n: absolute number.

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Table 2: Metabolic and hormonal disorders in hypertensive patients depending on VDR A/G polymorphic variants.

Values	VDR A/G polymorphic variants, n=100 (%)			χ^2 p
	AA-genotype	AG-genotype	GG-genotype	
Decrease of Vit D concentration (<30 ng/ml), n (%)	16 (69.56)	32 (64.0)	18 (66.67)	χ^2<1.0 p>0.05
Increase of parathormone concentration(>65.0 pg/ml), n (%)	4 (17.39)	10 (20.0)	7 (25.93)	χ^2<1.0 p>0.05
Decrease of ionized Ca^{2+} concentration (≤1.12 mmol/l), n (%)	2 (8.69)	5 (10.0)	5 (18.52)	χ^2=1.51 p>0.05
Fasting hyperglycemia (>6.1 mmol/l), n (%)	12 (52.17)	19 (38.0)	13 (48.15)	χ^2=1.54 p>0.05

Notes: Vit D: total serum 25-*hydroxyvitamin D* (D2 + D3 metabolites); OR: odds ratio; n: absolute number.

Table 3: The values of mineral metabolism depending on the AGTR1 A/C polymorphism.

Values	AGTR1 gene genotypes in the control group		AGTR1 gene genotypes in the study group	
			AA-	AC+CC-
Ionized calcium concentration, mmol/l	AA-	1.16±0.03	0.17±0.03	0.18±0.02
	AC+CC-	1.16±0.04		
Vit D concentration, ng/ml	AA-	23.72±0.96	21.44±1.16 p<0.05	22.66±1.02 p<0.05
	AC+CC-	26.18±1.64		
Parathormone concentration, pg/ml	AA-	58.47±3.57	56.74±3.61	65.84±4.25 p<0.05 p_{AA}=0.052
	AC+CC-	52.13±3.09		
	AC+CC-	5.23±0.29		

Notes: Vit D: total serum 25-*hydroxyvitamin D* (D2 + D3 metabolites); p: significance of differences with control group; $p_{AA:}$ significance of differences with AA-genotype carriers.

polymorphism were established (shown in Table 3). The serum level of Vit D in EAH patients was lower than in healthy individuals, regardless of AGTR1 gene genotypes, by 9.61% and 13.45% (p<0.05). On the contrary, the concentration of PTH was compensatory higher, but only in C-allele carriers – by 26.30% (p<0.05) and 16.04% (p_{AA} = 0.052), respectively, that resulted in an increase of ionized Ca^{2+} in these patients, insignificantly though.

There were no reliable changes in serum level of ionized Ca^{2+} and PTH, depending on polymorphic variants of VDR gene (rs2228570) in EAH patients found (shown in Table 4). However, the level of Vit D in GG-genotype carriers was lower than in A-allele carriers, especially in the control group: in EAH patients by 12.51% (p_{AG} = 0.048), in healthy individuals – by 18.33% (p_{AA} = 0.045) and 19.43% (p_{AG} = 0.04), respectively. Against this background, a compensatory increase of PTH was observed, but only in the control group – by 13.65% (p_{AA} = 0.049) and 19.57% (p_{AG} = 0.038).

One-way ANOVA analysis confirmed the association of VDR gene (rs2228570) in the control group with a Vit D level reduction in the blood and, marginally, with an increase in PTH level (F=3.47; p=0.047 and F=3.25; p=0.051), but only in GG-genotype carriers.

The epidemiological analysis indicated that the risk of EAH increases almost threefold with a decrease of Vit D concentration (<30 ng/ml) in the examined (OR – 2.90; 95%CI OR:1.0–8.59; p=0.048) (shown in Table 5). Moreover, fasting hyperglycemia increases the risk of EAH

Table 4: The values of mineral metabolism depending on the VDR (A/G) polymorphism.

Values	VDR gene genotypes in the control group		VDR gene genotypes in the study group		
			AA	AG	GG
Ionized calcium concentration, mmol/l	**AA**	1.17±0.04	1.18±0.3	1.18±0.02	1.16±0.02
	AG	1.15±0.03			
	GG	1.15±0.02			
Vit D concentration, ng/ml	**AA**	25.48±1.23	21.21±1.13 $p<0.05$	22.4±1.20 $p<0.05$	19.63±1.34 $p_{AG}=0.049$
	AG	25.83±1.18			
	GG	20.81±2.04 $p_{AA}=0.045$ $p_{AG}=0.04$			
Parathormone concentration, pg/ml	**AA**	55.75±3.21	63.29±6.38	57.12±4.96	62.46±4.99
	AG	52.99±2.87			
	GG	63.36±3.74 $p_{AA}=0.049$ $p_{AG}=0.038$			

Notes: Vit D: total serum 25-*hydroxyvitamin* D (D2 + D3 metabolites); p: significance of differences with control group; p_{AA}, p_{AG}: significance of differences with **AA**-genotype and **AG**-genotype carriers.

Table 5: Metabolic and hormonal risk factors of essential arterial hypertension in the observed population.

Potential risk factor	Parameters				
	RR	95% CI RR	OR	95% CI OR	p-Value
Decrease of Vit D concentration (<30 ng/ml), n (%)	1.16	0.99–1.36	2.90	1.0–8.59	0.048
Increase of parathormone concentration (>65.0 pg/ml), n (%)	1.06	0.29–3.88	1.07	0.21–5.46	>0.05
Decrease of ionized Ca^{2+} concentration (≤1.12 mmol/l), n (%)	0.33	0.18–1.35	0.26	0.15–1.41	>0.05
Fasting hyperglycemia (>6.1 mmol/l), n (%)	8.8	2.86–27.10	14.93	4.38–50.89	<0.001

Notes: Vit D: total serum 25-*hydroxyvitamin* D (D2 + D3 metabolites); RR: risk ratio; OR: odds ratio; 95% CI: confidence intervals.

almost 15 times (OR – 14.93; 95%CI OR:4.38–50.89; p<0.01). In addition, an increase of serum level of PTH (>65.0 pg/ml) and a decrease of ionized Ca^{2+} (≤1.12 mmol/l) showed no significant impact on the risk of EAH in the observed population (p>0.05).

The epidemiological analysis showed that the C-allele of AGTR1 gene (rs5186) increases the risk of EAH more than 2 times (OR – 2.31; 95% CI OR:1.19–4.47; p = 0.011), as well as AC- and the combination of AC- + CC-genotypes (OR – 2.09; 95% CI OR:1.03–4.25; p = 0.038 and OR – 2.30; 95% CI OR:1.14–4.64; p = 0.017) (shown in Table 6). Polymorphic variants of the VDR gene (rs2228570) are not additional risk factors of EAH in the examined.

Discussion

Metabolic and genetic predictors of EAH, that encode RAAS activity, have been commonly studied in recent decades both in Ukraine and worldwide [15–19], but a significant part of them

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Table 6: Polymorphic variants of AGTR1 (rs5186) та VDR (rs2228570) genes as additional risk factors of essential arterial hypertension in the observed population.

Potential risk factor	Parameters				
	RR	95% CI RR	OR	95% CI OR	p-Value
		AGTR1 (rs5186)			
AA-genotype	0.86	0.67–1.12	0.65	0.30–1.41	>0.05
AC- genotype	1.86	1.02–3.38	2.09	1.03–4.25	0.038
AC-, CC- genotypes	2.0	1.11–3.61	2.30	1.14–4.64	0.017
A- allele	0.93	0.82–1.04	0.65	0.32–1,30	>0.05
C- allele	2.14	1.17–3.94	2.31	1.19–4.47	0.011
		VDR (rs2228570)			
AA- genotype	0.77	0.45–1.30	0.70	0.34–1.44	>0.05
AG- genotype	1.07	0.77–1.50	1.14	0.60–2.17	>0.05
GG- genotype	1.16	0.66–2.03	1.22	0.58–2.56	>0.05
A-allele	0.90	0.72–1.12	0.81	0.51–1.27	>0.05
G- allele	1.11	0.88–1.41	1.24	0.79–1.95	>0.05

Notes: RR: risk ratio; OR: odds ratio; 95% CI: confidence intervals.

remains poorly elucidated. Wang L. et al. found that BsmI and FokI polymorphisms of the VDR gene are associated with hypertension in North Americans [20]. Research on mice with VDR gene knockout showed activation of certain parts of the RAAS with inhibition of synthesis of calcitriol, leading to increased renin expression, plasma levels of angiotensin II, left ventricular hypertrophy and resulted in an increase in water consumption, development of hypertension [21].

However, we have found that the genotypes and alleles of the VDR gene (rs2228570) are not additional risk factors of EAH in the examined subjects. Numerous studies have identified the association of 1166A>C polymorphism of the AGTR1 gene (rs5186), especially the CC-genotype, with arterial hypertension, vascular spasm, sodium retention, LVH, greater thickness of the interventricular septum and posterior wall of the left ventricle, less 24-hour urinary aldosterone excretion [14, 22–24]. We have studied the association of AGTR1 gene polymorphism with carbohydrate and vitamin D metabolism disorders, parathyroid hormone, ionized calcium as risk factors of EAH for the first time that may become a prerequisite for further research in this area.

Conclusions

1. The frequency of carbohydrate and 25-*hydroxyvitamin D* metabolism disorders, changes in parathyroid hormone and ionized calcium levels in hypertensive patients do not depend on polymorphic variants of genes AGTR1 (rs5186) and VDR (rs2228570).
2. EAH associates with increased parathyroid hormone level (>65.0 pg/ml) by 16.04% in C-allele carriers of AGTR1 gene (rs5186) and decreased 25-*hydroxyvitamin D* (<30 ng/ml) regardless of the genotypes of AGTR1 (rs5186) and VDR (rs2228570) genes. The C-allele of the AGTR1 gene increases the risk of EAH more than 2 times (OR – 2.31; p=0.011) and is considered as a prognostic marker of EAH in the observed. VDR gene is not an additional risk factor and prognostic marker of EAH in the examined.
3. Reduced serum level of 25-*hydroxyvitamin D* (<30 ng/ml) escalate the risk of EAH almost three times (p = 0.048), and fasting hyperglycemia (>6.1 mmol/l) leads to growth of the risk of EAH almost 15 times (p<0.001). An increase of parathyroid hormone (>65.0 pg/ml) and a

decrease of ionized Ca^{2+} concentration (≤1.12 mmol/l) do not influence the risk of EAH in the examined population (p>0.05).

Conflict of interest

The authors declare no conflict of interest.

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