Association between arterial hypertension and chronic obstructive pulmonary disease: role of AGT gene polymorphism

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Abstract

English:

Background: Chronic obstructive pulmonary disease (COPD) continues to cause a heavy health and economic burden in the Europe and around the world. Arterial hypertension (AH) is considered as one of the principal COPD-associated comorbidities. However, no data for association between gene polymorphism and AH in patients with COPD in Ukraine have ever been internationally published. We assessed the genotype and allele frequencies of angiotensinogen (AGT) M235T polymorphisms in patients with COPD and comorbid AH.

Methods: The study group consisted of 96 patients: Group 1 (25 individuals with COPD), Group 2 (23 individuals with AH) and Group 3 (28 individuals with COPD and AH). The control group consisted of 20 healthy subjects. M/T genotypes of AGT were determined by polymerase chain reaction amplification.

Results: The results of the study have not demonstrated any significant impact of alleles of AGT genes on the occurrence of diseases such as COPD, AH and combinations thereof. However, analysis of odds ratio has demonstrated the presence of a trend towards a protective role of the M allele of the AGT gene concerning occurrence of COPD, AH and their combinations. At the same time, the presence of the T allele of the AGT gene may increase the risk for occurrence of the above-mentioned diseases.

Conclusions: The study that we have conducted suggests that the presence of T allele of the AGT gene at position 235 of the peptide chain both in homozygous and heterozygous states may increase the risk for AH in patients with COPD.

Keywords

chronic obstructive pulmonary disease • arterial hypertension • angiotensinogen gene

Asociere între hipertensiunea arterială și boala pulmonară obstructivă cronică: rolul polimorfismului genic AGT

Rezumat

Romanian:

Context general: Boala pulmonară obstructivă cronică (BPOC) continuă să rămână o povară pentru sistemele de sănătate și pentru economie la nivel mondial. Hipertensiunea arterială (HTA) este considerată una dintre comorbiditățile majore asociate cu BPOC. Cu toate acestea, nu au fost publicate la nivel internațional date privind asocierea între polimorfismul genic și hipertensiunea arterială la pacienții cu BPOC din Ucraina. Am evaluat genotipul și frecvențele de alele ale polimorfismelor AGT M235T la pacienții cu boală pulmonară obstructivă cronică și hipertensiune arterială comorbidă.

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Metode: Grupul de studiu a fost format din 96 de pacienți: Grupul 1 (25 de persoane cu BPOC), Grupul 2 (23 de persoane cu HTA), Grupul 3 (28 de persoane cu BPOC și HTA). Grupul de control a fost format din 20 de subiecți sănătoși. Genotipurile M/T ale AGT au fost determinate prin amplificarea reacției în lanț a polimerazei.

Rezultate: Rezultatele studiului nu au demonstrat nici un impact semnificativ al alelelor genelor AGT asupra apariției unor boli precum BPOC, HTA și combinații ale acestora. Cu toate acestea, analiza ratelor de probă a demonstrat prezența unei tendințe către un rol protector al alelei M a genei AGT în ceea ce privește apariția BPOC, HTA și a combinațiilor acestora. În același timp, prezența alelei T a genei AGT poate crește riscul apariției bolii menționate mai sus.

Concluzii: Studiul pe care l-am realizat sugerează că prezența alelei T a genei AGT la poziția 235 a lanțului peptidic atât în stări homozigote, cât și heterozigote poate crește riscul de HTA la pacienții cu BPOC.

Cuvinte-cheie

boală pulmonară obstructivă cronică • hipertensiune arterială • gena angiotensinogenă

Introduction

The Global Burden of Disease Study estimated that chronic obstructive pulmonary disease (COPD) affected 251 million people worldwide and was the third leading cause of death in 2016, causing more than three million deaths (1). The prevalence of COPD in Europe has been estimated to range between 4% and 10%, and between 1994 and 2010, 2,348,184 deaths were attributed to COPD in the European Union (2). Ukraine is characterized with extremely high COPD mortality rates compared with other European countries: while the number of deaths per 100,000 of population is less than 20 in Greece, Sweden, Iceland and Norway, it is more than 80 in Ukraine (3). Despite high mortality rates, very limited epidemiological COPD data are available in Ukraine. The CORE study conducted across major cities in Ukraine, Kazakhstan and Azerbaijan from the first half of 2013 until the end of 2015 has showed that prevalence of COPD diagnosed by spirometry (based on the Global Initiative for Chronic Obstructive Lung Disease guideline, 2011; forced expiratory volume in 1 s [FEV₁]/forced vital capacity [FVC] < 0.70) was 31.9 (95% confidence interval [CI] 21.7–45.3) per 1,000 of population in Ukraine (4).

COPD is a complex respiratory disorder, which affects the course and development of some concomitant diseases; this makes COPD a systemic disorder (5). As expected, the most significant correlation was found between COPD and cardiovascular diseases (CVDs), whose prevalence is a global health problem that leads to impaired quality of life and shortens life expectancy (6-7). Arterial hypertension (AH) is a part of CVDs that symbolize the highest proportion of disease-related mortality causes such as cerebral vascular accident and acute myocardial infarction, reaching about two-fifths of the adult population in developed countries (8). AH is considered as one of the principal COPD-associated comorbidities. A population study has shown AH to be the highest prevalence comorbidity in patients with COPD among

the 82 studied comorbidities (24%) (9). Similar results were reported in the Fifth Korean National Health and Nutrition Examination Survey study, where only AH and history of pulmonary tuberculosis were independently associated with COPD among different 15 comorbidities (10). Another study showed that COPD is found in 25% of patients with CVDs (11). Comorbidity analysis suggests the need for active strategies looking for correlations between COPD and the incidence of AH.

Both hypertension and COPD are genetically determined conditions with multiple genes, combinations of genes, inter-gene interactions and epigenetic processes responsible for their occurrence (12). The renin-angiotensin system (RAS), the sympathetic nervous system, sodium and electrolyte balance and intracellular messengers have all been suggested to play an important role in the regulation of blood pressure and pathogenesis of AH. Thus, polymorphisms of RAS genes that encode angiotensinogen (AGT), angiotensin-converting enzyme (ACE) and angiotensinogen II type-1 receptor have been extensively investigated as potential loci for AH (13-14). The AGT gene is an important vascular lesion-related factor (15). It is located in the 1q42-43 region of the long arm of chromosome 1 and has a total length of 13 kb; the gene coding region is composed of five exons and four introns (16). Although other researches have identified the relations of gene polymorphisms in RAS with different clinical settings (17-21), we could not observe any report about AGT M235T polymorphism in patients with COPD. We believe eliminating RAS genes polymorphisms in COPD can provide benefits to improve clinical treatments and help us understand COPD pathophysiology and development of comorbidities.

Thus, the aim of this study was to establish the genotype and allele frequencies of AGT M235T polymorphisms in patients with COPD and comorbid AH.

Methods

The study group consisted of 96 patients admitted to the Ternopil University Hospital. We stratified patients into three groups: Group 1 (25 patients with COPD), Group 2 (23 patients with AH) and Group 3 (28 patients with COPD + AH). The control group consisted of 20 healthy subjects.

Inclusion criteria

The inclusion criteria included male patients 40–60 years of age at screening with a diagnosis of COPD and/or AH and informed consent form signed by patients prior to their participation in any study-related procedures. COPD was diagnosed according to Order 555 of Ministry of Health of Ukraine dated 27 June 2013 and according to the guidelines published by the American Thoracic Society and European Respiratory Society (GOLD, 2013). Airway obstruction was assessed using GOLD classification, 2008. The diagnosis of COPD with moderate (Stage 2) airway obstruction was confirmed with compatible clinical features concurrent with airflow limitation defined as FEV_1/FVC less than 0.70 (FEV_1/FVC ratio of 50–79% predicted).

The diagnosis of AH (Stage I) was made according to 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) Guidelines for the management of AH (21). Systolic (140–159 mmHg) and/or diastolic (90–99 mmHg) blood pressure were considered as the presence of Stage I AH. Left ventricular hypertrophy was confirmed by an electrocardiogram.

Exclusion criteria

The exclusion criteria were patients with bronchial asthma; α_1 -antitrypsin deficiency; active tuberculosis; lung cancer; significant bronchiectasis; sarcoidosis; pulmonary fibrosis; interstitial lung disease; signs and symptoms of clinically significant neurological, psychiatric, renal, hepatic, immunological, gastrointestinal and urogenital disorders; musculoskeletal conditions; disorders of the skin and sensory organs; endocrine disorders (uncontrolled diabetes or thyroid disease) or uncontrolled haematological disease; unstable liver disease and unstable or life-threatening heart disease; cancer patients not completely disease-free for a minimum of 5 years and patients with any drug, substance or alcohol abuse.

Sampling of venous blood for genotyping was performed under sterile conditions into 2.7 mL Monovettes with potassium salt of ethylenediaminetetraacetic acid as an anticoagulant; the samples were frozen and stored at -20°C . Molecular genetic studies were performed with extraction of DNA and with use of polymerase chain reaction (PCR) and further analysis for the length of restriction fragments. DNA was extracted from peripheral blood leukocytes using a standard salt precipitation method. Genotyping for the AGT

M235T was performed using PCR-based restriction fragment length polymorphism (RFLP). The primers used were 5'-CCGTTTGTGCAGGGCCTGGCTCTCT-3' (forward) and 5'-TGC TGT CCA CAC TGG ACC CC-3' (reverse). The PCR products were digested with 3 U of Tth111I (Fermentas), and the fragments were separated on a 3% agarose gel. Diagnostic fragments were visualized by ethidium bromide staining and ultraviolet transillumination. The heterozygous form (M/T) was indicated by the appearance of two fragments of 165 and 141 bp, while the homozygous form revealed only one band of 141 bp (T/T) and individuals lacking this mutation showed only one band of 165 pb (M/M). To assess genotyping reliability, we performed double-sampling PCR-RFLP in more than 20% of the samples and found no differences (14).

Statistical analysis

Statistical data analysis was carried out using Statistica 7.0 software. Assessment of genotypes of the selected sample for conformity to general population sample was guided by the Hardy–Weinberg principle. The observed frequencies and the expected frequencies calculated from the expression $p^2 + 2pq + q^2 = 1$ (Hardy–Weinberg equilibrium) were compared using the Pearson chi-square (χ^2) test. In case of probability value $p > 0.05$, a null hypothesis of equal samples was accepted, i.e. that the selected sample was equivalent to the general population.

Comparative analysis of frequency tables was performed using Pearson chi-square (χ^2) and Fisher's exact p (two-tailed) tests (in cases when expected frequencies of individual parameters did not exceed 5).

To assess the impact of the factor (the presence of a certain genotype or an allele of a gene) on the occurrence of the disease, odds ratio (OR) and its 95% CI and probability value p were calculated.

Results

The frequency distribution of polymorphic genotypes of the gene encoding angiotensinogen and assessment of compliance with the Hardy–Weinberg population equilibrium were carried out in groups of patients with COPD, AH and COPD + AH combination. A deviation from the Hardy–Weinberg equilibrium was found in the group of patients with COPD due to a lower rate of heterozygotes than theoretically expected (Table 1).

The deviation from the Hardy–Weinberg equilibrium in the group of patients with COPD is potentially attributable to the heterogeneity of the patient population. The frequencies of the genotype responsible for the M/T polymorphism of the AGT gene in the control group and in Groups 2 and 3 were

not found to deviate significantly from the Hardy–Weinberg equilibrium ($p > 0.05$; Table 1). The respective frequencies for the genotypes of the AGT gene were as follows: 24.0% for M/M, 75.0% for M/T and 1.8% for T/T in Test Group 1 with COPD; 26.1% for M/M, 56.5% for M/T and 17.4% for T/T in Group 2 with AH; 25.0% for M/M, 46.4% for M/T and 28.6% for T/T in Group 3 with COPD + AH and 30.0% for M/M, 65.0% for M/T and 5.0% for T/T in the control group (Table 2).

The frequencies of alleles for the AGT gene in patients with COPD, AH and COPD + AH and control group patients are given in Table 3. In the COPD group, the established distribution was AGT M allele (60.0%) and AGT T allele (40.0%); the respective distributions were 54.3% and 45.7% in the AH group, 48.2% and 51.8% in the COPD + AH group and 62.5% and 37.5% in the control group, with no significant differences across test groups and the control group.

The results of the study given in Table 4 have demonstrated absence of a statistically significant relationship between the

factor (presence of M/T alleles) and occurrence of the disease ($p > 0.05$).

Assessment of the probability value as part of analysis of OR has demonstrated absence of influence of a certain genotype on the occurrence of the disease ($p > 0.05$; Table 5).

The results of the study have not demonstrated any significant impact of alleles of AGT genes on the occurrence of diseases such as COPD, AH and combinations thereof. However, analysis of OR has demonstrated the presence of a trend towards a protective role of the M allele of the AGT gene concerning the occurrence of COPD, AH and their combinations (OR = 0.90, OR = 0.71 and OR = 0.56, respectively). At the same time, the presence of the T allele of the AGT gene may increase the risk for the occurrence of the above-mentioned disease (OR = 1.11, OR = 1.4 and OR = 1.79, respectively).

This is confirmed by a significant difference found when building a recessive inheritance model in combination of COPD and AH (Table 6). In a dominant model of

Table 1. Hardy–Weinberg equilibrium of the AGT gene M/T polymorphism in COPD, AH and their combination

Genotype		COPD		AH		COPD + AH		Control	
		Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed
Common homozygotes	M/M	9	6	6.8	6	6.5	7	7.8	6
Heterozygotes	M/T	11.8	18	11.4	13	14	13	9.4	13
Rare homozygotes	T/T	4.2	1	4.8	4	7.5	8	2.8	1
Chi-square (χ^2)		$\chi^2 = 6.70$, df = 2, $p < 0.04$		$\chi^2 = 0.45$, df = 2, $p > 0.05$		$\chi^2 = 0.14$, df = 2, $p > 0.05$		$\chi^2 = 2.95$, df = 2, $p > 0.05$	

AGT, angiotensinogen; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension.

Table 2. Genotype frequencies of the AGT gene M/T polymorphism in COPD, AH and their combination

Genotype frequencies		COPD		AH		COPD + AH		Control	
		n	%	n	%	n	%	n	%
M/M		6	24.0	6	26.1	7	25.0	6	30.0
M/T		18	72.0	13	56.5	13	46.4	13	65.0
T/T		1	4.0	4	17.4	8	28.6	1	5.0
Fisher's exact p (two-tailed; disease/ control group)		$p = 0.75$		$p = 0.76$		$p = 0.25$		–	

AGT, angiotensinogen; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension.

Table 3. Allele frequencies of the AGT gene M/T polymorphism in COPD, AH and their combination

Allele frequency		COPD		AH		COPD + AH		Control	
		n	%	n	%	n	%	n	%
AGT M allele		30	60.0	25	54.3	27	48.2	25	62.5
AGT T allele		20	40.0	21	45.7	29	51.8	15	37.5
Pearson chi-square (χ^2 ; disease/control group)		$\chi^2 = 0.06$, df = 1, $p = 0.81$		$\chi^2 = 0.58$, df = 1, $p = 0.44$		$\chi^2 = 1.92$, df = 1, $p = 0.17$		–	

AGT, angiotensinogen; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension.

inheritance of the AGT gene in combination of COPD and AH, no significant differences from the control group have been detected (the probability value for chi-square: $p > 0.05$); however, in this setting, there is also a trend towards increased probability of the occurrence of disease in the presence of the T allele (Table 7). Therefore, the presence of the T allele (both in homozygous and heterozygous states) may increase the risk for the above-mentioned diseases.

In groups of subjects without combined disease (in the group of patients with COPD and in the group of patients with AH), no significant differences were found in the analysis of

dominant and recessive types of inheritance for the AGT gene (M and T alleles) (in these cases, the probability value for χ^2 was $p > 0.05$).

Discussion

COPD is a heterogeneous condition that has a single common denominator: chronic airflow obstruction. Because currently available treatments have minimal impact on disease progression, a strategy to prevent the development of COPD is a critical priority. Personal direct

Table 4. OR for alleles in different study groups

Group	Alleles					
	AGT M allele			AGT T allele		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
COPD	0.90	0.38–2.11	>0.05	1.11	0.47–2.61	>0.05
AH	0.71	0.3–1.69	>0.05	1.4	0.59–3.32	>0.05
COPD + AH	0.56	0.24–1.28	>0.05	1.79	0.78–4.09	>0.05

OR, odds ratio; AGT, angiotensinogen; CI, confidence interval; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension.

Table 5. OR for genotypes in different study groups

Group	Genotype					
	M/M		M/T		T/T	
	OR	95% CI	OR	95% CI	OR	95% CI
COPD	0.74	0.20–2.77	1.38	0.39–4.92	0.79	0.05–13.5
AH	0.82	0.22–3.13	0.70	0.20–2.41	4.00	0.41–39.18
COPD + AH	0.78	0.22–2.81	0.47	0.14–1.52	7.60	0.87–66.67

Notes: *p* coefficient for OR – $p > 0.05$ in all cases.

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension.

Table 6. A recessive model of the AGT gene inheritance in combination of COPD and AH

Genotypes	COPD + AH	Control	χ^2	<i>p</i>	OR	95% CI
	%	%				
M/M + M/T genotype	71.4	95.0	4.25	0.04	0.13	0.01–1.15
T/T genotype	28.6	5.0			7.60	0.87–66.67

AGT, angiotensinogen; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension; OR, odds ratio; CI, confidence interval.

Table 7. A dominant model of AGT gene inheritance in combination of COPD and AH

Genotypes	COPD + AH	Control	χ^2	<i>p</i>	OR	95% CI
	%	%				
M/M genotype	25.0	30.0	0.15	0.7	0.78	0.22–2.81
M/T + T/T genotype	75.0	70.0			1.29	0.36–4.64

AGT, angiotensinogen; COPD, chronic obstructive pulmonary disease; AH, arterial hypertension; OR, odds ratio; CI, confidence interval.

cigarette smoking is the most important single causal factor for developing COPD (22); however, only a small fraction of smokers develops a clinical presentation of COPD (23). Analysis of literature suggests that other risk factors biologically interact with cigarette smoking and potentiate the development of airflow obstruction: genetic factors, longstanding asthma, outdoor air pollution, second-hand smoke exposure, biomass smoke and indoor air pollution, occupational exposures, diet and tuberculosis (24-28).

Complications and comorbidities are an important consideration to take into account when managing the process of shaping the models of prevention, diagnosis and treatment of COPD (29). As expected, the most significant correlation was found between COPD and CVDs. Actually, COPD was found to be a predecessor of CVDs (6,30). Frequent combinations of and interactions between these conditions may be attributable to several causes due to the presence of common links of pathogenesis (31). As a result of pulmonary tissue inflammation in COPD, molecules with proinflammatory, profibrous, procoagulant and vasoconstrictor effects are released into systemic circulation. These molecules are capable of modifying endothelial function, thereby creating conditions for a persistent elevation of blood pressure (32). On the other hand, hyperactivation of neurohormonal systems such as RAS, which is typical for AH, may be involved in pulmonary inflammation, as well as in remodelling of lung parenchyma and bronchioles. Via type 1 receptors in the lungs, angiotensin II promotes activation of immunocompetent cells and the discharge of proinflammatory cytokines; it also induces proliferation of fibroblasts and apoptosis of bronchial epithelium and activates the processes associated with oxidative stress (33).

The RAS is one of the main regulatory systems for blood pressure. It has also a role in cardiovascular remodelling and vascular tone (14). Gonzalez et al. found that the baseline plasma renin activity had a significant, independent, specific and direct long-term association with CVD mortality in subjects with hypertension (34). The angiotensinogen gene (*AGT*) is localized on the long arm of chromosome 1 in 1q42-q43 locus and contains five exons and four introns. In the *AGT* gene, the best studied variants include the polymorphic M235T and T174M variants. The T174M (rs4762) polymorphism is characterized by a replacement of threonine with methionine at position 174 in the peptide chain, which is caused by a point replacement of cytosine with thymine at position 521 of the *AGT* gene (C521T). The M235T (rs699) polymorphism is a replacement of methionine with threonine at position 235 of the peptide chain, which is caused by a point replacement of thymine with cytosine at position 704 of the *AGT* gene (T704C) (35,36). It has been reported that *AGT* M235T polymorphism is associated with the increased risk for systemic artery hypertension in Caucasian-Brazilians

and that *AGT* M235T may be an independent risk factor for in-stent restenosis (37). Additionally, other *AGT* promoter polymorphisms, including G217A and A-6G, were significantly associated with stroke in patients with atrial fibrillation (38). At the same time, a meta-analysis of epidemiological findings revealed no correlation between polymorphism of M235T with hypertrophic cardiomyopathy in European populations, while in Asian populations, there has been an association with the sporadic form of hypertrophic cardiomyopathy (35).

The polymorphic variant included in our study was the single-nucleotide replacement of thymine with cytosine at position 704 of the second exon of the angiotensinogen gene, which led to the Met → Thr change at position 235 of the final product (M235T). The data that we have received suggest the absence of a significant impact of *AGT* alleles or *AGT* genes on the occurrence of diseases such as COPD, AH and their combination among the patients of the Ukrainian population. In another study conducted in Ukraine, which assessed haplotype frequencies depending on the studied polymorphic variants of the *AGT* gene in different age groups of women with AH, no significant differences compared to controls have likewise been detected (39). A study by Simonyte et al. of the frequencies of *AGT* genotypes and alleles using a multivariate logistic regression analysis could not demonstrate any association between *AGT* M235T polymorphism and hypertension (40). Niu et al. also found no association of AH with *AGTM235T* polymorphisms, even after adjustment for age, gender or severity of the disease (41). Likewise, Caulfield et al. have not found any association with polymorphisms of the *AGTM235T* gene (42). However, according to the results obtained in a study by Mohana et al., the presence of 235M/174M haplotype suggests an increased risk of AH in women (43). The first report on association of M235 T molecular variants with hypertension in Caucasians was presented by Jeunemaitre et al. (44). In a study of M235T (T704C) polymorphism, Sethi et al. have found that the presence of polymorphic alleles leads to a significant increase in angiotensin-I plasma levels, accompanied by an increase in angiotensin II levels; therefore, this polymorphism is considered to be associated with hypertension (45). The results of the study by Kolovou et al. suggest that only the frequency of the *AGTM235T* (rs699) variant was significantly different between patients with AH and controls (46). The results by Shamaa et al. have shown a positive risk of AH in the presence of T allele in a homozygous or heterozygous state, suggesting a relationship between the polymorphism of *AGT* genes (M235T) and risk for hypertension in Egyptian subjects (47). This is why some studies confirm the association between *AGT* polymorphism and AT, while others disprove it.

The results of our study in a group of patients with COPD have shown a significant deviation from the Hardy-Weinberg

equilibrium for the polymorphism of M235T AGT gene, which is consistent with the data given by Ayada et al. (14). The later authors attributed such result to a gene drift, having assumed that the rare T/T genotype was causing a gene drift in the COPD population. It is quite possible that the T allele is disappearing in the COPD population due to its negative impact, which can also be a sign of the correlation between the T/T genotype and the development of COPD. In our study, interesting results have been obtained for analysis of OR in combination of COPD and AH. These results demonstrated a trend towards a protective role of the M allele of the AGT gene concerning the occurrence of COPD, AH and their combination, while the presence of the T allele of the AGT gene could increase the risk for these conditions. A study on the role of AGT polymorphism in the occurrence of AH in COPD in Ukraine was conducted for the first time; virtually no data on this issue could be found in the available literature. The majority of the studies relate to the association of I/D polymorphism of the ACE gene with the risk for COPD (48-50). It is worth noting that the DD genotype of ACE is generally associated with increased circulating and cellular levels of ACE and increased cardiovascular risk (51). There are data on association of AGT polymorphism (M235T) with right ventricular hypertrophy in patients with severe COPD (23). The present study has some limitations that should be considered in the interpretation of our results: sample size is too small, that is why it is difficult to find significant relationships from the data; the inclusion in the study group only of patients with Stage 2 COPD and Stage I AH and the patients were not randomly selected, generating a potential selection bias. Therefore, we cannot rule out the hypothesis that the patients evaluated do not represent the whole population of COPD patients in the Ternopil region of Ukraine. However, our results reflect a more heterogeneous real-world population, representative of clinical practice.

Conclusion

The study that we have conducted suggests that the presence of T allele of the angiotensinogen gene at position 235 of the peptide chain both in homozygous and heterozygous states may increase the risk for AH in patients with COPD.

Ethical approval

The study protocol was approved by the Medical Ethics Committee of I. Horbachevsky Ternopil State Medical University (No 55-04/11/2019), and the study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 1983. Informed consent was obtained from all patients.

Conflict of interest

The author declares that there is no potential conflict of interest.

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