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ОЦЕНКА ВЛИЯНИЯ ПОЛИМОРФИЗМА A1166C ГЕНА *AGTR1* НА ФОРМИРОВАНИЕ КОМОРБИДНОЙ ПАТОЛОГИИ, АССОЦИИРОВАННОЙ С КАРДИОВАСКУЛЯРНЫМ РИСКОМ, У ПАЦИЕНТОВ С АНКИЛОЗИРУЮЩИМ СПОНДИЛИТОМ

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Assessment of The Effect of The A1166C Polymorphism of The *AGTR1* Gene on The Formation of Comorbidity Associated with Cardiovascular Risk in patients with ankylosing spondylitis

Резюме

Анкилозирующий спондилит (АС) — это хроническое воспалительное заболевание, характеризующееся поражением аксиального скелета, периферических суставов и околосуставного аппарата, манифестацией системных проявлений с преимущественным вовлечением сосудистой оболочки глаза, кожи с развитием псориаза и кишечника. Для АС характерен более ранний дебют артериальной гипертензии (АГ), а также ассоциированный с АГ более высокий уровень кардиоваскулярного риска (КВР). Эндотелиальная дисфункция как начальный этап развития сердечно-сосудистых заболеваний (ССЗ) может возникать вследствие активации прогормона ренина и высокой активности ангиотензина (Ang) II. Ang II участвует не только в регуляции артериального давления, но и выполняет гемопозитические функции, в основном эритропоз и миелопоэз. Несколько исследований показали связь полиморфизма гена рецептора к ангиотензину II 1-го типа *AGTR1* (1166A>C) с АГ, вазоконстрикцией и задержкой натрия в организме. Следовательно, потенциально важно оценить роль олигонуклеотидного полиморфизма (ОНП) A1166C гена *AGTR1* в клинической манифестации АС, а также его значение в развитии коморбидной патологии и формировании КВР, включая АГ. **Цель исследования:** оценить влияние полиморфизма A1166C гена *AGTR1* на развитие коморбидной патологии и формирование КВР, включая АГ. **Материалы и методы:** В исследование было включено 176 пациентов с диагнозом АС. Проводилось генотипирование полиморфизма A1166C гена *AGTR1* методом полимеразной цепной реакции. Статистический анализ проводился с использованием критерия Краскела-Уоллиса. **Результаты.** У пациентов с генотипом AA выявлен более высокий индекс BASMI (Bath Ankylosing Spondylitis Metrology Index) ($p=0,024$, $p_{1,3}=0,023$). У гомозигот CC фиксировались более низкие уровни эритроцитов ($p=0,025$, $p_{2,3}=0,02$) и гемоглобина ($p=0,031$, $p_{2,3}=0,042$), при генотипе AA — меньшее количество тромбоцитов ($p=0,0001$, $p_{1,3}=0,001$). Больше содержание глюкозы зарегистрировано у гомозигот CC ($p=0,0001$, $p_{1,3}=0,001$, $p_{1,2}=0,025$), триглицеридов — у гетерозигот АС ($p=0,038$). Наибольшая частота энтезитов зарегистрирована для пациентов с генотипом CC ($p_{2,3}=0,006$, $p=0,015$). У гетерозигот АС выявлена большая встречаемость АГ ($p_{1,2}=0,05$, $p=0,025$), дислипидемии ($p_{1,2}=0,012$, $p_{2,3}=0,006$, $p=0,031$). Сахарный диабет был выявлен только среди пациентов с генотипом CC ($p_{1,3}=0,007$, $p=0,017$). Поражение почек чаще определялось у носителей аллеля А ($p_{1,3}=0,015$, $p_{2,3}=0,004$, $p=0,023$). Выявлены статистические различия в отношении частоты выявления отдельных степеней АГ ($p=0,0001$): у гетерозигот АС — 2 (AA 26 (27,1%); АС 4 (33,3%); СС 14 (24,1%)) и 3 степени (AA 0 (0,0%) против АС 2 (16,7%) СС 0 (0,0%), $p_{1,2}<0,001$, $p_{2,3}=0,004$). **Заключение.** Продemonстрировано влияние ОНП

1166A>C гена *AGTR1* на формирование АГ, регуляцию гемопоэза, уровни метаболических показателей, глюкозы и липидов и ассоциированных метаболических заболеваний в виде сахарного диабета, дислипидемии, патологии почек у пациентов с АС.

Ключевые слова: анкилозирующий спондилит, артериальная гипертензия, дислипидемия, метаболический синдром, ангиотензин-превращающий фермент (АПФ), *AGTR1*, полиморфизм генов, A1166C

Конфликт интересов

Авторы заявляют, что данная работа, ее тема, предмет и содержание не затрагивают конкурирующих интересов

Источник финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Исследование соответствовало этическим нормам Хельсинкской декларации (2013 г.). Обследование пациентов с применением генотипирования было одобрено локально-этическим комитетом ФГАОУ ВО «КФУ им. В.И. Вернадского» (Протокол № 8 заседания «Комитета по биомедицинской этике» от 27.11.2025 г.), проведено с соблюдением этических принципов и наличием информированного согласия на обследование. Все участники подписали письменное информированное согласие на участие в исследовании.

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by damage to the axial skeleton, peripheral joints and periarticular apparatus, manifestation of systemic manifestations with predominant involvement of the vascular membrane of the eye, skin with the development of psoriasis and intestines. AU is characterized by an earlier onset of arterial hypertension (AH), as well as a higher level of cardiovascular risk (CVR) associated with AH. Endothelial dysfunction as the initial stage of the development of cardiovascular diseases (CVD) can occur due to the activation of the prohormone renin and high activity of angiotensin (Ang) II. Ang II is involved not only in the regulation of blood pressure, but also performs hematopoietic functions, mainly erythropoiesis and myelopoiesis. Several studies have shown the association of *AGTR1* (1166A>C) angiotensin II type 1 receptor polymorphism with hypertension, vasoconstriction, and sodium retention in the body. Therefore, it is potentially important to evaluate the role of oligonucleotide polymorphism (SNP) A1166C of the *AGTR1* gene in the clinical manifestation of AS, as well as its significance in the development of comorbid pathology and the formation of CVR, including hypertension. **Aim:** to evaluate the effect of the A1166C polymorphism of the *AGTR1* gene on the development of comorbid pathology and the formation of CFS, including AH. **Materials and methods:** The study included 176 patients diagnosed with AS. Genotyping was carried out according to the A1166C polymorphism of the *AGTR1* gene by the polymerase chain reaction method (PCR). The statistical analysis was carried out using the Kruskal-Wallis criterion. **Results:** Patients with the AA genotype had a higher BASMI (Bath Ankylosing Spondylitis Metrology Index) ($p=0.024$, $p_{1,3}=0.023$). CC homozygotes had lower levels of red blood cells ($p=0.025$, $p_{2,3}=0.02$) and hemoglobin ($p=0.031$, $p_{2,3}=0.042$), while AA genotypes had lower platelet counts ($p=0.0001$, $p_{1,3}=0.001$). Higher glucose levels were recorded in CC homozygotes ($p=0.0001$, $p_{1,3}=0.001$, $p_{1,2}=0.025$), triglycerides — in heterozygotes AC ($p=0.038$). The highest incidence of enthesitis was recorded for patients with the CC genotype ($p_{2,3}=0.006$, $p=0.015$). High incidence of hypertension ($p_{1,2}=0.05$, $p=0.025$), dyslipidemia ($p_{1,2}=0.012$, $p_{2,3}=0.006$, $p=0.031$) was found in heterozygotes of AC. Diabetes mellitus was detected only among patients with the CC genotype ($p_{1,3}=0.007$, $p=0.017$). Kidney damage was more often detected in carriers of the A allele ($p_{1,3}=0.015$, $p_{2,3}=0.004$, $p=0.023$). Statistical differences were found in the frequency of detection of individual degrees of hypertension ($p=0.0001$): in heterozygotes of AC — 2 (AA 26 (27.1%); AC 4 (33.3%); CC 14 (24.1%)) and grade 3 (AA 0 (0.0%) versus AC 2 (16.7%) CC 0 (0.0%), $p_{1,2}<0.001$, $p_{2,3}=0.004$). **Conclusion:** The obtained results reveal a wide range of functions of the SNP 1166A>C of the *AGTR1* gene, extending beyond participation in the formation of hypertension, and include the regulation of hematopoiesis, metabolic parameters, glucose and lipids in particular, and the formation of comorbid pathology in the form of diabetes mellitus, dyslipidemia, kidney pathology in patients with AS, which determines the potential and feasibility of genotyping patients with AS with the identification of SNPs in order to personalize approaches to pharmacotherapy of AS and monitoring these indicators in the presence of a risk of developing conditions associated with this SNP.

Key words: ankylosing spondylitis, arterial hypertension, dyslipidemia, metabolic syndrome, angiotensin converting enzyme (ACE), *AGTR1*, gene polymorphism, A1166C (rs5186)

Conflict of interests

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests

Sources of funding

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Conformity with the principles of ethics

The study corresponded to the ethical standards of the Helsinki Declaration (2013). The examination of patients using genotyping was approved by the local Ethics committee of the V.I. Vernadsky CFU (Protocol No. 8 of the meeting of the Committee on Biomedical Ethics dated 11/27/2025), conducted in compliance with ethical principles and informed consent to the examination. All participants signed a written informed consent to participate in the study

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AH — arterial hypertension, AxSpA — axial spondylarthritis, ACE — angiotensin converting enzyme, AS — ankylosing spondylitis, IBD — inflammatory bowel disease, HSC — haematopoietic stem cells, DNA — deoxyribonucleic acid, IHD — ischaemic heart disease, CVR — cardiovascular risk, BMI — body mass index, HDL — high-density lipoproteins, LDL — low-density lipoproteins, NSAIDs — non-steroidal anti-inflammatory drugs, NSAID gastropathy — NSAID-associated gastropathy, KSD — kidney stone disease, SNP — single nucleotide polymorphism, PCR — polymerase chain reaction, RAAS — rennin-angiotensin-aldosterone system, CRP — C-reactive protein, DM2 — type 2 diabetes mellitus, ESD — erythrocyte sedimentation rate, CVD — coronary vascular diseases, SpA — spondylarthritis, ED — endothelial dysfunction, *AGTR1* — type 1 angiotensin II receptor, Ang II — angiotensin II, ASAS — Assessment of SpondyloArthritis International Society, ASDAS-CRP — Ankylosing Spondylitis Disease Activity Score, BASDAI — Bath AS Disease Activity Index, BASMI — Bath AS Metrology Index, HLA B27 — human leucocyte antigen B27, MAPK — mitogenic-activated protein kinase, VEGF — vascular endothelial growth factor, VEGFR2 — VEGF receptor

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disorder, associated with the development of an inflammatory process in axial and peripheral joints and in peri-axial structures, with systemic manifestations, related to uvea involvement, such as uveitis and iridocyclitis, skin conditions (psoriasis), and bowel inflammations. [1, 2]. Clinically, AS manifests as inflammatory back pain and gradual progression of irreversibly restricted mobility in the spine caused by ankylosis [3].

Patients with AS have earlier onset of arterial hypertension (AH), as well as a higher cardiovascular risk (CVR) resulting from AH [2, 3]. AH is a multigenic condition and is triggered by an interaction of environmental and genetic predictors together with epigenetic factors. Renin-angiotensin-aldosterone system (RAAS) is a complex multiple-level mechanism, regulating vascular tone, metabolic homeostasis, and water-electrolytic balance [4].

Endothelial dysfunction (ED) is associated with vasoconstrictive, pro-adhesive, pro-thrombotic, proliferative, and pro-inflammatory processes, which potentiate atherosclerotic lesions and are an initial stage in the development of cardiovascular diseases (CVDs) [5]. In individuals with AH, ED, which causes reduced NO availability, impairs endothelium-dependent vasodilation [6].

ED can be a result of (pro)renin receptor (PRR) activation and high angiotensin (Ang) II activity [7]. Renin can interact with PRR, stimulating RAAS, catalysing Ang I production [8], thus triggering activation of mitogenic-activated protein kinase (MARK) pathways [9] in the presence of V-ATPase, as well as Wnt/ β -catenin pathway regulation [10].

Studies of vascular reconstruction demonstrated that Ang II intensifies angiogenic functions of progenitor cells, which is mainly a result of elevated levels of vascular endothelial growth factor (VEGF) and its receptor VEGFR2. Excessive vascular permeability in the presence of Ang II and VEGF can stimulate progenitor cell transmigration to damaged areas and facilitate vascular reparation [11].

Simultaneously intensified activity of the ACE/Ang II/AGT1R pathway slows down cardiovascular reconstruction and postnatal vasculogenesis, at least partially

due to inhibition of the reparative functions of progenitor cells. AGT1P activation by hypertensive concentrations of Ang II reduced the number of circulating progenitor cells in the experimental mice model and inhibited their functions involved in vascular restoration, leading to endothelial damage and impaired vascular regeneration [12].

Of note, Ang II is involved not only in blood pressure regulation, but it also has hematopoietic functions, mostly erythropoiesis and myelopoiesis, which was demonstrated with the help of angiotensin receptor blockers in vitro or in the mice model of genetic deficit of angiotensin converting enzyme (ACE) [13, 14, 15]. ACE is essential for normal hematopoiesis, while ACE inhibitors increase the risk of anaemia [16].

Therefore, the study of type 1 angiotensin II receptor (*AGTR1*) gene is very important for the evaluation of the risk of AH in patients with AS, including its participation in vasculogenesis and hematopoiesis. A number of studies demonstrated the association between polymorphism of *AGTR1* (1166A>C, rs5186) with AH, vasoconstriction and sodium retention in the body [17, 18].

Therefore, it is potentially essential to assess the role of polymorphism A1166C of the *AGTR1* gene in clinical presentation of AS, as well as its significance for the development of comorbidity and CVR, including AH.

Objective of the study: to assess the implications of polymorphism A1166C of the *AGTR1* gene for the development of comorbidity and CVR, including AH.

Materials and methods

The study enrolled 176 patients with confirmed AS, who were admitted to the rheumatology ward of N. A. Semashko Republican Clinical Hospital, Simferopol, Crimea. Biological material (whole blood) was taken from all patients upon admission. Patients were included into the study group provided they had confirmed AS. Inclusion criteria were: age of 18 to 55 years old; inpatient and outpatient patients with verified AS, meeting the modified 1984 New York criteria and classification of the ASAS (Assessment of SpondyloArthritis International Society) experts issued in 2009; symptom duration of under 20 years; informed consent; positive result for

human leucocyte antigen (HLA) B27. Exclusion criteria: lack of informed consent; age under 18 years old and over 55 years old; symptom duration of over 20 years; chronic grade III pulmonary heart disease; chronic stage V kidney disease; hepatic failure; acute or chronic infections; cancer; negative HLA-B27.

Information on comorbidities was retrieved from medical records of previously hospitalised patients.

Over a half of all subjects were men (115 (65.3 %)); mean age was 44 [38; 49] years old; AS duration upon enrollment was 11 [8; 20] years. Body weight index corresponded to overweight (26.1 [24; 30] kg/m²). Patients had high AS activity (BASDAI: 7.4 [6.8; 7.9],

ASDAS-CRP: 4.2 [3.8; 4.5]) and moderate dysfunction (BASMI: 4.0 [3.0; 6.0]). Clinical blood count results (Hb (141.0 [128.0; 151.0] g/L), WBC (7.1 [5.45; 8.82] ×10⁹/L), RBC (4.7 [4.3; 5.1] ×10¹²/L), and platelets (273.0 [231.5; 312.0] ×10⁹/L) were normal, while ESR (20.5 [10.0; 29.5] mm/h) and CRP (6.65 [2.85; 14.65] mL/L) were over the reference range. As for metabolic parameters, cholesterol (5.6 [4.6; 6.3] mmol/L) and LDL (3.4 [2.7; 4.0] mmol/L) levels were higher than normal. HDL, triglycerides, glucose, uric acid, creatinine, urea, and iron were within the reference range. Clinical and laboratory characteristics of patients enrolled into the study are presented in Table 1.

Table 1. Clinical and laboratory characteristics of patients with ankylosing spondylitis

Characteristics		Patients with ankylosing spondylitis (n=176)
Gender	Male. abs. (%)	115 (65.3)
	Female. abs. (%)	61 (34.7)
Age, full years		44 [38; 49]
Duration of the disease, full years		11 [8; 20]
BMI, kg/m ²		26.1 [24; 30]
BASDAI		7.4 [6.8; 7.9]
ASDAS-CRP		4.2 [3.8; 4.465]
BASMI		4.0 [3.0; 6.0]
Haemoglobin, g/l		141.0 [128.0; 151.0]
White blood cells, ×10 ⁹ /l		7.1 [5.45; 8.82]
Red blood cells, ×10 ¹² /l		4.655 [4.3; 5.1]
Platelets, ×10 ⁹ /l		273.0 [231.5; 312.0]
ESR, mm/h		20.5 [10.0; 29.5]
CRP, mg/l		6.65 [2.85; 14.65]
Cholesterol, mmol/l		5.6 [4.6; 6.32]
LDL, mmol/l		3.425 [2.67; 3.995]
HDL, mmol/l		1.5 [1.28; 1.8]
Triglycerides, mmol/l		1.24 [0.89; 1.715]
Glucose, mmol/l		5.1 [4.5; 5.68]
Uric acid, mcmol/l		307.0 [242.0; 422.5]
Creatinine, mcmol/l		81.0 [70.4; 91.5]
Urea, mmol/l		5.01 [4.2; 5.94]
Iron, mmol/l		14.9 [11.3; 20.5]

Notes: Ankylosing spondylitis — AS, Body Mass Index — BMI, Bath AS Disease Activity Index — BASDAI, Ankylosing Spondylitis Disease Activity Score with calculation of CRP — ASDAS-CRP, Bath AS Metrology Index — BASMI, erythrocyte sedimentation Rate — ESR, C-reactive protein — CRP, low-density lipoproteins — LDL, high-density lipoproteins — HDL

The majority of patients had X-ray stage II AS (108 (61.4%)), while stage III and stage IV was diagnosed in 30 (17.0%) and 34 (19.3%) patients, respectively. X-ray changes in hip joints were absent in 30 (17.0%) patients; X-ray stage I, II, III, and IV was reported in 44 (25.0%), 74 (42.1%), 26 (14.8%), and 2 (1.1%) patients, respectively. Extraaxial manifestations were arthritis (156 (88.6%)), enthesitis (100 (56.8%)), and dactylitis (4 (2.3%)). Spondylitis as a manifestation of the late clinical stage of AS was reported in 54 (30.7%) patients. Extraaxial manifestations were observed in 40 (22.7%) patients; eye disorders prevailed (30 (17.0%)), mostly in the form of uveitis (20 (11.4%)); psoriasis (18 (10.2%)) and inflammatory bowel disease (6 (3.4%)) were less common.

Clinical characteristics of patients depending on manifestations and progression of ankylosing spondylitis are presented in Table 2.

The most common CVR-associated comorbidities were dyslipidemia (90 (51.1%) patients); AH (60 (34.1%)), where stage II (34 (19.3%)), grade 2 (44 (25.0%)), risk 3 (44 (25.0%)) prevailed; obesity (38 (21.6%)), and

hyperuricemia (20 (11.4%)). GI disorders were reported in 30 (17.0%) patients, and NSAID-associated gastropathy prevailed (18 patients (10.2%)).

The clinical characteristics of patients with ankylosing spondylitis with and without comorbidities are presented in Table 3.

The study was conducted at the Molecular Biology Centre for the Shared Use of Scientific Equipment, Vernadsky Crimean Federal University. Whole blood of patients with AS was used to extract deoxyribonucleic acid (DNA) with the help of DNA Express Blood kit (Litekh, Russia) in accordance with the manufacturer's instructions. Polymorphism A1166C of the *AGTR1* gene was analysed using allele-specific PCR kits (Litekh, Russia). Amplification products were detected using horizontal electrophoresis with 3% agarose gel.

The study complied with the ethical principles of the Declaration of Helsinki (2013). Patient genetic typing was approved by the Local Ethics Committee at the Vernadsky Crimean Federal University (Meeting Minutes No. 8 of the Biomedical Committee dated 27.11.2025).

Table 2. Clinical characteristics of patients with ankylosing spondylitis

Characteristics	AS (n=176)
Sacroiliitis, the X-ray stage	
– I	0
– II	108 (61.4%)
– III	30 (17.0%)
– IV	34 (19.3%)
Coxitis, the X-ray stage	
– 0	30 (17.0%)
– I	44 (25.0%)
– II	74 (42.1%)
– III	26 (14.8%)
– IV	2 (1.1%)
Arthritis	156 (88.6%)
Enthesitis	100 (56.8%)
Dactylitis	4 (2.3%)
Spondylitis	54 (30.7%)
Extraskeletal manifestations	40 (22.7%)
Eye lesions	30 (17.0%)
– uveitis	20 (11.4%)
– iridocyclitis	6 (3.4%)
– episcleritis	4 (2.3%)
Psoriasis	18 (10.2%)
Inflammatory bowel disease	6 (3.4%)

Table 3. Comorbidities in patients with ankylosing spondylitis

Comorbidities	Patients with ankylosing spondylitis (n=176)
Arterial hypertension, abs. (%)	n=60 (34.1 %)
– stage	
– 1, abs. (%)	16 (10.8 %)
– 2, abs. (%)	34 (19.3 %)
– 3, abs. (%)	10 (5.7 %)
– degree	
– 1, abs. (%)	14 (8.0 %)
– 2, abs. (%)	44 (25.0 %)
– 3, abs. (%)	2 (1.1 %)
– risk	
– 1, abs. (%)	0 (0.0 %)
– 2, abs. (%)	8 (4.5 %)
– 3, abs. (%)	44 (25.0 %)
– 4, abs. (%)	8 (4.5 %)
Dyslipidemia, abs. (%)	90 (51.1 %)
Diabetes mellitus, abs. (%)	4 (2.3 %)
Coronary heart disease, abs. (%)	6 (3.4 %)
Hyperuricemia, abs. (%)	20 (11.4 %)
Gout, abs. (%)	6 (3.4 %)
Gastrointestinal diseases, abs. (%)	n=30 (17.0 %)
– NSAID-gastropathy, abs. (%)	18 (10.2 %)
– Erosive gastropathy, abs. (%)	12 (6.8 %)
– GOUT/GOUT, abs. (%)	2 (1.1 %)
– Gastroesophageal reflux disease, abs. (%)	2 (1.1 %)
Kidney diseases, abs. (%)	n=12 (6.8 %)
– Chronic pyelonephritis, abs. (%)	6 (3.4 %)
– Urolithiasis, abs. (%)	6 (3.4 %)
Osteoporosis, abs. (%)	6 (3.4 %)
Obesity, abs. (%)	n=38 (21.6 %)
– 1st degree, abs. (%)	26 (14.8 %)
– 2nd degree, abs. (%)	12 (6.8 %)
– 3rd degree, abs. (%)	0 (0.0 %)
Overweight, abs. (%)	44 (25.0 %)
Body weight deficiency, abs. (%)	2 (1.1 %)
Smoking, abs. (%)	18 (10.2 %)

The study was conducted in accordance with the ethical principles. All subjects signed the informed consent forms for the participation in the study.

The data were analysed using IBM SPSS Statistics 27 package. The Shapiro-Wilk test was used to check the normality of quantitative indicator distribution. Groups were compared with the Kruskal-Wallis test. Results were statistically significant at 0.05. The rate of qualitative attributes was tested using the Pearson’s chi-square test or Fisher’s test. Distribution was normal at $p\geq 0.1$ if the Kolmogorov-Smirnov test was used.

Study results

Patients with genotype AA had higher BASMI values vs. allele C carriers (AA 5.0 [4.0; 6.0]; AC 3.0 [3.0; 7.0]; CC 4.0 [3.0; 5.0], $p=0.024$, $p_{1,3}=0.023$). At the same time, homozygote of allele CC carriers showed significantly lower RBC (AA 4.7 [4.3; 5.12] $\times 10^{12}/L$; AC 5.29 [4.63; 5.6] $\times 10^{12}/L$; CC 4.57 [4.38; 4.93] $\times 10^{12}/L$, $p=0.025$, $p_{2,3}=0.02$) and Hb levels (AA 143 [128; 152] g/L; AC 150 [141; 153] g/L; CC 140 [126; 143] g/L, $p=0.031$, $p_{2,3}=0.042$); while AA homozygotes had lower platelet counts (AA 252 [223; 297] $\times 10^9/L$; AC 282 [236; 338]

Table 4. Comparison of clinical and laboratory parameters in patients with ankylosing spondylitis and various variants of single nucleotid polymorphism (SNP) A1166C AGTR1 gene

Signs	AGTR1 A-1166C			p
	AA (n=104)	AC (n=14)	CC (n=58)	
Age, full years	43.0 [39.0-49.0]	46.0 [36.0-50.0]	44.0 [37.0-48.0]	>0.05
Gender	8 (57.1 %)	56 (63.6 %)	>0.05	>0,05
	6 (42.9 %)	32 (36.4 %)		
Duration of the disease, full years	11.0 [8.5; 18.0]	10.0 [5.0; 30.0]	13 [8.0;20.0]	>0.05
BASDAI	7.4 [6.8; 7.8]	7.7 [7.4; 8.0]	7.4 [6.8; 7.8]	>0.05
ASDAS-CRP	4.2 [3.8; 4.5]	3.9 [3.47; 4.6]	4.08 [3.8; 4.4]	>0.05
BASMI	5.0 [4.0; 6.0]	3.0 [3.0; 7.0]	4.0 [3.0; 5.0]	0.024 p _{1,3} =0.023
BMI, kg/m², Me (Q1-Q3)	26.8 [24.0; 31.6]	29.0 [25.25; 31.7]	25.7 [24.0; 28.1]	>0.05
White blood cells, ×10 ⁹ /l	6.86 [5.5; 8.81]	7.62 [6.49; 9.6]	7.6 [5.3; 8.69]	>0.05
Red blood cells, ×10 ¹² /l	4.7 [4.3; 5.12]	5.29 [4.63; 5.6]	4.57 [4.38; 4.93]	P=0.025 p _{2,3} =0.02
Platelets, ×10 ⁹ /l	252 [223; 297]	282 [236; 338]	283 [254; 333]	p=0.0001 p _{1,3} =0.001
Haemoglobin, g/l	143 [128; 152]	150 [141; 153]	140 [126; 143]	p=0.031 p _{2,3} =0.042
ESR, mm/h	20 [10; 29]	27 [4; 36]	20 [10; 30]	>0.05
CRP, mg/l	8.0 [2.7; 16.0]	8.6 [6.1; 18.5]	5.2 [4.3; 6.1]	>0.05
Glucose, mmol/l	4.8 [4.36; 5.4]	5.4 [5.1; 5.95]	5.4 [4.9; 5.8]	p=0.0001 p _{1,3} =0.001 p _{1,2} =0.025
Cholesterol, mmol/l	5.6 [4.6; 6.5]	6.3 [4.8; 6.7]	5.3 [4.3; 6.1]	>0.05
LDL, mmol/l	3.5 [2.9; 4.2]	3.7 [3.0; 4.8]	3.2 [2.6; 3.8]	>0.05
HDL, mmol/l	1.5 [1.3; 2.1]	1.3 [1.0; 1.5]	1.6 [1.5; 1.8]	>0.05
Triglycerids, mmol/l	1.3 [0.9. 1.7]	1.5 [1.0; 4.1]	0.9 [0.8; 1.2]	0.038
Creatinine, mcmol/l	80.7 [70.3; 100.0]	80.0 [64.7; 88.0]	81.3 [74.0; 87.1]	>0.05
Urea, mmol/l	4.9 [4.2; 6.1]	5.4 [4.9; 5.9]	5.0 [4.0; 5.9]	>0.05
Urea acid, mcmol/l	331.0 [262.0; 446.0]	311.8 [277.0; 346.0]	262.0 [217.0; 356.0]	>0.05
Iron, mcmol/l	13.9 [11.7; 20.6]	16.4 [14.0; 29.5]	15.0 [10.7; 20.4]	>0.05

Notes:
p_{1,2} — differences identified between AA and AC genotypes
p_{1,3} — differences identified between AA and CC genotypes
p_{2,3} — differences identified between AC and CC genotypes
Ankylosing spondylitis — AS, Body Mass Index — BMI, Bath AS Disease Activity Index — BASDAI, Ankylosing Spondylitis Disease Activity Score with calculation of CRP — ASDAS-CRP, Bath AS Metrology Index — BASMI, erythrocyte sedimentation Rate — ESR, C-reactive protein — CRP, low-density lipoproteins — LDL, high-density lipoproteins — HDL.

$\times 10^9/L$; CC 283 [254; 333] $\times 10^9/L$, $p=0.0001$, $p_{1,3}=0.001$). As far as metabolic parameters are concerned, allele C carriers demonstrated higher glucose concentration (AA 4.8 [4.36; 5.4] mmol/L; AC 5.4 [5.1; 5.95] mmol/L; CC 5.4 [4.9; 5.8] mmol/L, $p=0.0001$, $p_{1,3}=0.001$, $p_{1,2}=0.025$); while AC homozygotes had lower triglycerides values (AA 1.3 [0.9, 1.7] mmol/L; AC 1.5 [1.0; 4.1] mmol/L; CC 0.9 [0.8; 1.2] mmol/L, $p=0.038$). There were no statistically significant differences in other clinical and laboratory results (Table 4).

Patients with genotype AC had the lowest rate of enthesitis, while the highest enthesitis rate was reported in patients with genotype CC (AA 56 (53.8 %); AC 4 (28.6 %); CC 40 (69.0 %), $p_{2,3}=0.006$, $p=0.015$). There were no statistically significant differences in extraaxial manifestations when genotypes were compared (Table 5). Also, there were no statistically significant difference in comparison groups as regards X-ray stages of sacroilitis and coxitis and extraaxial manifestations of AS (Table 5).

Table 5. Comparison of clinical manifestations of ankylosing spondylitis depending on different variants of the A1166C polymorphism of the AGTR1 gene

	AA (n=104)	AC (n=14)	CC (n=58)	p	p (total)
Clinical manifestations					
Arthritis	94 (90.4 %)	12 (85.7 %)	50 (86.2 %)	-	>0.05
Enthesite	56 (53.8 %)	4 (28.6 %)	40 (69.0 %)	p _{2,3} =0.006	=0.015
Dactylitis	4 (3.9 %)	0 (0.0 %)	0 (0.0 %)		-
Spondylitis	28 (28.0 %)	4 (28.6 %)	22 (37.9 %)	-	>0.05
Radiographic stage of sacroiliitis					
II	62 (62.0 %)	8 (57.1 %)	38 (65.5 %)	-	p>0.05
III	18 (18,0 %)	4 (28,6 %)	8 (13,8 %)	-	
IV	20 (20,0 %)	2 (14,3 %)	12 (20,7 %)	-	
Radiographic stage of coxitis					
0	18 (17,3 %)	2 (14,3 %)	10 (17,2 %)	-	p>0,05
I	22 (21.2 %)	4 (28.6 %)	18 (31.0 %)	-	
II	46 (44.2 %)	6 (42.9 %)	22 (37.9 %)	-	
III	16 (15.4 %)	2 (14.3 %)	8 (13.8 %)	-	
IV	2 (1.9 %)	0 (0.0 %)	0 (0.0 %)	-	
Extraskeletal manifestations					
Extraskeletal manifestations	0 (0.0 %)	28 (21.5 %)	6 (23.1 %)	-	p>0.05
Eye lesions	26 (25.0 %)	4 (28.6 %)	10 (17.2 %)	-	p>0.05
– uveit	22 (22.5 %)	4 (28.6 %)	4 (7.1 %)	-	p>0.05
– iridocyclitis	14 (14.3 %)	2 (14.3 %)	4 (7.1 %)	-	p>0.05
– episclerite	4 (4.1 %)	2 (14.3 %)	(0.0 %)	-	p>0.05
Psoriasis	4 (4.1 %)	0 (0.0 %)	(0.0 %)	-	p>0.05
IBD	10 (10.0 %)	2 (14.3 %)	6 (10.7 %)	-	p>0.05

Notes
* $p_{1,2}$ — differences identified between AA and AC genotypes
** $p_{1,3}$ — differences identified between AA and CC genotypes
*** $p_{2,3}$ — differences identified between AC and CC genotypes
Inflammatory bowel disease — IBD.

Table 6. Comparison of comorbid pathology depending on SNP A1166C of the AGTR1 gene in patients with ankylosing spondylitis

Comorbid pathology	AA (n=104)	AC (n=14)	CC (n=58)	p	P (total)
AH	32 (37.2 %)	8 (80.0 %)	20 (35.7 %)	$p_{1,2}=0.05$	$=0.025$
Dyslipidemia	52 (53.1 %)	12 (85.7 %)	26 (46.4 %)	$p_{1,2}=0.012$ $p_{2,3}=0.006$	$=0.031$
CHD	4 (4.2 %)	0 (0.0 %)	2 (3.6 %)	-	$p>0.05$
DM 2	0 (0.0 %)	0 (0.0 %)	4 (7.1 %)	$p_{1,3}=0.007$	$=0.017$
Hyperuricemia	16 (16.7 %)	0 (0.0 %)	4 (7.4 %)	-	$p>0.05$
Gout	6 (6.3 %)	0 (0.0 %)	0 (0.0 %)	-	$p>0.05$
Renal lesions	10 (10.5 %)	2 (14.3 %)	0 (0.0 %)	$p_{1,3}=0.015$ $p_{2,3}=0.004$	$=0.023$
– Chronic pyelonephritis	6 (6.3 %)	0 (0.0 %)	0 (0.0 %)	-	
– Urolithiasis	4 (4.2 %)	2 (14.3 %)	0 (0.0 %)	-	
Osteoporosis	2 (2.1 %)	0 (0.0 %)	4 (7.1 %)	-	$p>0.05$
Smoking	10 (10.4 %)	4 (28.6 %)	4 (7.4 %)	-	$p>0.05$

Notes
 $p_{1,2}$ — differences identified between AA and AC genotypes
 $p_{1,3}$ — differences identified between AA and CC genotypes
 $p_{2,3}$ — differences identified between AC and CC genotypes
Arterial hypertension — AH, coronary heart disease — CHD, type 2 diabetes mellitus — DM2.

Table 7. Comparison of the stage, degree and risk of arterial hypertension in patients with ankylosing spondylitis depending on the SNP A1166C of the AGTR1 gene

	AA (n=104)	AC (n=14)	CC (n=58)	p	p (общее)
Stage					
I	8 (8.3 %)	2 (16.7 %)	6 (10.7 %)	-	p>0.05
II	16 (16.7 %)	6 (50.0 %)	12 (21.4 %)	-	
III	8 (8.3 %)	0 (0.0 %)	2 (3.6 %)	-	
Degree					
1	6 (6.3 %)	2 (16.7 %)	6 (10.3 %)	-	=0.0001 p _{1,2} <0.001 p _{2,3} =0.004
2	26 (27.1 %)	4 (33.3 %)	14 (24.1 %)	-	
3	0 (0.0 %)	2 (16.7 %)	0 (0.0 %)		
Risk					
1	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-	p>0.05
2	4 (4.0 %)	0 (0.0 %)	4 (7.1 %)	-	
3	24 (24.0 %)	6 (42.9 %)	14 (25.0 %)	-	
4	4 (4.0 %)	2 (14.3 %)	2 (3.6 %)	-	

Notes
 $p_{1,2}$ — differences identified between AA and AC genotypes
 $p_{1,3}$ — differences identified between AA and CC genotypes
 $p_{2,3}$ — differences identified between AC and CC genotypes
Arterial hypertension — AH

AC heterozygote demonstrated the highest rate of AH cases (AA 32 (37.2%); AC 8 (80.0%); CC 20 (35.7%), $p_{1,2}=0.05$, $p=0.025$). In addition, this patient group had the highest number of dyslipidemia cases (AA 52 (53.1%); AC 12 (85.7%); CC 26 (46.4%), $p_{1,2}=0.012$, $p_{2,3}=0.006$, $p=0.031$). Diabetes mellitus was reported only in patients with genotype CC (AA 0 (0.0%); AC 0 (0.0%); CC 4 (7.1%), $p_{1,3}=0.007$, $p=0.017$). Kidney damage as a comorbidity was recorded in allele A carriers (AA 10 (10.5%); AC 2 (14.3%); CC 0 (0.0%), $p_{1,3}=0.015$, $p_{2,3}=0.004$, $p=0.023$). Also, homozygote of AA carriers demonstrated higher rates of chronic pyelonephritis (AA 6 (6.3%); AC 0 (0.0%); CC 0 (0.0%)) and KSD (AA 4 (4.2%); AC 2 (14.3%); CC 0 (0.0%)). There were no statistically significant differences regarding other comorbidities (Table 6).

AC carriers demonstrated higher rates of grade 2 (AA 26 (27.1%) vs. AC 4 (33.3%); CC 14 (24.1%)) and grade 3 AH (AA 0 (0.0%); AC 2 (16.7%); CC 0 (0.0%), $p_{1,2}<0.001$, $p_{2,3}=0.004$). In general, intergroup differences were statistically significant ($p=0.0001$). There were no statistically significant differences in the rates of individual AH grades and risks between groups (Table 7).

Discussion

Currently, literature references do not report studies of the clinical parameters of AS and the association with SNP A1166C of the *AGTR1* gene. As for the clinical parameters, this study was the first to demonstrate higher BASMI values in AA homozygote. Moreover, analysis of clinical manifestations of the disease showed that CC genotype carriers had the highest rate of enthesitis.

Assessment of laboratory parameters and comorbidity manifestations yielded some interesting results.

ACE and RAAS are known to have an essential role in blood pressure regulation. However, not less interesting is the presence of ACE and local RAAS in bone marrow, which impact the peptide chain contributing to haematopoiesis regulation. ACE is expressed over the entire duration of hematopoietic tissue development [19]. Even at the early stages of fetation, before blood circulation has been established, local ACE production can be observed. Local ACE is likely to facilitate the development of haematopoietic stem cells (HSCs) and other haematopoietic cells in the adult bone marrow.

AT1-mediated Ang II signalling is essential for myeloid differentiation and functional maturation. Pilot studies show that enzymatic activity of ACE can be required to sustain haematopoietic homeostasis. For example, ACE inhibition blocked haemangioblast expansion and differentiation as endothelium or multipotent haematopoietic precursors. In turn, ACE inhibition

significantly reduced the ability of the embryoid body to produce haematopoietic colony-forming cells.

This study of patients with AS demonstrated for the first time that SNP A1166C genotype CC of the *AGTR1* gene caused lower RBC count and Hb and higher platelet levels. Therefore, our study was the first to show the differences in RBC and platelets production depending on genetic variants of SNP A1166C of the *AGTR1* gene, confirming genetic predisposition to lower RBC and Hb levels and higher platelet values in patients with genotype CC.

Ang II-triggered increase in oxidative stress, inflammation and free fatty acid levels promotes β -cell dysfunction in patients with diabetes [20]. Various organs have a role to play in regulation of glucose homeostasis, including pancreas, adipose tissue, skeletal muscles, and liver. It is worth noting that these organs have their own local RAAS, the activation of which is associated with diabetic pathology. It appears that RAAS activation boosts effects of other pathogenic pathways, including glucotoxicity, lipotoxicity and increased glycation, thus leading to hyperglycaemia and insulin resistance [21, 22]. On the contrary, hyperglycaemia, hypercholesterolemia and insulin resistance can increase the activity of RAAS components [23, 24].

In this study, allele C carriers had higher glucose levels vs. homozygotes AA, while AA and AC genotype carriers had higher triglyceride levels, again confirming the role of RAAS in glucose and Hb regulation, having the same genetics with SNP A1166C of the *AGTR1* gene.

When comorbidity of patients with AS was analysed, the role of SNP A1166C of the *AGTR1* gene in the metabolic syndrome was demonstrated by a higher rate of dyslipidemias in allele A carriers, particularly in heterozygote AC carriers, while type 2 diabetes mellitus (DM2) was reported only in genotype CC carriers.

During nephrogenesis, RAAS components demonstrate high expression and play a vital role in the regular structure of kidneys and their physiological function [25]. In kidneys, Ang II is expressed in significantly higher concentrations in the interstitial space. Local Ang II production can significantly affect kidney function by changing glomerule haemodynamics, inhibiting sodium excretion, and narrowing small arterioles [26]. Moreover, excessive RAAS activity directs pro-inflammatory and profibrotic factors to damage kidneys [27], while RAAS inhibition demonstrated efficiency in reducing renal fibrosis.

According to available data [28, 29], it has been demonstrated that the *AGTR1* gene contributes to chronic kidney damage. This study also demonstrated higher rates of renal pathologies in allele A carriers.

AGT1R activation by Ang II causes vasoconstriction and boosts the activity of the sympathetic nervous

system. It results in elevation in BP and aldosterone secretion, as well as heart hypertrophy and fibrosis. Numerous studies report the association between polymorphism 1166A>C (rs5186) of the *AGTR1* gene and arterial hypertension, vasoconstriction, and sodium retention [30]. The study by Semianiv et al. identified the association between allele C of the *AGTR1* gene (rs5186) and AH severity. This study demonstrated a higher rate of AH and more cases of grade 2 and 3 AH in genotype AC carriers, underlining a higher probability of AH development and higher severity of AH in genotype AC carriers with AS.

Conclusion

The results do not suggest any significant impact of SNP 1166A>C of the *AGTR1* gene on clinical manifestations of AS, except for BASMI and the rate of enthesitis. However, the results of the study demonstrated intriguing data on the role of SNP 1166A>C of the *AGTR1* gene in the hemopoiesis, namely reduced RBC and Hb levels, and higher platelet counts in genotype CC carriers.

Of special interest are the metabolic parameters: high glucose values in allele C carriers and DM2 only in homozygote CC. In turn, allele A was associated with higher blood triglyceride concentrations and dyslipidemia, especially in heterozygote AC. It is worth noting that allele A carriage was also associated with higher rates of renal pathologies and AH, and their severity.

The results of the study uncover the vast spectrum of functions of SNP 1166A>C of the *AGTR1* gene beyond contribution to AH. The results include regulation of hemopoiesis, metabolic mechanisms and comorbidities in patients with AS. It shows the significance and viability of genetic typing of patients with AS and identifying SNP 1166A>C of the *AGTR1* gene in order to provide patient-specific drug therapy of AS and monitor these parameters in the presence of a risk of SNP-associated conditions.

Вклад авторов:

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Гаффарова А.С.: существенный вклад в замысел и дизайн исследования, сбор данных, анализ и интерпретация данных, подготовка статьи, критический пересмотр в части значимого интеллектуального содержания

Белоглазов В.А.: существенный вклад в замысел и дизайн исследования, анализ и интерпретация данных, критический пересмотр в части значимого интеллектуального содержания

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Contribution of Authors

All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

Gaffarova A.S.: significant contribution to the conception and design of the study, data collection, analysis and interpretation of data, preparation of the article, critical revision in terms of meaningful intellectual content

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