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Short Communication

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The angiotensinogen gene polymorphism, lifestyle factors, associated diseases and gastric areas of inflammatory and preneoplastic lesions in a Romanian sample of patients

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Abstract

The aim of our study was to evaluate the association between variant genotype of angiotensinogen (AGT) c.-58A>C, lifestyle factors and clinical factors and corporeal extension of gastric inflammatory and preneoplastic lesions. ***Methods:*** *Our study included 209 subjects who underwent a complete set of gastric biopsies, followed by genotyping. They were included to study inflammatory gastric changes and preneoplastic lesions and were grouped according to the localization of changes.* ***Results:*** *No significant statistical associations were noticed between AGT c.-58A>C genotypes and the corporeal extension of the inflammation or preneoplastic injury groups. Extending preneoplastic lesions to the gastric body was associated with smoking habits (p=0.01) and additionally, there was a significant association between nicotine consumption and the body extension of preneoplastic lesions (p=0.01). The use of acenocoumarol was frequently associated with the progression of histological lesions to preneoplastic lesions (p=0.01). Compared with the wild-type AA genotype, the combined genotypes AA+CC of AGT c.-58A>C were significantly associated with the progression of inflammatory gastric lesions' according to the regular ingested doses of nonsteroidal anti-inflammatory drugs (NSAIDs).* ***Conclusion:*** *The AGT c.-58A>C polymorphism is not associated with extension of the gastric lesions. In accordance with nicotine and alcohol consumption, the acenocoumarol co-treatment and multiple cardiac pathologies are associated with the corporeal progression of these injuries. The age below 70 years and NSAIDs treatment for the patients with heterozygous AC genotype and variant homozygous CC genotype for the mentioned SNP have been associated with the corporeal extension of gastric inflammation.*

Keywords: *AGT gene polymorphism, lifestyle factors, extension of gastric lesions*

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Introduction

Recent evidence provided by global cancer societies highlights that cancer remains a major cause of death worldwide, estimating 9.6 million deaths in 2018. One of the most common malignancy worldwide is gastric cancer which remains the third cause of death (783,000 deaths annually) of all malignancies globally (1, 2). Nevertheless, the rate of incidence of this type of cancer has fallen in last decades due to some factors, which together constitute primary prevention and which include increasing hygiene standards, balanced nutrition, and eradication of Helicobacter pylori (H. pylori) (3). Gastric cancer tends to develop slowly over several years, premalignant lesions often occurring in the stomach mucosa. It is known that initial changes cause very rare symptoms, patients being usually diagnosed in an advanced phase of the disease. Furthermore, for patients' monitoring, assessment, and inclusion in national or regional health programs, adequate knowledge of risk factors is required. Mucosal inflammation is a complex biochemical protective mechanism to the gastric cellular tissue injury. The most frequent type of gastric cancer, namely intestinal cancer, develops through a cascade of recognizable precursors, initially by inducing chronic gastric inflammation that progresses to atrophy, metaplasia, dysplasia, and carcinoma. Risk factors such as intragastric distribution and extent of histological changes were identified for gastric cancer (4). Also, this process is multifactorial, with both lifestyle and genetic factors impact in it. Recognizing and studying these factors can be an effective step for preventing and minimizing their impact worldwide (5).

The renin-angiotensin system (RAS) has a regulatory role in cardiovascular and renal physiology. Over the last decade, several studies have shown that RAS evolved from a straightforward linear pathway through a two-stage process. The angiotensinogen (AGT) is converted to angiotensin I (Ang I) and angiotensin II (Ang II) by the enzyme conversion of renin and angiotensin (ACE) in a structure involving ACE correspondents and different angiotensin peptides. These final products have several additional functions and a counter-regulatory role (6). Recent epidemiological studies suggest that the renin-angiotensin system plays a significant role also in carcinogenesis, not just in homeostasis (7).

Regarding RAS involvement at gastric level, RAS components were found in the biopsy samples of the gastric antrum and corpus mucosa from healthy adults (8). In mesenchymal cells of the lamina propria and vascular endothelial cells, renin and angiotensin were aborted. Over time, several functional or pathogenic roles that have been attributed to RAS, were described in the literature. (9). A role of this system seen in gastric inflammation is about a higher expression of angiotensin type 1 receptor (ATR1) in patients with positive H. pylori and a significant amplification of neutrophil infiltration (8).

To date, the relationship between *AGT* polymorphisms and their associations with gastric lesions is still unclear, although there are some studies that are focused on the evaluation of the gene variants involved in RAS and involved in the development of gastric cancer (10, 11). Moreover, it has been recently reported that *AGT* c.-58 A>C polymorphism influences the *AGT* promoter activity and blood levels of AGT, being associated with gastric cancer susceptibility (10, 12). Thus, we performed this study, in order to evaluate the associations between variant genotypes of *AGT* c.-58A>C, lifestyle (drugs, smoking, alcohol) and clinical factors and corporeal extension of gastric inflammatory and preneoplastic lesions.

Material and methods

Subjects

Our study consisted of 209 subjects with a mean age of 61.55 ± 13.76 years, referred to 3rd Med-

ical Clinic of Târgu Mureş Emergency County Hospital for endoscopic evaluation. The study protocol was approved in advance by the Ethical Committee of the Emergency Clinical County Hospital of Târgu Mureș. All subjects included in the study signed the informed consent.

We collected clinical and medical data of consecutive patients referred for endoscopy, with at least four routine biopsies, two from the antrum and two from the corpus. Firstly, the geneticall-ly tested subjects (n=209) were included in the study and they were grouped according to the type of lesion, inflammatory and preneoplastic. Then they were divided according to the localization of lesions into the antrum gastritis group, antrum and/or body gastritis group and the control group without gastric inflammation/ premalignant lesions. All associations were evaluated taking into account this classification.

In the inflammatory lesions group the subjects were divided into antrum gastritis group (n=18), antrum and/or body gastritis group (n=107) and the control group (n=84) without gastric inflammation.

In the preneoplastic lesions group the subjects were divided into antral group (n=35), antrum and/or corpus gastric group (n=39) and the control group (n=130) without premalignant lesions.

Multiple data on alcohol or tobacco consumption have been recorded, for which chronic alcohol users were considered to have consumed at least ten units of pure alcohol per week and those patients who smoke more than 5 cigarettes/day or those who quit smoking nicotine in the last 5 years have been considered smokers. Regarding the administration of associated therapy, we investigated the possible side effects of regular doses of non-steroidal anti-inflammatory drugs given at least one week before endoscopy, of long-term antiplatelet therapy (low-dose aspirin 75-100 mg/day) as well as doses for therapeutic INR (International Normalized Ratio) of acenocoumarol ingested at least one month before endoscopy. In addition, personal pathological history data on other associated co-morbidities, such as high blood pressure, presence of cardiac disease with or without heart failure or diabetes mellitus diagnosis, have been collected. Each diagnosis was proven by specialists blinded to the clinical registrations, both endoscopically and histopathologically, using a modified Lanza score (13), respectively the update version of Sydney System for classification of the gastric injuries.

Genotyping of AGT c.-58 A>C

DNA was extracted from venous blood samples of each subject collected in EDTA (Ethylenediaminetetraacetic acid)-containing tubes, using a commercially available kit (Quick-gDNAMini-Prep, ZymoResearch, USA). The genotypes of the investigated polymorphism of *AGT* gene, namely c.-58 A>C gene polymorphism, were established by using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique and specific restriction enzyme as previously described (14, 15, 16).

The inclusion criteria for both groups were: adult subjects without malignancies, with complete medical and clinical data, referred for endoscopic evaluation, with at least four routine biopsies (two from the antrum and two from the corpus) who signed the informed consent. The subjects with negative endoscopy and without histologic lesions were included in the control group. The subjects who did not meet simultaneously all the inclusion criteria and also the subjects in whom the blood was not harvested on EDTA-containing tubes, were excluded.

Statistical analysis

Differences in the *AGT* c.-58 A>C genotypes/ allele frequency between the control and inflammatory or premalignant lesion groups, the association among these and the lifestyle factors were determined by the Chi^2 analysis with

Yates's correction where appropriate or with Fisher test, using GraphPad Prism 8 version (GraphPad Software Inc., California, USA). The p-value < 0.05 was considered to indicate statistically significant differences.

Results

The genotypes and alleles distribution between the groups is illustrated in Table 1. No significant associations (p>0.05) were noticed between *AGT* c.-58A>C genotypes (wild-type AA, heterozygous AC, and variant homozygous CC), alleles and the corporeal extension of the inflammation from without gastric inflammation towards antral gastric inflammation and antral and corpus or gastric corpus inflammation. Similar results were obtained for the corporeal extension of the preneoplastic injuries from without gastric preneoplastic lesions towards antral and/or corpus gastric preneoplastic wounds (Table 1).

Regarding the demographic and clinical aspects of patients, divided into three groups for each type of lesion, ageing was not associated with the evolution of gastric lesions (p>0.05).

Our data revealed a significant difference regarding some behavioral factors and the corporeal extension of the inflammatory lesions. Extending preneoplastic lesions to the gastric body was associated with smoking habits [p=0.01, $\chi2$=8.10, degrees of freedom (df)=2] and additionally, there was a significant association between nicotine consumption and the type of body extension (antral, antrum and/or corpus gastric) of the preneoplastic lesions (p<0.01, $\chi2$=6.68, df=1).

We investigated the possible side effects caused by the most frequent medications used globally, NSAIDs, the long-term antiplatelet therapy and the ingestion of acenocoumarol drug on extension of gastric histologic changes using bivariate analysis, both on gastric inflammatory lesions and on preneoplastic lesions. There was no significant association between antiplatelet or NSAIDs consumption between patients without histologic lesions and patients with inflammatory or preneoplastic lesions at the antrum or corpus gastric level. Nevertheless, the frequent use of acenocoumarol was associated with the histologic lesions through progression from without gastric premalignant injuries to preneoplastic lesions in the antrum and corpus or corpus gastric mucosa (p<0.01, $\chi2$ =9.55, df=2).

For the patients included in the study, cardiovascular disorders, such as high blood pressure had a tendency toward statistical signification for a positive association with the progression of preneoplastic gastric lesions (p=0.05, $\chi2$ =5.71, df=2). Moreover, we found a significant association between these comorbidities and the corporeal extension of the preneoplastic lesions (p=0.02, $\chi2$ =5.09, df=1).

As shown in Table 2, the age below or equal to 70 years in accordance with heterozygous and variant homozygous genotype was significantly associated with the body extension of inflammatory lesions at the gastric level (p=0.04, $\chi2$=4.15, df=1). The bivariate data analysis highlights a statistically insignificant result between the combined genotypes AC+CC of *AGT* c.-58 A>C single nucleotide polymorphism (SNP) and the extent of inflammatory or premalignant gastric injuries in association with the lifestyle factors, like smoking habit or alcohol consumption.

Compared with the wild-type genotype (AA), the combined genotypes with the variant allele (AC+CC) of *AGT* c.-58 A>C SNP were significantly associated with progression of the inflammatory gastric lesions in subjects who regularly ingested doses of NSAIDs (p=0.04, $\chi2$=6.1, df=2). Furthermore, we noticed a significant association between the combined variant genotypes and the corporeal extension of the gastric inflammatory lesions (p=0.01, $\chi2$ =6.03, df=1).

A statistically significant association was observed between patients without cardiovascular disease with the variant alleles of *AGT c.-58A>C*

Table 1. The genotypes and allele distribution between studied groups

	Inflammatory gastric group					Preneoplastic gastric group				
	Without inflammatory lesions	Antral gastric lesions	P value/ OR/ IC95%	Antral and corpus or gastric corpus inflammation	P value/ OR/ IC95%	Without preneoplastic lesions	Antral gastric lesions	P value/ OR/ IC95%	Antral and corpus or gastric corpus preneoplastic lesions	P value/ OR/ IC95%
AA[r]	44	12	-	65	-	71	24	-	24	-
AC	35	6	0.557/ 0.628/ 0.214-1.844	41	0.441/ 0.793/ 0.438-1.433	55	11	0.193/ 0.591/ 0.266-1.311	14	0.456/ 0.753/ 0.356-1.590
CC	5	0	-	1	0.082/ 0.135/ 0.015-1.199	4	0	-	1	1/ 0.739/ 0.078- 6.949
AC+CC	40	6	0.398/ 0.550/ 0.188-1.603	42	0.246/ 0.710/ 0.398-1.267	59	11	0.138/ 0.551/ 0.249- 1.219	15	0.444/ 0.752/ 0.361-1.564
A allele[r]	123	30	-	171	-	197	59	-	62	-
C allele	45	6	0.289/ 0.546/ 0.213-1.401	43	0.123/ 0.687/ 0.426-1.109	63	11	0.129/ 0.583/0.288 -1.178	16	0.496/0.807/ 0.434-1.498

r = reference;

SNP and the progression of inflammatory gastric lesions (p=0.02, $\chi 2$ =4.82, df=1) (Table 2).

Discussion

The present study was designed to evaluate the associations between *AGT* c.58 A>C SNP, lifestyle (drugs, smoking, alcohol) and clinical factors and corporeal extension of gastric inflammatory and preneoplastic lesions.

It is known that a higher basal promoter activity in transiently transfected HepG2 cells possessed reporter constructs containing the *AGT c.*-58 C allele than those containing allele A. Despite the description in the literature that the risk is significantly increased for gastric cancer in *AGT c.*-58 C allele-bearing individuals versus those carrying allele A (17), our results suggest that the presence of C allele for the *AGT* c.-58C was not associated with the progression of both gastric inflammatory and premalignant lesions, in patients included in the study.

No significant differences were observed in the genotype frequencies of *AGT c.*-58 A>C polymorphisms in relation with the type of the lesions for both groups of patients. Contrary to our results, one study describes the implication of the variant allele of the mentioned SNP in the risk of gastric cancer in the population of Japan (17).

Numerous studies highlight the influence of the chemical components of cigarette smoke (increasing apoptosis, decreasing cell proliferation, blood vessel formation and the synthesis of mucus in the gastrointestinal mucosa by interfering epidermal growth factor level and polyamines synthesis which are important in keeping the mucosal integrity) on the progress of ulcer and the delay in healing this pathology (18). Similar to these findings, our results underline the attribution of smoking in the development of preneoplastic gastric lesions and their role in the corporeal extension of these types of injuries.

There are no clear published data regarding the influence of drug consumption and inflammatory or premalignant gastric changes. The research performed by Shen XM. et al in a case-control study on 168 patients with resectable gastric cancer showed that the pre-operatic mean platelet volume (MPV) was significantly higher in patients with gastric cancer compared with the healthy control group and a low pre-operatic MPV level and antiplatelet therapy independently related to better histopathological features and improved overall survival in gastric cancer patients (19). On the one hand, there is a concordance of our findings regarding that NSAIDs and antiplatelet therapy was not associated with the occurrence of inflammatory or premalignant gastric lesions (p>0.05) and the data described in the literature which demonstrate that regular use of non-selective NSAIDs, including aspirin, is an effective chemopreventive strategy for the development of gastric cancer. However, there are other studies that describe the causative inflammation role of NSAIDs in colorectal cancer, infections, polyps, or enteropathies (20). On the other hand, our results highlight that patients undergoing anticoagulation therapy are predisposed to the body extension of pre-existing premalignant lesions, fact sustained by a statistically significant association.

It is recognized that apart from hypertension, heart failure and coronary heart disease were not clearly established as risk factors for premalignant gastric lesions. In the present study, we found a positive association between cardiovascular diseases and the preneoplastic gastric lesions. Moreover, our findings revealed a significant association between these comorbidities and the corporeal extension of the preneoplastic lesions. Other studies underlined the fact that in patients with cardiovascular diseases (coronary artery disease, heart failure, peripheral arterial disease or cerebrovascular disease), chronic statin therapy has a potential protective effect and

Table 2. The association between life style factors, variant genotype of (AGT) c.-58A>C and gastric lesions

Factors	Genotypes of AGT c.-58A>C	Without inflammatory lesions **vs.** antral gastric lesions **vs.** antral and corpus or gastric corpus inflammation n = 209	Chi square test for independence p value/chi-square (χ^2)	Without preneoplastic lesions **vs.** antral gastric lesions **vs.** antral and corpus or gastric corpus preneoplastic lesions n = 204	Chi square test for independence p value/chi-square (χ^2)
Age					
≤70	AA[r]	27/8/47	0.102/4.559	51/13/17	0.382/1.922
	AC+CC	35/5/30		49/9/9	
>70	AA[r]	17/4/18	0.351/2.093	20/11/7	0.238/2.863
	AC+CC	5/1/12		10/2/6	
Smoking[a]					
Yes	AA[r]	3/1/9	-	6/1/4	0.784/0.484
	AC+CC	1/0/4		2/1/2	
No	AA[r]	41/11/56	0.422/1.725	65/23/20	0.220/3.028
	AC+CC	39/6/38		57/10/13	
Alcohol[b]					
Yes	AA[r]	6/1/3	-	5/0/3	-
	AC+CC	0/0/0		0/0/0	
No	AA[r]	38/11/62	0.253/2.746	65/23/22	0.26/2.689
	AC+CC	40/6/42		59/11/15	
Aspirin					
Yes	AA[r]	23/3/27	0.868/0.281	31/12/9	-
	AC+CC	23/4/24		32/0/9	
No	AA[r]	21/9/38	0.208/3.14	40/12/15	0.064/5.491
	AC+CC	17/2/18		27/1/6	
NSAIDs					
Yes	AA[r]	2/2/11	0.047*/6.1	9/4/2	0.849/0.325
	AC+CC	6/2/3		6/4/1	
No	AA[r]	42/10/54	0.53/1.269	62/20/22	0.15/3.793
	AC+CC	34/4/39		53/7/14	
ACO					
Yes	AA[r]	7/2/9	0.9/0.209	8/4/6	0.826/0.382
	AC+CC	4/1/7		4/3/5	
No	AA[r]	37/10/56	0.284/2.511	63/20/18	0.145/3.858
	AC+CC	36/5/35		55/8/10	

(continued on page 408)

Table 2. (continued from page 407)

Factors	Genotypes of AGT c.-58A>C	Without inflammatory lesions **vs.** antral gastric lesions **vs.** antral and corpus or gastric corpus inflammation	Chi square test for independence	Without preneoplastic lesions **vs.** antral gastric lesions **vs.** antral and corpus or gastric corpus preneoplastic lesions	Chi square test for independence
		n = 209	p value/chi-square (χ^2)	n = 204	p value/chi-square (χ^2)
HT					
Yes	AA[r]	37/10/50	0.715/0.669	54/21/20	0.459/1.555
	AC+CC	30/5/36		44/10/15	
No	AA[r]	7/2/15	0.162/3.631	17/3/4	-
	AC+CC	10/1/6		15/1/0	
HF					
Yes	AA[r]	25/4/34	0.952/0.097	37/13/12	0.88/0.253
	AC+CC	20/3/24		28/8/10	
No	AA[r]	19/8/31	0.232/2.914	34/11/12	0.112/4.371
	AC+CC	20/3/18		31/3/5	
DM					
Yes	AA[r]	8/3/14	0.561/1.154	15/8/2	0.210/3.115
	AC+CC	9/3/8		16/2/2	
No	AA[r]	36/9/51	0.358/2.052	56/16/22	0.699/0.715
	AC+CC	31/3/34		43/9/13	
CVD					
Yes	AA[r]	16/2/17	0.425/1.709	18/8/7	0.875/0.265
	AC+CC	8/1/17		13/6/7	
No	AA[r]	28/10/48	0.066/5.431	53/16/17	0.098/4.630
	AC+CC	32/5/25		46/5/8	

[a]>5 cigarettes/day including quitters during the past 5 years; [b]consumption of >10 units/week; **NSAIDs** - presence of NSAIDs or antiplatelet therapy; **ACO** - presence of acenocoumarol therapy; **HT** - hypertension; **HF** - heart failure; **DM** - diabetes mellitus; **CVD** - cardiovascular disease; [r]reference. *p<0.05

appears to be associated with a reduced risk for premalignant gastric lesions (21). Taking into account the reports on the association of 8 polymorphisms of the genes involved in RAS system, respectively on the *ACE* gene, *ATR1* and *AGT* genes, including the c.-58 A>C polymorphism and cardiovascular studies, one suggests that Chinese patients who have a specific genetic variation or polymorphism in these genes may be more liable to develop atrial fibrillation when exposed to lifestyle factors that elevate atrial pressure (22). In our study, we noticed that the presence of AC/CC genotypes of *AGT* c.-58 A>C was associated with the progression of gastric inflammatory lesions in patients without cardiovascular disease. Contrariwise, recent research in this respect, demonstrates that congestive heart failure has a tendency towards statistical significance in influencing the progression of critical gastro-duodenal lesions (23).

In literature, the findings of large-scale follow-up studies are principally all in agreement that inflammatory and premalignant lesions increase with age (24). In the study performed by Heuch et al, in one Norwegian population on 572 cases of gastric cancer diagnosed in women aged less than 80 years, underlined that age was inversely associated with gastric cancer (25). Likewise, we also found an association between both heterozygous and variant homozygous genotype for *AGT* c.-58 A>C and the corporeal extension in the gastric inflammation in patients aged less than or equal to 70 years, suggesting the association of genetic variants and lifestyle factors in gastric histopathological changes, according to age.

For the same SNP, the subjects with heterozygous (AC genotype) and the variant homozygous (CC genotype) with regular doses of NSAIDs ingestion had a significantly high occurrence of gastric inflammatory lesions. In addition, there is a significant association between combined variant genotypes, ingestion of regular doses of NSAIDs and the corporeal extension of the gastric inflammatory lesions. Similar with our findings, previous studies reported that variant C allele and variant homozygous (CC) genotype, were simultaneously associated with H. pylori infection, NSAIDs co-therapy, gastro-duodenal ulcer occurrence in low-dose aspirin consumers (26).

The small number of cases included in our study, from a single geographical region, as well as from a single medical clinic, are the limitations of the present research. Overall, according to our knowledge, this study underlines the idea that it is the first to investigate the associations between *AGT* c.-58A>C SNP, lifestyle (drugs, smoking, alcohol) and clinical factors on corporeal extension of gastric inflammatory and preneoplastic lesions. However, further studies are required for the elucidation of the role of RAS on the progression of different types of gastric lesions in relation to other diseases, treatments or lifestyle factors.

Conclusions

Given the results of the current study, the *AGT* c.-58 A>C polymorphism in the RAS was not associated with the extension of the gastric lesions, both the inflammatory and the preneoplastic lesions. However, in association with lifestyle factors (smoking and alcohol consumption), acenocoumarol co-treatment or multiple cardiac pathologies are associated with the corporeal progression of these injuries. The age below 70 years and NSAIDs treatment for the patients with the heterozygous AC genotype and the variant homozygous CC genotype for the mentioned SNP have been associated with the corporeal extension of gastric inflammation. More frequently the progression of gastric inflammatory lesions was observed in patients without cardiovascular disease in the presence of AC/CC genotypes of *AGT* c.-58 A>C.

Abbreviations

AGT - Angiotensinogen
NSAIDs - Nonsteroidal anti-inflammatory drugs
RAS - Renin-angiotensin system
Ang I - Angiotensin I
Ang II - Angiotensin II
ACE - Enzyme conversion of renin and angiotensin
ATR1 - Angiotensin type 1 receptor
INR - International Normalized Ratio
EDTA - Ethylenediaminetetraacetic acid
PCR-RFLP - Polymerase chain reaction–restriction fragment length polymorphism technique
df - degrees of freedom
SNP - Single nucleotide polymorphism
MPV - Mean platelet volume

Authors' contribution

MA (Conceptualization; Data curation; Formal analysis; Writing – original draft)
FT (Investigation; Writing – review & editing)
GAC (Investigation; Formal analysis)
SM (Investigation; Validation)
AN (Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation, Writing – review & editing)

Conflict of interest

None to declare.

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References

1. World Health Organization: http://www.who.int/news-room/fact-sheets/detail/cancer - accessed on 31st October 2018;
2. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, Polkowski WP. Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer Manag Res. 2018 Feb;10:239-248. DOI: 10.2147/CMAR.S149619
3. González CA, Agudo A. Carcinogenesis, prevention and early detection of gastric cancer: where we are and where we should go. Int J Cancer. 2012 Feb;130(4):745-53. DOI: 10.1002/ijc.26430
4. Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). Endoscopy. 2012 Jan; 44(1):74-94. DOI: 10.1055/s-0031-1291491
5. Karimi P, Islami F, Anandasabapath S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev. 2014 May; 23(5):700-13. DOI: 10.1158/1055-9965.EPI-13-1057
6. Garg M, Angus PW, Burrell LM, Herath C, Gibson PR, Lubel JS. Review article: the pathophysiological roles of the renin-angiotensin system in the gastrointestinal tract. Aliment Pharmacol Ther. 2012 Feb; 35(4): 414-28. DOI: 10.1111/j.1365-2036.2011.04971.x
7. Sugimoto M, Yamaoka Y, Shirai N, Furuta T. Role of renin-angiotensin system in gastric oncogenesis. J Gastroenterol Hepatol. 2012 Mar; 27(3):442-451. DOI: 10.1111/j.1440-1746.2011.06964.x
8. Hallersund P, Elfvin A, Helander HF, Fändriks L. The expression of renin-angiotensin system components in the human gastric mucosa. J Renin Angiotensin Aldosterone Syst. 2011 Mar; 12(1):54-64. DOI: 10.1177/1470320310379066
9. Carl-McGrath S, Gräntzdörffer I, Lendeckel U, Ebert MP, Röcken C. Angiotensin II-generating enzymes, angiotensin-converting enzyme (ACE) and mast cell chymase (CMA1), in gastric inflammation may be regulated by H. pylori and associated cytokines. Pathology. 2009; 41(5):419-27. DOI: 10.1080/00313020902885037
10. Sugimoto M, Furuta T, Shirai N, Ikuma M, Sugimura

H, Hishida A. Influences of chymase and angiotensin I-converting enzyme gene polymorphisms on gastric cancer risks in Japan. Cancer Epidemiol. Biomarkers Prev. 2006 Oct;15(10):1929-1934; DOI: 10.1158/1055-9965.EPI-06-0339
11. Ebert MP, Lendeckel U, Westphal S, Dierkes J, Glas J, Folwaczny C, et al. The angiotensin I-converting enzyme gene insertion/deletion polymorphism is linked to early gastric cancer. Cancer Epidemiol. Biomarkers Prev. 2005 Dec;14(12):2987-9; DOI: 10.1158/1055-9965.EPI-05-0411
12. Perdomo-Pantoja A, Mejía-Pérez SI, Reynoso-Noverón N, Gómez-Flores-Ramos L, Soto-Reyes E, Sánchez-Correa TE, et al. Angiotensinogen rs5050 germline genetic variant as potential biomarker of poor prognosis in astrocytoma. PLoS One. 2018 Nov 1;13(11):e0206590; DOI: 10.1371/journal.pone.0206590
13. Lanza FL, Collaku A, Liu DJ. Endoscopic comparison of gastroduodenal injury with over-the-counter doses of new fast-dissolving ibuprofen and paracetamol formulations: a randomized, placebo-controlled, 4-way crossover clinical trial. Clin Exp Gastroenterol. 2018 Apr;11:169-77; DOI: 10.2147/CEG.S153231
14. Bănescu C. Do we really need genetic tests in current clinical practice? Rev Romana Med Lab. 2019;27(1):9-14; DOI: 10.2478/rrlm-2019-0010
15. Shiotani A, Nishi R, Yamanaka Y, Murao T, Matsumoto H, Tarumi K, et al. Renin-angiotensin system associated with risk of upper GI mucosal injury induced by low dose aspirin: renin angiotensin system genes' polymorphism. Dig Dis Sci. 2011 Feb;56(2):465-71. DOI: 10.1007/s10620-010-1382-3
16. Zhang N, Yang L, Cui H, Fu W. Epidemiological Study of AGT Gene Polymorphism among Chinese Subjects with Primary Hypertension. Adv Pharmacoepidem Drug Safety. 2012;1:110. DOI: 10.4172/2167-1052.1000110
17. Sugimoto M, Furuta T, Shirai N, Kodaira C, Nishino M, Ikuma M, et al. Role of angiotensinogen gene polymorphism on Helicobacter pylori infection-related gastric cancer risk in Japanese. Carcinogenesis. 2007 Sept; 28(9):2036-40. DOI: 10.1093/carcin/bgm074
18. Zhang L, Ren JW, Wong CC, Wu WK, Ren SX, Shen J, et al. Effects of cigarette smoke and its active components on ulcer formation and healing in the gastrointestinal mucosa. Curr Med Chem. 2012;19(1):63-9. DOI: 10.2174/092986712803413926
19. Shen XM, Xia YY, Lian L, Zhou C, Li XL, Han SG, et. al. Mean platelet volume provides beneficial diagnostic and prognostic information for patients with resectable gastric cancer. Oncol Lett. 2016;12(4):2501-6; DOI: 10.3892/ol.2016.4913
20. Onişor D, Boeriu A, Pascarenco O, Brusnic O, Dobru D. Role of fecal calprotectin as a biomarker of intestinal inflammation in ulcerative colitis: a prospective study. Rev Romana Med Lab. 2018;26(3):335-43; DOI: 10.2478/rrlm-2018-0006
21. Negovan A, Ţilea I, Voidăzan S, Mocan S, Szoke A, Stoica A, et al. Chronic Statin Therapy and Histologic Gastric Changes. J Interdiscip Med. 2019;3:221-4; DOI: 10.2478/jim-2018-0039
22. Tsai CT, Lai LP, Lin JL, Chiang FT, Hwang JJ, Ritchie MD, et. al. Renin-Angiotensin System Gene Polymorphisms and Atrial Fibrillation. Circulation. 2004 Apr; 109(13):1640-6. DOI: 10.1161/01.CIR.0000124487.36586.26
23. Negovan A, Iancu M, Moldovan V, Sàrkàny K, Bataga S, Mocan, S, et al. The contribution of clinical and pathological predisposing factors to severe gastro-duodenal lesions in patients with long-term low-dose aspirin and proton pump inhibitor therapy. Eur J Intern Med. 2017 Oct; 44:62-6. DOI: 10.1016/j.ejim.2017.05.017
24. Song H, Ekheden IG, Zheng Z, Ericsson J, Nyrén O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. BMJ. 2015 Jul;351:h4134. DOI: 10.1136/bmj.h4134
25. Hcuch I, Kvale G. Menstrual and reproductive factors and risk of gastric cancer: a Norwegian cohort study. Cancer Causes Control. 2000 Nov;11(9):869-74; DOI: 10.1023/A:1008975817061
26. Negovan A, Voidăzan S, Pantea M, Moldovan V, Bataga S, Cozlea L, et al. AGT A-20C (rs5050) gene polymorphism and ulcer occurrence in patients treated with low-dose aspirin: a case-control study. Rev Romana Med Lab. 2015;23(2):179-87. DOI: 10.1515/rrlm-2015-0017