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Is there a possible relationship between gastric intestinal metaplasia and systemic arterial stiffness?

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ABSTRACT

Background and aim: *Helicobacter pylori (H. pylori)* is closely associated with pre-neoplastic lesions such as atrophic gastritis (AG) and gastric intestinal metaplasia (GIM). The relationshionship between inflammation, hyperhomocysteinemia and arterial stiffness is of pathophysiological relevance for the development of cardiovascular disease. This study aimed to investigate the relationship between vitamin B12, folic acid, homocysteine (Hcy) and pulse wave velocity (PWV) levels in patients with GIM, AG and non-atrophic non-metaplastic chronic gastritis.

Patients and methods: ninety-seven patients with GIM, 67 patients with AG and 69 patients with chronic gastritis were included in the study. Glucose, creatinine, total cholesterol, triglyceride, low-density lipoprotein, cholesterol, high-density lipoprotein cholesterol, vitamin B12, folic acid and Hcy levels were measured by biochemical methods. PWV and other vascular parameters were measured using the Phsyio-port AS device.

Main results: PWV was higher in patients with GIM and AG than in controls ($p < 0.05$ and $p < 0.05$, respectively). Vitamin B12 levels were significantly lower in patients with GIM and AG than in controls ($p < 0.01$ and $p < 0.01$, respectively). Folic acid levels were significantly lower in patients with GIM than in controls ($p < 0.05$). Hcy levels were significantly higher in patients with GIM and AG than in controls ($p < 0.001$ and $p < 0.05$, respectively). A logistic regression analysis showed that GIM, AG and vitamin B12 deficiency were predictors for arterial stiffness.

Conclusions: PWV values increased in patients with GIM and AG compared to non-atrophic non-metaplastic chronic gastritis, without different conventional cardiovascular risk factors.

Key words: Gastric intestinal metaplasia. Atrophic gastritis. Chronic gastritis. Pulse wave velocity. Arterial stiffness.

INTRODUCTION

Helicobacter pylori (H. pylori) is a human gastric pathogen that causes chronic and progressive gastric mucosal inflammation and is closely associated with gastric inflammation-associated pre-neoplastic lesions such as atrophic gastritis, gastric intestinal metaplasia and eventually, gastric cancer (GC) (1,2). Atrophic gastritis (AG) is characterized by the the presence of chronic inflammatory cells, including lymphocytes and plasma cells that expand the lamina propria and the disappearance of the normal glandular elements. Gastric intestinal metaplasia (GIM) at the histological level is characterised by goblet and absorptive cells or columnar non-absorptive cells (3,4). Both GIM and AG are closely associated with immune activation and localized or systemic inflammation (5-8).

The relationship between inflammation and arterial stiffness is of pathophysiological relevance for the development of cardiovascular disease (CVD) (9-11). Pulse wave velocity (PWV) is a well known indicator of arterial stiffness. Arterial stiffness is an independent risk factor for future cardiovascular events and can be used as an indicator of subclinical cardiac damage. Arterial stiffness is involved in the pathophysiology of myocardial infarction, stroke or heart failure, especially in patients with hypertension and diabetes mellitus (12).

Several studies have shown a relationship between AG and early atherosclerosis or arterial stiffness (13,14). However, the association with GIM and CVD or arterial stiffness has never been observed before. AG and GIM are the histopathologic entites that reflect the ordinal phases during the conversion of chronic gastric inflammation to carcinoma, for whatever reason. Can two ordinal phases in the same process lead to different clinical outcomes in terms of CVD risk? This question has led to the development of this study. Thus, the aims of the study were to assess the association of arterial stiffness using PWV and parameters of vascular function (such as central blood pressure) with biochemical parameters, including vitamin B12 and homocysteine (Hcy),

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in patients with GIM, GA and non-atrophic non-metaplastic chronic gastritis. It is important to note that there were no differences in the conventional atherosclerosis factors.

PATIENTS AND METHODS

Demographic characteristics (sex, age and menopause), comorbidities (history of hyperlipidemia and history of cardiovascular disease in the family) and body mass index (BMI) of 2,625 prospective and consecutive endoscopy patients from the Usak University, Gastroenterology polyclinic, were recorded between December 2017 and July 2018; 1,605 patients with blood glucose, creatinine, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) parameters that were evaluated within the last month before endoscopy were included in the study and 1,020 patients were excluded. Rapid urease tests were performed routinely in all patients and biopsy samples were taken according to updated Sydney system (15). The inclusion criteria were as follows: individuals between 18 and 70 years of age and the presence of GIM, AG or non-atrophic non-metaplastic chronic gastritis. Accordingly, 1,123 patients were assessed for inclusion into the study according to the inclusion criteria and 482 patients were excluded. The exclusion criteria included: a) previous *H. pylori* eradication; b) intake of antibiotics, proton pump inhibitors or H2-receptor blockers during the previous two months; c) impaired renal function (serum creatinine ≥ 1.2 mg/dl); d) a history or presence of cardiovascular disease (myocardial infarction, congestive heart failure, valvular heart disease and atrial fibrillation); e) hypertension, defined by blood pressure > 140/90 mmHg or the use of antihypertensive medication; f) peripheral artery disease; g) cerebrovascular events; h) diabetes mellitus; i) immune-mediated and chronic inflammatory disorders such as thyroid disease, type 1 diabetes mellitus, rheumatic diseases, liver disease and celiac disease; j) active infection; k) evidence of liver and renal disease; l) chronic obstructive lung disease; m) pulmonary hypertension; n) metabolic syndrome; o) smoking; p) alcohol use; q) cardiovascular and metabolic drug use, including lipid-lowering medication, hormone replacement therapy, nitrates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics; r) the use of drugs that affect folic acid, vitamin B12 and Hcy levels in plasma; s) a vegetarian diet; t) a history or presence of other causes of vitamin malabsorption, such as partial or subtotal gastrectomy, ileal resection, Crohn's ileitis, coeliac disease or small bowel bacterial overgrowth; u) underweight patients with a body mass index < 18.5; v) gastrointestinal hemorrhage; w) pregnancy; and x) patients with a malignancy and taking cytotoxic medication, cachexia, malnourishment or a reported history of an eating disorder, as well as those patients who refused to participate in the study.

Five hundred and fifty-six patients were excluded from the study according to the exclusion criteria. The study cohort included 567 patients that were split into three pre-groups of gastric intestinal metaplasia, atrophic gastritis and non-atrophic non-metaplastic chronic gastritis, according to their histopathological evaluation. Patients with similar demographic characteristics, comorbidities and laboratory findings were included in the pre-groups and homogeneity was achieved. Each group was matched with regard to other factors such as sex, age, history of hyperlipidemia, menopause, family history of cardiovascular disease, BMI and glucose, creatinine and lipid parameters. Thus, after patient selection and informed consent, the final study cohort included 233 patients and 334 patients were excluded. Finally, there were three homogeneous groups defined as gastric intestinal metaplasia group (GIMG), with 97 patients; atrophic gastritis group (AGG), with 67 patients; and non-atrophic non-metaplastic chronic gastritis-control group (CG), with 69 patients. Informed consent was obtained from all participants in the study. The aims of the study were explained to the participants and they were asked to complete a standard questionnaire about age, sex, weight and height. BMI was calculated as the body weight divided by the square of the height in meters.

Histopathologic evaluation

Mucosal samples of all patients were stained with hematoxylin and eosin and histopathologic parameters were determined according to updated Sydney system (15). Hematoxylin-eosin stained sections were evaluated for the presence of intestinal metaplasia, gastric atrophy, nonatrophic gastritis (with no intestinal metaplasia) and *H. pylori* according to the updated Sydney system.

Assessment of *H. pylori* infection

H. pylori infection was assessed by both histopathologic examination and the local rapid urease test. Subjects were considered as *H. pylori* positive if the bacteria were histopathologically detected and/or the local rapid urease test was positive.

Blood samples and biochemical analyses

Venous blood samples were obtained from the patients within the 12 h fasting period. The blood samples were collected in two types of tubes that contain EDTA anticoagulant or clot activator. The blood samples were centrifuged within an hour at 4,000 rpm for 15 minutes in order to obtain plasma or serum for glucose, creatinine, total cholesterol, triglyceride, LDL-C, HDL-C, vitamin B12, folic acid and Hcy analysis. The serum glucose, creatinine, total cholesterol, triglyceride and HDL-C levels were analyzed by Abbott Diagnostics using the Abbott Architect c16000 analyzer (Abbott Park, Illinois, U.S.A.) with the corresponding reagents (Architect Abbott Glucose reagent, Abbott Architect creatinine reagent). LDL-C levels were calculated using the Friedewald formula (16). Serum vitamin B12 and folic acid levels were determined via the chemiluminescent enzyme immunoassay method using the Advia Centaur® XP Analyzer (Siemens Healthineers, Switzerland, U.S.). Plasma Hcy levels were determined via the fluorescence polarization immunoassay using the Immulite® 2000 Immunoassay System (Siemens Healthineers, Switzerland, U.S.) and original reagent. Plasma Hcy levels were defined as high when the levels were > 12.2 µmol/l according to our laboratory reference values. Vitamin B12 levels were defined as low when the levels were < 214 pmol/l according to our laboratory reference values. Folic acid level was

defined as low when the levels were < 5.38 ng/ml according to our laboratory reference values.

Measurement of arterial parameters

All patients fasted overnight and were asked to refrain from caffeine intake within four hours prior to the study visit. Vascular measurements were performed using a PHYSIOPORT AS automatic device (PAR Medizintechnik GmbH & Co. KG Berlin, Germany) and the parameters were automatically calculated with this device. The following parameters were calculated non-invasively using the same device in order to determine arterial stiffness status and central hemody-namics. PWV (m/s), augmentation pressure (AugP-mmHg), augmentation index (AIx-%), pulse transit time (PTT-ms), peripheral systolic and diastolic blood pressure (mmHg) (pSBP, pDBP), peripheral pulse pressure (pPP- mmHg), mean blood pressure (MBP- mmHg), central systolic and diastolic blood pressure (mmHg) (cSBP, cDBP) and cen-tral pulse pressure (cPP-mmHg). The device automatically detects brachial artery pulsations by the oscillometric prin-ciple. After a special preprocessing of the recorded pulse waves, the central pressure waveform was determined by the central blood pressure values. Therefore, a self-determined transfer function was used in the frequency domain (Fourier transform) and the pulse waves were decomposed in their multiples of sine and cosine waves. Subsequently, the wave parts in the frequency domain were assembled to project the way and the modification of the waves by the vessels between the upper arm and the heart (17). As previously mentioned, the current hypertension guidelines include PWV in the list of factors that influence the prognosis of hypertensive patients. A threshold PWV value greater than 10 m/s is considered as an index of large artery stiffening and an indicator of sub-clinical organ damage (18). The present study was performed according to the ethics guidelines of the Declaration of Helsinki of biomedical research involving human participants. All patients provided their written informed consent before inclusion into the study and ethics committee approval was also obtained. This study was performed in accordance with the approval of the ethics board of the Usak University Faculty of Medicine dated April 25th 2018, Nr.40-4-13.

Statistical analysis

Data were analyzed using the SPSS 23.0 software. Analysis of variance (ANOVA) with the multiple comparison (with post hoc test and Tukey alpha) method was used to compare the mean of each value between the groups. Stepwise multiple logistic regression was used, considering a normal/high (≤ 10 m/s *versus* > 10 m/s) PWV level as the independent variable. Age, sex (female or male), menopause (presence *versus* absence), BMI, hyperlipidemia (positive *versus* no history), family history of cardiovascular disease (positive *versus* no history), *H. pylori* status (positive or negative), vitamin B12 level (low *versus* normal), folic acid level (low *versus* normal), Hcy level (high *versus* normal), gastric intestinal metaplasia (presence *versus* absence) and atrophic gastritis (presence *versus* absence) parameters were also included. A p value less than 0.05 was considered as statistically significant. Reference values are indicated above.

RESULTS

Analysis of population characteristics, conventional cardiovascular risk factors and *Helicobacter* status of study groups

The characteristics of the GIMG, AGG and CG groups are shown in table 1. There were no significant differences in age, sex, menopause, history of hyperlipidemia and family history of cardiovascular disease among the groups. However, BMI was significantly higher in CG (25.08 ± 3.62) than in GIMG (23.24 ± 2.74, p = 0.001). *H. pylori* positivity was significantly higher in CG (79%) than in GIMG (59%) (p = 0.016). There was no significant difference in *H. pylori* positivity between the CG (79%) and AGG (73%) groups (p = 0.677); 63% (61/97) of cases with GIM in this study were accompanied by gastric atrophy.

Analysis of laboratory findings of study groups

Serum glucose, creatinine, total cholesterol, triglyceride, LDL-C and HDL-C levels of the groups are shown in table 2. There were no significant differences in glucose,

Table 1. *Population characteristics in controls and patients with gastric intestinal metaplasia and atrophic gastritis*

Parameters	Gastric intestinal metaplasia group	Atrophic gastritis group	Controls	p
Age (years)	52.17 ± 15.01	45.71 ± 15.37	53.23 ± 13.90	NS
Sex (female/male) (%)	54/46	61/39	66/34	NS
Menopause (%)	20	16	17	NS
History of hyperlipidemia (%)	6	7	8	NS
History of cardiovascular disease in family (%)	4	7	4	NS
H. pylori positivity* (%)	59	73	79	$p < 0.05^{\dagger}$
Body mass index (kg/m^2)	23.24 ± 2.74	24.05 ± 2.90	25.08 ± 3.62	$p < 0.05^{\dagger}$

*Subjects were considered as *H. pylori* positive if the bacteria were detected histopathologically and/or the local rapid urease test was positive. †There was a difference between the gastric intestinal metaplasia group and controls. Analysis of variance (ANOVA) with the multiple comparison (with post hoc test and Tukey alpha) method was used to compare the mean of each value between the groups. p < 0.05 was considered as statistically significant.

Table 2. *Laboratory characteristics in controls and patients with gastric intestinal metaplasia and atrophic gastritis*

Parameters	Gastric intestinal metaplasia group	Atrophic gastritis group	Controls	p
Glucose (mg/dl)	98.36 ± 18.24	96.80 ± 14.80	96.56 ± 16.53	NS
Creatinine (mg/dl)	0.72 ± 0.13	0.74 ± 0.13	0.69 ± 0.12	NS
Triglyceride	148.87 ± 75.26	133.41 ± 58.37	157.40 ± 91.41	NS
Total cholesterol	181.38 ± 45.72	185.52 ± 47.85	197.38 ± 51.82	NS
HDL-C	52.61 ± 64.41	58.42 ± 56.13	52.44 ± 13.44	NS
LDL-C	107.71 ± 35.10	110.84 ± 37.31	115.80 ± 37.15	NS

Results are presented as mean ± SD. LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein. Analysis of variance (ANOVA) with the multiple comparison (with post hoc test and Tukey alpha) method was used to compare the mean of each value between the groups. $p < 0.05$ was considered as statistically significant.

creatinine, total cholesterol, triglyceride, LDL-C and HDL-C levels among the three groups. Serum vitamin B12, folate and Hcy levels of the groups are shown in figure 1. Serum vitamin B12 levels were significantly lower in GIMG and AGG than in controls (252.88 ± 95.92 pmol/l, 259.37 ± 71.92 pmol/l *versus* 365.91 ± 130.23 pmol/l; $p < 0.001$ and $p < 0.001$, respectively). There were no significant differences in vitamin B12 levels in the GIMG and AGG groups ($p = 0.915$). Serum folate levels were significantly lower in GIMG than in controls (14.22 ± 6.08 ng/ml *versus* 17.26 ± 5.54 ng/ml; $p = 0.005$), although serum folate levels in AGG were lower in than controls, which was non-significant (14.86 ± 6.73 ng/ml *versus* 17.26 ± 5.54 ng/ml; $p = 0.06$). There was no significant difference in folate levels in GIMG and AGG groups ($p = 0.786$). Serum Hcy levels were significantly higher in GIMG and AGG compared to controls (11.34 ± 4.82 µmol/l, 9.16 ± 4.07 µmol/l *versus* 6.98 ± 6.52 µmol/l; $p < 0.001$ and $p = 0.041$, respectively). Serum Hcy levels were significantly higher in GIMG than in AGG (11.34 ± 4.82 µmol/l *versus* 9.16 ± 4.07 µmol/l; $p = 0.025$).

Analyses of vascular function parameters of study groups

The analyses of vascular function parameters of the GIMG, AGG and CG are shown in table 3. Peripheral systolic blood pressure, peripheral pulse pressure, central systolic blood pressure, central pulse pressure, the augmentation pres-

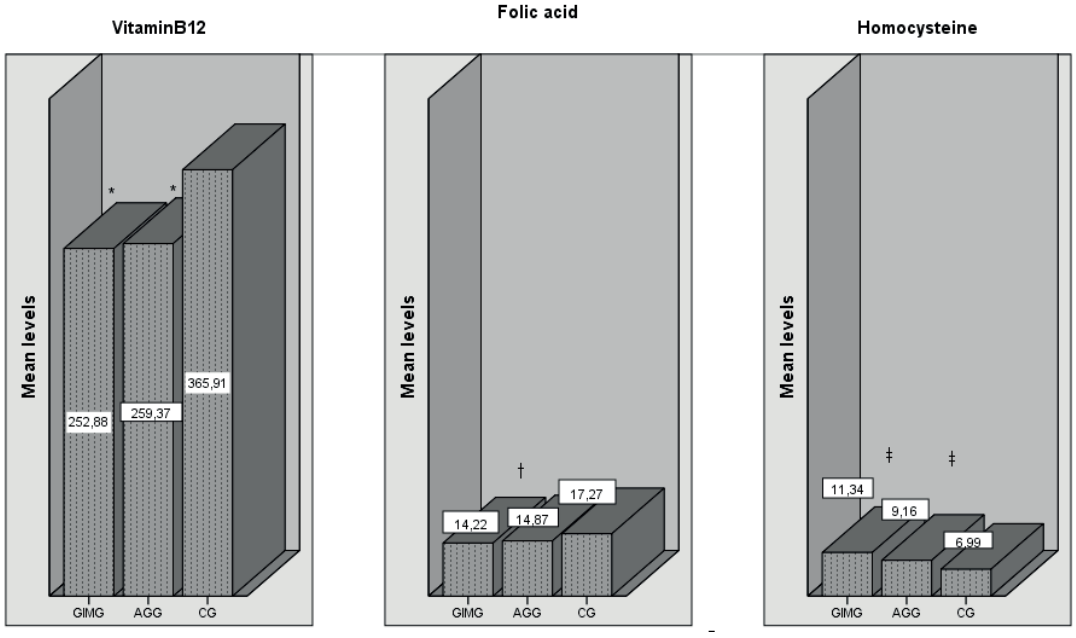

Fig. 1. *Serum vitamin B12 levels of patients with gastric intestinal metaplasia, atrophic gastritis and controls. Folic acid levels of patients with gastric intestinal metaplasia, atrophic gastritis and controls. Homocysteine levels of patients with gastric intestinal metaplasia, atrophic gastritis and controls. *Serum vitamin B12 levels were significantly lower in the GIMG and AGG than in CG, $p < 0.001$. †Serum folic acid levels were significantly lower in GIMG than in CG, $p < 0.05$. ‡Serum homocysteine levels were significantly higher in GIMG and AGG than in CG, $p < 0.05$. GIMG: Gastric intestinal metaplasia group; AGG: Atrophic gastritis group; CG: Control group.*

Table 3. *Comparative analyses of vascular function parameters in patients with gastric intestinal metaplasia, atrophic gastritis and controls*

Parameters	Gastric intestinal metaplasia group	Atrophic gastritis group	Controls	p
pSBP (mmHg)	134.63 ± 17.02	134.28 ± 14.61	124.47 ± 14.39	p < 0.001
pDBP (mmHg)	79.47 ± 11.35	78.00 ± 10.10	75.82 ± 11.22	NS
pPP (mmHg)	56.63 ± 12.70	58.80 ± 11.60	48.49 ± 10.85	p < 0.05
pMAP (mmHg)	95.22 ± 14.62	95.65 ± 16.57	91.52 ± 12.87	NS
cSBP (mmHg)	121.50 ± 19.57	120.70 ± 16.68	110.97 ± 16.40	p < 0.001
cDBP (mmHg)	78.72 ± 11.69	77.91 ± 10.00	76.14 ± 12.21	NS
cPP (mmHg)	42.83 ± 13.56	43.70 ± 12.53	35.49 ± 11.25	p < 0.001
AugP (mmHg)	8.94 ± 3.63	8.98 ± 3.58	7.43 ± 3.76	p < 0.05
Aix (%)	21.63 ± 7.87	23.20 ± 14.45	22.62 ± 10.49	NS
Pulse wave velocity (m/s)	10.07 ± 1.79	9.85 ± 1.84	8.99 ± 1.95	p < 0.05

Results were presented as the mean ± SD. pSBP: peripheral systolic blood pressure; pDBP: peripheral diastolic blood pressure; pPP: peripheral pulse pressure; pMAP: peripheral mean arterial pressure; cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cPP: central pulse pressure; AugP: augmentation pressure; AIx: the augmentation index. Analysis of variance (ANOVA) with the multiple comparison (with post hoc test and Tukey alpha) method was used to compare the mean of each value between the groups. $p < 0.05$ was considered as statistically significant.

sure and pulse wave velocity were significantly higher in GIMG and GAG than in controls. The mean pulse wave velocity was 10.07 ± 1.79 m/s in GIMG and 9.85 ± 1.84 m/s in AGG and 8.99 ± 1.95 m/s in controls (p = 0.01 and p = 0.021, respectively). There was no significant difference in pulse wave velocity levels between GIMG and AGG (p = 0.732). In GIMG, 49.5% of the subjects (48/97) had a PWV value greater than 10 m/s. This prevalence was 47.8% in AGG (32/67) and 18.8% in CG (13/69). There were significant differences between groups (p < 0.001).

The results from the stepwise multiple logistic regression analysis are shown in table 4. The presence of gastric intestinal metaplasia (odds ratio of 3.187, 95% confidence interval 1.454-6.985, p = 0.004), atrophic gastritis (odds ratio 3.371, 95% confidence interval 1.822-8.512, p = 0.003) and low vitamin B12 levels (odds ratio 3.491, 95% confidence interval 1.911-6.375, p < 0.001) were predictors for arterial stiffness or elevated PWV. There was no significant association for any of the other variables included in the analysis.

DISCUSSION

In this study, there was a significant association between the presence of GIM and AG and arterial stiffness. There was also a significant association between GIM and AG with vitamin B12, folate and Hcy levels. The relationship between GIM, AG and arterial stiffness is possibly related to both chronic inflammatory process and hyperhomocysteinemia.

H. pylori is the most common cause of chronic gastritis. Duodenal ulcer, gastric ulcer and GC are well known diseases associated with *H. pylori* (19). Population studies reported that the prevalence of *H. pylori* infection was 39.9-84.2% in adults (20). The Pelayo Correa "cascade" describes a sequence of histological lesions leading to the possible development of GC, beginning with chronic gastritis and evolving to AG, GIM and finally cancer (21). *H. pylori* induced T helper 1 (Th1) predominant persistent immune activation and localized and systemic inflammation are seen during the natural course of both GIM and AG. Th1 immune response and IFN-γ released from Th1-cells may be important in the progression of GA and intestinal metaplastic formation in a concurrent infection model with *Helicobacter felis* and helminth. Hence, a Th1 predominant inflammatory response to *H. pylori* may be a key factor of the transdifferentiation to AG and GIM (5). The nuclear factor kappa B (NF-κB) pathway, which regulates the expression of a wide variety of inflammatory cytokines, is another critical pathway involved in *H. pylori* induced gastritis and metaplasia (6-8). CVD is one of the most important extradigestive diseases that is thought to be related to *H. pylori* infection. CVD is a chronic inflammatory and progressive disease and its etiopathogenesis has dramatically changed over the last decades, on the basis of the new molecular and cellular biology findings. Persistent immune activation (22), localized and systemic inflammation (23) and elevation of plasma Hcy levels contributes to the development of atherosclerosis, resulting in ischemic heart diseases and strokes. Possible mechanisms between inflammation and arterial stiffness may be related to changes within the vessel wall such as inflammatory cell infiltration or vascular dysfunction (9). Furthermore, various pro-inflammatory mediators and markers of oxidative stress promote an increased production of matrix metalloproteinases, with subsequent degeneration of compliant elastin fibers. This, in turn, leads to decreased arterial compliance (10,11). Hyperhomocysteinemia may cause damage to the intima of the vascular wall (24). Deficiencies of vitamin B12 and folate are common etiologies of hyperhomocysteinemia. A frequent cause of vitamin B12 deficiency is AG. Previous reports suggest that AG is an important contributing factor to hyperhomocysteinemia, possibly via vitamin B12 malabsorption (25). We have already previously investigated the relationship between AG and premature atherosclerosis

Table 4. *Parameters associated with elevated pulse wave velocity in the study groups*

Predictors for pulse wave velocity	Logistic regression analysis		
	Odds ratio	95% CI	p
Age	1.019	0.988-1.052	NS
Sex	1.638	0.873-3.076	NS
Body mass index	0.947	0.816-1.099	NS
Menopause	1.456	0.636-3.337	NS
History of hyperlipidemia	0.683	0.226-2.067	NS
History of cardiovascular disease in family	0.768	0.215-2.736	NS
H. pylori positivity	1.480	0.803-2.729	NS
Low vitamin B12 level	3.491	1.911-6.375	< 0.001
Low folic acid level	1.520	0.800-2.890	NS
Homocysteine level	0.641	0.346-1.187	NS
Presence of gastric intestinal metaplasia	3.187	1.454-6.985	< 0.05
Presence of atrophic gastritis	3.371	1.822-8.512	< 0.05

CI: confidence interval. Stepwise multiple logistic regression was used, considering a normal/high (≤ 10 m/s versus > 10 m/s) pulse wave velocity level as the independent variable. The parameters of age (continuous variable), sex (female or male), body mass index, menopause (presence *versus* absence), hyperlipidemia (positive *versus* no history), family history of cardiovascular disease (positive *versus* no history), *H. pylori* status (positive or negative), vitamin B12 level (low *versus* normal), folic acid level (low *versus* normal), Hcy level (high *versus* normal), gastric intestinal metaplasia (presence *versus* absence) and atrophic gastritis (presence *versus* absence) were also included. A p value less than 0.05 was considered as statistically significant. See the text for reference values.

and found a correlation between AG and premature atherosclerosis, in which carotid intima-media thickness was increased in subjects with AG (13).

Arterial stiffness is an early indicator or precursor of atherosclerosis and various atherosclerosis-related diseases, such as heart failure, stroke and peripheral artery disease. These are associated with an increased risk of cardiovascular events (26). In the early 2000s, a simple device for the measurement of the brachial-ankle PWV was launched for clinical use (27). Technological advances have now enabled the attainment of central hemodynamics from brachial pulse waves using a blood pressure cuff and an automated device (28). PWV and arterial stiffness measurements performed with this method are valid and reliable compared to other invasive and non-invasive estimation methods (29). It is generally accepted that PWV measurement is the most rapid, reproducible, easy, low-cost and noninvasive method for arterial stiffness assessment (17). The 2007 European guidelines for CVD prevention listed aortic stiffness as an organ damage target that should be detected in the clinical practice (30). Arterial stiffness, assessed by PWV evaluation, is an independent predictor of CVD. Increased arterial stiffness is correlated with the aging process and atherosclerosis risk factors, such as hypertension, diabetes, dyslipidemia, obesity and smoking (31).

Recent studies have shed new light on the importance and the role of inflammation in the pathogenesis of arterial stiffness. In fact, it increases in association with inflammatory diseases, such as inflammatory bowel disease and celiac disease (23,32). It is also well known that even acute, mild or transient inflammatory stimuli may lead to the disruption of the elastic properties of large arteries and a reduction in inflammation can reduce arterial stiffness (32,33).

Various studies have shown that there was a correlation between *H. pylori* and CVD or arterial stiffness (34-37). There are also studies in which no correlation was determined between the levels of *H. pylori* and arterial stiffness (38,39). Torisu et al. reported a positive relationship between AG and arterial stiffness in middle-aged subjects (37). However, the study groups did not include GIM and there was no histopathological evaluation and serum Hcy measurements. The main objective of this study was to comparatively evaluate arterial stiffness among subjects with GIM, AG and non-atrophic non-metaplastic chronic gastritis. This study indicated that both GIM and AG highly affect PWV and other parameters of arterial stiffness, mainly peripheral pulse pressure, central pulse pressure and the increased pressure. In addition, only the presence of gastric intestinal metaplasia, atrophic gastritis and low vitamin B12 level were predictors of arterial stiffness, according to the stepwise multiple logistic regression analaysis. This case may reflect the ongoing chronic inflammatory process in GIM and AG. In our study, *H. pylori* detection was lower in the AGG and GIMG groups, compared to the CG group. Especially in the GIMG group, this difference was statistically significant. This figure may be related with a longer duration of gastric inflammation and the ''vanishing'' phenomenon of the *H. pylori* infection.

The most common and well-known cause of cobalamin and folate deficiency is atrophic gastritis (40). The loss of intrinsic factors and the decrease of gastric acid production lead to cobalamin and folic acid malabsorption. However, folic acid and serum B12 deficiency were observed in patients with intestinal metaplasia and atrophic gastritis in our study. Thus, it seems that gastric intestinal metaplasia in vitamin and micronutrient deficiency is as important as atrophic gastritis. Furthermore, GIM may be a contributing factor of hyperhomocysteinemia, possibly via vitamin B12, and folate malabsorption is as important as atrophic gastritis. In this study, BMI was significantly lower in patients with GIM compared to controls. We think that this may be related to B12, folate deficiency and a decreased appetite in patients with GIM.

In conclusion, this study shows that PWV and the other parameters of arterial stiffness values increase in patients with GIM and AG compared to non-atrophic non-metaplastic chronic gastritis, without different conventional cardiovascular risk factors. Not only atrophic gastritis but also gastric intestinal metaplasia may be a contributing factor of arterial stiffness, possibly via inflammation triggered by persistent immune activation and hyperhomocysteinemia. In the clinical practice, the determination of arterial stiffness by PWV in patients with GIM and AG may help to estimate the degree of inflammation and hyperhomocysteinemia induced damage to the arterial system. Further studies will be required to clarify these observations.

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