

A comparative study investigating the relationship between hyperhomocysteinemia and red cell distribution width (RDW) in cases of gastric intestinal metaplasia and atrophic gastritis

Gastrik intestinal metaplazi ve atrofik gastrit olgularında hiperhomosisteinemi ve eritrosit dağılım genişliği (RDW) ilişkisini araştıran karşılaştırmalı bir çalışma

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Abstract

Purpose: Hyperhomocysteinemia is a recognized independent risk factor for cardiovascular diseases, often linked to vitamin B12 and folate deficiencies. Atrophic gastritis (AG) and gastric intestinal metaplasia (GIM) represent distinct histological patterns of chronic gastric mucosal damage, both implicated in impaired vitamin B12 absorption. This study aimed to evaluate and compare serum homocysteine levels and their relationships with vitamin B12, folate and Red Cell Distribution Width (RDW) in patients diagnosed with GIM, AG, and non-atrophic, non-metaplastic chronic gastritis.

Materials and methods: The study enrolled 110 individuals categorized into three groups: GIM (n=46), AG (n=31), and control subjects with chronic gastritis without atrophy or metaplasia (n=33). Biochemical measurements included vitamin B12, folate, RDW and homocysteine. Participants with known cardiovascular risks or vitamin supplementation were excluded to reduce confounding factors.

Results: Both GIM (11.49±4.95 µmol/L) and AG (9.37±3.87 µmol/L) groups exhibited significantly elevated homocysteine levels compared to controls (7.03±6.64 µmol/L; $p<0.01$ and $p=0.042$, respectively). Vitamin B12 concentrations were considerably lower in GIM (253.88±95.78 pmol/L) and AG (251.83±63.70 pmol/L) patients versus controls (363.69±123.41 pmol/L; $p<0.01$ for both). Folate levels were significantly diminished in the GIM group compared to controls ($p=0.02$). RDW showed a slight, non-significant increase in the GIM and AG groups compared to controls (16.11±2.72, 16.23±2.32, 15.17±2.27, respectively; $p=0.069$). Logistic regression identified male gender and presence of GIM or AG as independent predictors of hyperhomocysteinemia.

Conclusion: Similar to AG, GIM is linked to increased serum homocysteine levels likely due to compromised vitamin B12 absorption. These findings highlight GIM as a potential metabolic risk factor for vitamin B12-related abnormalities, especially in patients lacking traditional cardiovascular risk factors.

Keywords: Hyperhomocysteinemia, vitamin B12, metaplasia.

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Öz

Amaç: Hiperhomosisteinemi, genellikle vitamin B12 ve folat eksiklikleri ile ilişkilendirilen ve kardiyovasküler hastalıklar için bağımsız bir risk faktörü olarak kabul edilen bir durumdur. Atrofik gastrit (AG) ve gastrik intestinal metaplazi (GIM), kronik mide mukozası hasarının farklı histolojik formları olup, her ikisi de vitamin B12 emilimini olumsuz etkileyebilir. Bu çalışmanın amacı, GIM, AG ve atrofik olmayan, metaplazik olmayan kronik gastritli hastalarda serum homosistein düzeylerini ve bunların vitamin B12, folat konsantrasyonları ve Eritrosit Dağılım Genişliği (RDW) ile ilişkilerini karşılaştırmaktır.

Gereç ve yöntem: Toplam 110 hasta çalışmaya dahil edildi: GIM (n=46), AG (n=31) ve kontrol grubu olarak atrofik ve metaplazik olmayan kronik gastritli hastalar (n=33). Serum vitamin B12, folat, RDW ve homosistein düzeyleri ölçüldü. Bilinen kardiyovasküler risk faktörleri olan ve vitamin takviyesi kullanan hastalar çalışmadan çıkarıldı.

Bulgular: GIM (11,49±4,95 µmol/L) ve AG (9,37±3,87 µmol/L) gruplarında homosistein seviyeleri, kontrollerden anlamlı şekilde yüksek bulundu (7,03±6,64 µmol/L; sırasıyla $p<0,01$ ve $p=0,042$). Vitamin B12 düzeyleri GIM (253,88±95,78 pmol/L) ve AG (251,83±63,70 pmol/L) gruplarında kontrol grubuna göre anlamlı derecede düştü (363,69±123,41 pmol/L; $p<0,01$). Folat düzeyleri de GIM grubunda kontrole göre anlamlı oranda azaldı ($p=0,02$). RDW, GIM ve AG gruplarında hafifçe yükseldi ancak bu artış istatistiksel olarak anlamlı değildi (sırasıyla 16,11±2,72, 16,23±2,32, 15,17±2,27; $p=0,069$). Lojistik regresyon analizinde erkek cinsiyet ve GIM veya AG varlığı hiperhomosisteinemi için bağımsız belirleyiciler olarak saptandı.

Sonuç: AG gibi, GIM de muhtemelen vitamin B12 emilimindeki bozukluk nedeniyle serum homosistein düzeylerinde artışla ilişkilidir. Bu sonuçlar, özellikle geleneksel kardiyovasküler risk faktörleri bulunmayan hastalarda, GIM'nin vitamin B12'ye bağlı metabolik sorunlarda potansiyel bir etken olarak değerlendirilmesi gerektiğini göstermektedir.

Anahtar kelimeler: Hiperhomosisteinemi, vitamin B12, metaplazi.

Kutluana U. Gastrik intestinal metaplazi ve atrofik gastrit olgularında hiperhomosisteinemi ve eritrosit dağılım genişliği (RDW) ilişkisini araştıran karşılaştırmalı bir çalışma. Pam Tıp Derg 2025;18:811-816.

Introduction

Homocysteine (Hcy) is a sulfur-containing amino acid produced during the metabolism of methionine, an essential amino acid obtained from dietary sources. Normally, homocysteine undergoes remethylation back to methionine via the enzyme methionine synthase, which requires vitamin B12 and folate as cofactors, or it is converted into cystathionine through the transsulfuration pathway involving vitamin B6. Deficiencies in vitamin B12 or folate disrupt these metabolic pathways, resulting in elevated plasma homocysteine levels, a condition known as hyperhomocysteinemia [1].

Hyperhomocysteinemia has been implicated in a variety of pathological processes, including endothelial dysfunction, oxidative damage, vascular smooth muscle proliferation, and increased platelet aggregation—all contributing factors to atherosclerosis. Numerous studies have confirmed elevated homocysteine as an independent risk factor for cardiovascular diseases, stroke, thromboembolism, and some neurodegenerative disorders [2]. Therefore, understanding the causes behind hyperhomocysteinemia is essential for reducing the burden of these conditions worldwide.

Among less commonly recognized causes are gastrointestinal disorders that impair nutrient absorption, particularly vitamin B12. Atrophic gastritis (AG) is a chronic inflammatory disease characterized by progressive loss of gastric glands, especially parietal cells responsible for secreting intrinsic factor (IF), which is crucial for vitamin B12 absorption in the ileum. The decrease in IF production leads to vitamin B12 deficiency despite sufficient dietary intake. Gastric intestinal metaplasia (GIM) is histologically characterized by the substitution of the normal gastric epithelium with intestinal-type cells. Often considered a premalignant lesion in gastric carcinogenesis, GIM frequently develops following chronic *Helicobacter pylori* infection or autoimmune gastritis [3]. In a study conducted in Türkiye, the prevalence of

GIM in the population was found to be 9.7%, with a higher prevalence in men (6.7%) [4]. However, its effect on micronutrient absorption, especially vitamin B12, is not well studied. Since GIM alters the normal gastric mucosal architecture, it may similarly impair IF secretion and vitamin B12 uptake, potentially leading to hyperhomocysteinemia.

Red Cell Distribution Width (RDW), a standard parameter in complete blood counts, reflects the variability in red blood cell size (anisocytosis). Elevated RDW has recently been linked to increased systemic inflammation, cytokine release, and diseases such as cardiovascular disease, rheumatoid arthritis, and inflammatory bowel disease [5-7].

While the relationship between AG and vitamin B12 deficiency has been extensively studied [8, 9], data on GIM's role in this context is limited. This study aims to fill that gap by comparing serum homocysteine levels and their correlation with vitamin B12, folate, and RDW among patients with AG, GIM, and chronic gastritis without atrophy or metaplasia, excluding those with known cardiovascular or systemic risk factors. We hypothesize that GIM, similar to AG, may contribute to hyperhomocysteinemia through malabsorption of vitamin B12.

Materials and methods

Study design and population

This cross-sectional study was conducted between July 2019 and October 2020 and included 110 patients undergoing upper gastrointestinal endoscopy. Based on histopathological analysis, participants were classified into three groups:

- Gastric Intestinal Metaplasia (GIM) group (n=46)
- Atrophic Gastritis (AG) group (n=31)
- Control group with non-atrophic, non-metaplastic chronic gastritis (n=33)

Groups were matched regarding sex, age, menopausal status, *Helicobacter pylori* infection, and family history of gastric carcinoma.

Inclusion and exclusion criteria

Exclusion criteria included any history of cardiovascular disease, diabetes mellitus, renal insufficiency, hypothyroidism, alcohol or tobacco use, vitamin supplementation, previous *Helicobacter pylori* eradication therapy, recent use (within 2 months) of antibiotics, NSAIDs, statins, proton pump inhibitors, H₂-receptor blockers, antiplatelet or anticoagulant agents, leukocyte-modulating medications, pregnancy, presence of atrophic metaplastic gastritis or refusal to consent.

Biochemical analysis

Blood samples were collected after overnight fasting. Serum vitamin B12 and folate levels were measured by chemiluminescent enzyme immunoassay using the Advia Centaur® XP Analyzer (Siemens Healthineers, Switzerland). Plasma homocysteine was quantified by fluorescence polarization immunoassay with the Immulite® 2000 system (Siemens Healthineers). RDW was analyzed via the Mindray BC-6800 hematology analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China).

Histopathologic evaluation

Gastric mucosal biopsies were stained with hematoxylin and eosin and evaluated according to the updated Sydney system. The presence of intestinal metaplasia, atrophic gastritis, non-atrophic gastritis, and *Helicobacter pylori* infection was determined histologically [10].

Helicobacter pylori assessment

H. pylori infection was assessed both histologically and with a rapid urease test. Patients were considered positive if either method confirmed the presence of *H. pylori*.

Statistical analysis

We conducted statistical analyses using Statistical Package for Social Sciences (SPSS) for Windows version 25.0. Continuous variables are expressed as mean $\pm$ standard deviation. The Kolmogorov–Smirnov test was employed to check the normality of these variables.

Between-group comparisons of means were performed using analysis of variance (ANOVA) followed by post hoc testing and Tukey's method. For categorical data, we applied either the chi-square test or Fisher's exact test, depending on expected cell frequencies. To determine independent predictors of hyperhomocysteinemia, we used linear logistic regression modeling. The following covariates were included: *H. pylori* infection (positive/negative), sex (female/male), menopausal status (presence versus absence), family history of gastric carcinoma (presence versus absence), presence of GIM, and presence of AG. A value of $p < 0.05$ was deemed to indicate statistical significance.

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval date: 19/06/2019 and approval number: 180-08-14).

Results

The demographic and clinical characteristics of the groups (GIM, AG, and controls) are summarized in Table 1. No significant differences were observed between groups regarding age, gender distribution, menopausal status, family history of gastric cancer, or *Helicobacter pylori* positivity. The most common complaints in GIM cases were, in order: dyspepsia (12/46, 26.1%), fatigue (20/46, 43.5%), and epigastric pain (7/46, 15.2%). There was no significant difference between the GIM, AG (dyspepsia 11/31, 35.5%, fatigue 12/31, 38.7%, epigastric pain 3/31, 19.4%), and control (dyspepsia 9/33, 27.3%, fatigue 10/33, 30.3%, epigastric pain 5/33, 15.2%) groups in terms of these complaints (between groups respectively $p = 0.648$ Chi-square=0.868, $p = 0.492$ Chi-square=1.418, $p = 0.868$ Chi-square=0.282). Complete metaplasia was present in 32 (69.5%) cases in the GIM, and incomplete metaplasia was present in 14 (30.5%) cases. Serum homocysteine concentrations were significantly elevated in both the GIM (11.36 ± 4.94 $\mu\text{mol/L}$) and AG (9.34 ± 4.07 $\mu\text{mol/L}$) groups compared to the control group (6.97 ± 6.62 $\mu\text{mol/L}$; $p = 0.00$). Levels of vitamin B12 were substantially lower in the GIM (252.03 ± 94.91 pmol/L) and

AG (260.59 ± 74.25 pmol/L) groups relative to controls (363.42 ± 130.45 pmol/L), with statistically significant differences (GIM vs controls $p=0.0001$, AG vs control $p=0.0001$, between groups $p=0.0001$). Although RDW values tended to be higher in the GIM ($17.46 \pm 12.18\%$) and AG ($17.27 \pm 4.49\%$) groups than in controls ($15.06 \pm 2.30\%$), this difference did not reach statistical significance ($p=0.168$). Folate levels were notably lower in the GIM group compared to controls (14.31 ± 6.16 ng/ml vs. 17.08 ± 5.59 ng/ml, $p=0.020$). Logistic regression analysis identified male gender ($\beta=2.073$, $p=0.008$) and the presence of either

GIM or AG ($\beta=2.074$, $p=0.000$) as independent predictors of hyperhomocysteinemia. Although RDW values tended to be higher in the GIM ($17.46 \pm 12.18\%$) and AG ($17.27 \pm 4.49\%$) groups than in controls ($15.06 \pm 2.30\%$), this difference did not reach statistical significance ($p=0.168$). Folate levels were notably lower in the GIM group compared to controls (14.31 ± 6.16 ng/ml vs. 17.08 ± 5.59 ng/ml, $p=0.020$). Logistic regression analysis identified male gender ($\beta=2.073$, $p=0.008$) and the presence of either GIM or AG ($\beta=2.074$, $p=0.000$) as independent predictors of hyperhomocysteinemia.

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

Parameters	Gastric intestinal metaplasia group	Gastric atrophy group	Controls	p
Age (years) ¹	52.41 $\pm$ 15.29	49.01 $\pm$ 15.40	53.39 $\pm$ 14.07	0.090 (F=4.684)
Sex (female %) ²	55.4	61.3	69.7	0.192 (cs=1.25)
Menopause (%) ²	20.7	16.1	18.2	0.77 (cs=3.36)
H.pylori positivity (%) ³	56.5	66.1	74.2	0.068 (cs=0.22)
History of gastric carcinoma in family (%) ²	3.3	6.5	3.0	0.540 γ
Homocysteine (μ mol/L) ¹	11.36 $\pm$ 4.94	9.34 $\pm$ 4.07	6.97 $\pm$ 6.62	0.000* (F=13.198)
Vitamin B12 (pmol/L) ¹	252.03 $\pm$ 94.91	260.59 $\pm$ 74.25	363.42 $\pm$ 130.45	0.000* (F=25.945)
Folic acid (ng/ml) ¹	14.31 $\pm$ 6.16	14.98 $\pm$ 6.72	17.08 $\pm$ 5.59	0.020* (F=4.006)
RDW (%) ¹	17.46 $\pm$ 12.18	17.27 $\pm$ 4.49	15.06 $\pm$ 2.30	0.168 (F=1.800)

Subjects were considered *Helicobacter pylori* (H.pylori) positive to be positive for H. pylori infection if the bacteria were histopathologically detected and/or the local rapid urease test was positive. 1Analysis of variance (ANOVA) test was used. 2Chi square test were used. 3Fisher's Exact test was used. *: $p<0.05$ was considered to be statistically significant. ANOVA and Chi square test were used. F: Analysis of variance (ANOVA) test was used. Cs: Chi square test were used. γ : Fisher's Exact test was used. * $P<0.05$ was considered to be statistically significant

Discussion

Our findings demonstrate that both atrophic gastritis and gastric intestinal metaplasia are linked with significantly increased serum homocysteine levels compared to patients with chronic gastritis without atrophic or metaplastic changes. These elevated homocysteine levels coincide with decreased vitamin B12 concentrations, reinforcing the concept that structural changes in the gastric mucosa, whether through glandular atrophy or epithelial metaplasia, can compromise vitamin B12 absorption and lead to metabolic disturbances like hyperhomocysteinemia.

No significant difference in RDW values was found between the groups, potentially due to the sample size or the absence of an inflammatory response sufficient to affect RDW in GIM and AG.

Atrophic gastritis and gastrointestinal metaplasia are important precancerous lesions of the stomach, but they are often overlooked because they are clinically asymptomatic and silent [11]. The most common etiological causes of both processes are H. pylori infection and autoimmunity [11-13]. The increasing prevalence and clinical significance of atrophy and metaplasia are attributed to factors such

as increased human lifespan, environmental diversity, changes in gastric microbiota, and decreased microbial diversity [14]. In addition to being precancerous lesions, they can also lead to micronutrient deficiencies, particularly deficiencies in vitamin B12, folic acid, and iron [15]. Evidence supporting the relationship between elevated homocysteine levels, an independent cardiovascular risk factor, and vitamin B12 deficiency continues to grow today [16, 17]. Previous studies have extensively documented vitamin B12 deficiency and related metabolic effects in atrophic gastritis [8, 9, 12, 15]. The novelty of our study lies in highlighting that GIM, despite lacking clear glandular atrophy, also associates with comparable vitamin B12 deficiency and elevated homocysteine. The underlying mechanisms remain unclear but may involve replacement of gastric epithelial cells with intestinal-type epithelium, which could reduce intrinsic factor secretion and disrupt the gastric environment needed for vitamin B12 uptake [18].

Importantly, our cohort excluded individuals with conventional cardiovascular risk factors, strengthening the notion that GIM independently contributes to hyperhomocysteinemia via impaired vitamin B12 metabolism. The logistic regression further confirmed the independent predictive roles of GIM, AG, and male sex in elevated homocysteine levels.

H. pylori is the important cause of atrophic gastritis and GIM [9, 11-13]. *H. pylori*-induced T helper 1 dominant localized and systemic inflammation plays a crucial role in the progression from chronic gastritis to atrophy and metaplasia. However, in our study, no significant difference was found between the groups in terms of *H. pylori* positivity. We believe that this situation is related to the decrease in *H. pylori* colonization over time due to reduced acidity in atrophic and/or metaplastic tissue (vanishing phenomenon) [19, 20].

There is also a rare national study in the literature that does not support the relationship between GIM, vitamin B12 deficiency, and anemia [21]. Nevertheless, clinically, it is important to recognize GIM as a potential cause of vitamin B12 deficiency and related metabolic

disorders, especially in populations with high *H. pylori* prevalence. Screening and nutritional intervention may help reduce cardiovascular risks linked to subclinical vitamin B12 deficiency.

Limitations include the cross-sectional design, biopsy-based histology, which may not capture mucosal heterogeneity, and lack of methylmalonic acid measurements. Future longitudinal studies with larger samples and more specific markers are warranted to better understand these relationships.

In summary, our results suggest that gastric intestinal metaplasia, similarly to atrophic gastritis, may contribute to elevated homocysteine levels through vitamin B12 malabsorption. Clinicians should consider GIM in the differential diagnosis of hyperhomocysteinemia and vitamin B12 deficiency.

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