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Contemporary Views on Common Risk Factors and Pathophysiological Mechanisms of Acid-Related Gastrointestinal Disorders and Ischemic Heart Disease

Raupov Abdurahmon Ortiq o'g'li
Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi.,
e-mail: raupov.abdurahmon@bsmi.uz

Resume: The comorbidity of ischemic heart disease and acid-related gastrointestinal illnesses is examined in this review, with an emphasis on common risk factors and pathophysiology connections. It draws attention to the part that pharmaceutical interactions, metabolic imbalance, and systemic inflammation play in the development of illness. The results provide insights for better clinical management of comorbid illnesses and are based on meta-analyses and extensive investigations.

Keywords: comorbidity, gastroesophageal reflux disease, ischemic heart disease , anticoagulants, pathophysiological mechanisms

Modern medicine continues to progress dynamically; however, most clinical trials forming the basis of treatment protocols still exclude patients with comorbidities. In real-world practice, multiple concurrent diseases are the norm rather than the exception, and their coexistence significantly complicates both diagnostic and therapeutic decision-making—particularly when therapy for one condition may aggravate or contraindicate treatment for another. Although the concept of cumulative or multiple risk has been introduced to guide management, it does not fully reflect the day-to-day difficulties faced by clinicians in treating multimorbid patients. [1]

The interrelationship between **gastroesophageal reflux disease (GERD)** and **ischemic heart disease (IHD)** is well documented. These disorders are frequently linked through overlapping risk factors such as male sex, obesity, diabetes mellitus, hypertension, tobacco use, and alcohol consumption. GERD can provoke myocardial ischemia via mechanisms including vagal-mediated coronary artery spasm triggered by acid reflux, lowered esophageal sphincter tone, and sympathetic hyperactivity. In individuals suffering from both GERD and IHD, episodes of heartburn often coincide with ischemic pain or arrhythmias. In rare cases, a large paraesophageal hernia may mechanically compress the left atrium, impairing myocardial perfusion and leading to ischemic events or rhythm disturbances. [2]

A population-based cohort analysis has demonstrated that GERD is associated with a markedly higher risk of IHD—approximately 82% greater than that observed in controls (11.8 vs 6.5 per 1000 person-years; aHR = 1.49, 95% CI: 1.34–1.66). This relationship persisted after adjusting for age, sex, and multiple cardiovascular risk factors, including diabetes, hypertension, hyperlipidemia, and chronic lung diseases. Conversely, IHD itself can influence esophageal function by reducing mucosal perfusion due to endothelial dysfunction, as well as inducing esophageal dysmotility. Moreover, commonly prescribed cardiac agents—beta-blockers, nitrates, calcium channel blockers, and antiplatelets—can reduce lower esophageal sphincter tone, exacerbating reflux symptoms. Although **proton pump inhibitors (PPI)** can relieve GERD manifestations and may indirectly

stabilize cardiac function by modulating esophagocardiac reflexes, prolonged PPI therapy has been linked to endothelial dysfunction and may increase atherosclerotic risk. [3]

Peptic ulcer disease (PUD) affects approximately 11–14% of men and 8–11% of women globally. Patients with IHD are particularly vulnerable to PUD due to overlapping risk factors such as smoking and inadequate diet, as well as chronic use of antiplatelet medications. Low-dose aspirin, a cornerstone in IHD prevention, increases the incidence of upper gastrointestinal injury by two- to fourfold. Notably, many ulcer cases are asymptomatic—up to two-thirds are detected incidentally. NSAID-induced ulcer bleeding accounts for over 20,000 and 16,500 annual deaths in the UK and USA, respectively. Data from the UK Biobank and ESTHER cohort studies, with over a decade of follow-up, revealed that short-term aspirin therapy (<1 year) significantly raises the risk of ulceration (HRs: 1.82 and 1.66 in Biobank; 2.83 and 3.89 in ESTHER), whereas long-term use (>1 year) confers a milder risk increase (HRs: 1.27 and 1.33). [4]

Combined administration of aspirin and PPIs has been shown to mitigate the risk of peptic ulceration and may enhance adherence to cardiovascular therapy by reducing gastrointestinal discomfort. Nevertheless, PPIs do not fully prevent mucosal injury. In a prospective study of 1,000 stable IHD patients—most post-PCI and on dual antiplatelet therapy—gastric erosions and ulcerations were frequently observed despite concurrent PPI use. Beyond drug effects, mucosal ischemia due to systemic atherosclerosis, *Helicobacter pylori* infection, and PPI-induced dysbiosis may contribute to ulcerogenesis. The REGATA-1 trial reported *H. pylori* positivity in 87.5% of severe GI bleeding cases, emphasizing its etiological role. [5,6]

Infectious factors are also implicated in the pathogenesis of IHD. Growing evidence supports the involvement of *H. pylori* in atherogenesis through systemic inflammation, oxidative stress, and endothelial dysfunction. Patients with *H. pylori* infection have a significantly higher prevalence of coronary stenosis (7.6% vs 2.9%, P=0.01). Possible mechanisms include elevated inflammatory cytokines, altered lipid metabolism, enhanced platelet activity, and increased homocysteine levels. Eradication therapy has demonstrated improvement in angina frequency, exercise tolerance, and overall cardiovascular outcomes. Consequently, screening and eradication of *H. pylori* in IHD patients on long-term antiplatelet or PPI therapy is strongly recommended. [7,8]

Inflammatory bowel disease (IBD), a systemic inflammatory condition, has also been linked to cardiovascular morbidity. A meta-analysis encompassing nine clinical trials showed a 35% higher risk of IHD among IBD patients (OR = 1.35; 95% CI: 1.19–1.52). The chronic inflammatory burden in IBD promotes vascular endothelial dysfunction, leukocyte adhesion, and cytokine-mediated atherogenesis. Overexpression of CRP, IL-1, IL-6, and TNF-α contributes to accelerated atherosclerosis. [9–11]

IBD additionally predisposes to both arterial and venous thrombotic events through persistent systemic inflammation and coagulation cascade activation. Elevated levels of clotting factors (V, VIII, fibrinogen, von Willebrand factor) and thrombin markers (D-dimer, fibrinopeptide A, prothrombin fragments) have been documented, reflecting a hypercoagulable state. [13–15] Moreover, altered gut microbiota composition, characterized by reduced microbial diversity and decreased short-chain fatty acid (SCFA) production, is thought to further facilitate dyslipidemia and vascular injury. [16]

Managing thrombotic complications in patients with concurrent IHD and IBD poses significant clinical challenges. Active IBD phases markedly heighten gastrointestinal bleeding risk (up to 6%), yet withholding antithrombotic therapy increases ischemic events. Balancing thrombosis prevention against hemorrhagic complications thus requires individualized strategies. Unfortunately, robust data on optimal antithrombotic management in this comorbid population remain scarce. [17,18]

Therapeutic approaches for IBD include **5-aminosalicylic acid (5-ASA),** corticosteroids, immunomodulators, and biologic agents. Interestingly, 5-ASA therapy appears to confer modest cardiovascular protection (OR = 1.16 vs 1.36 in non-users). In contrast, chronic corticosteroid use may increase gut permeability, exacerbate ulcer formation, and induce prothrombotic changes by

enhancing platelet aggregation and reducing endothelial prostacyclin synthesis. [19] **Anti-TNF biologics**, though effective in controlling inflammation, exert mixed cardiovascular effects. In a nationwide cohort of 50,756 IBD patients, anti-TNF therapy was associated with a slightly reduced IHD risk (aHR = 0.85, 95% CI: 0.59–1.24), but possibly an increased stroke risk (aHR = 1.42, 95% CI: 0.82–2.45). Overall, the data suggest potential cardioprotection with caution warranted regarding cerebrovascular events. [20]

Conclusion. The intricate interplay between acid-related gastrointestinal disorders (GERD, PUD, IBD) and ischemic heart disease (IHD) necessitates a patient-centered, multidisciplinary management model. GERD can intensify myocardial ischemia through esophagocardiac reflexes and may worsen under the influence of cardiac drugs. PUD frequently complicates long-term antiplatelet therapy, underlining the value of concurrent PPI prophylaxis and H. pylori eradication. IBD amplifies cardiovascular risk via chronic inflammation, coagulation abnormalities, and microbiota disruption, while its treatment introduces both protective and adverse cardiovascular effects. Future therapeutic strategies should focus on harmonizing gastrointestinal protection with cardiovascular safety, integrating anti-inflammatory control, microbiome preservation, and careful antithrombotic use to improve outcomes in multimorbid patients.

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