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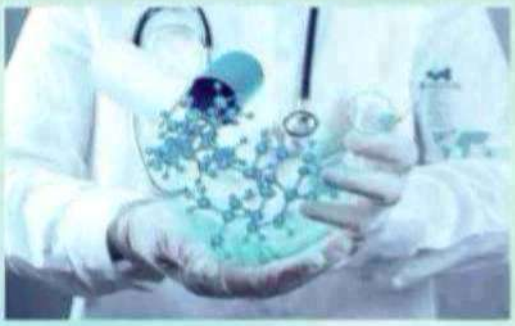

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COMORBIDITY OF ACID-RELATED GASTROINTESTINAL DISORDERS AND ISCHEMIC HEART DISEASE: MODERN PERSPECTIVES ON SHARED RISK FACTORS AND PATHOPHYSIOLOGICAL MECHANISMS *(literature review)*

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✓ ***Resume***

This review explores the comorbidity between acid-related gastrointestinal disorders and ischemic heart disease, focusing on shared risk factors and pathophysiological links. It highlights the role of systemic inflammation, metabolic imbalance, and pharmacological interactions in disease progression. The findings are based on meta-analyses and large-scale studies, offering insights for improved clinical management of comorbid conditions.

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

КОМОРБИДНОСТЬ ЗАБОЛЕВАНИЙ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА И СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ: СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ ОБ ОБЩИХ ФАКТОРАХ РИСКА И ПАТОФИЗИОЛОГИЧЕСКИХ МЕХАНИЗМАХ

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✓ ***Резюме***

В настоящем обзоре рассматривается коморбидность кислотозависимых заболеваний желудочно-кишечного тракта и ишемической болезни сердца с акцентом на общие факторы риска и патофизиологические связи. Подчёркивается роль системного воспаления, метаболического дисбаланса и фармакологических взаимодействий в прогрессировании заболеваний. Представленные выводы основаны на данных метаанализов и крупномасштабных исследований и направлены на улучшение клинического ведения пациентов с коморбидной патологией.

Ключевые слова: коморбидность, гастроэзофагеальная рефлюксная болезнь, ишемическая болезнь сердца, антикоагулянты, патофизиологические механизмы

OSHQOZON-ICHAK TRAKTINING KISLOTAGA BOG'LIQ KASALLIKLARI VA YURAK ISHEMIK KASALLIKLARINING KOMORBIDLIGI: UMUMIY XAVF OMILLARI VA PATOFIZIOLOGIK MEXANIZMLAR BO'YICHA ZAMONAVIY QARASHLAR *(adabiyotlar sharhi)*

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✓ ***Rezyume***

Ushbu maqolada kislotaga bog‘liq oshqozon-ichak tizimi kasalliklari va ishemik yurak kasalligi o‘rtasidagi komorbidlik, umumiy xavf omillari va patofiziologik bog‘liqliklarga e'tibor qaratilgan. Yallig‘lanish, metabolik disbalans va farmakologik o‘zaro ta’sirlarning kasallikning rivojlanishidagi roli ta'kidlangan. Olingan natijalar va keng ko‘lamli tadqiqotlarga asoslanib, komorbid kasalliklarni klinik boshqarishni yaxshilash uchun muhim tavsiyalar beradi.

Kalit so‘zlar: komorbidlik, gastroezofageal refluks kasalligi, yurak ishemik kasalligi, antikoagulyantlar, patofiziologik mexanizmlar

Relevance

Modern medicine is constantly evolving, yet clinical studies underlying guidelines and protocols typically exclude comorbidity as a factor. In clinical practice, comorbid pathology is commonly encountered, complicating the diagnosis and treatment of each disease, especially when one condition contraindicates life-saving medications for another. The proposed model of multiple or cumulative risk facilitates patient management, but fails to address many practical challenges faced by clinicians [1].

The connection between gastroesophageal reflux disease (GERD) and ischemic heart disease (IHD) is well-established. These conditions share common risk factors, including male gender, obesity, diabetes, hypertension, smoking, and alcohol consumption. GERD may trigger myocardial ischemia through reflex spasm of the coronary arteries caused by acid reflux, decreased pressure in the lower esophageal sphincter, and sympathetic activation. In patients with both GERD and IHD, episodes of heartburn and myocardial ischemia, as well as arrhythmias, often coincide. A rare phenomenon is the mechanical impact of paraesophageal hernias on the left atrium, which can reduce heart perfusion, leading to ischemia, angina, and arrhythmias [2].

A nationwide cohort study on GERD patients revealed its association with an increased risk of ischemic heart disease (IHD). The incidence of IHD was 82% higher in the GERD cohort compared to the non-GERD group (11.8 vs 6.50 per 1000 person-years), with aHR = 1.49 (95% CI = 1.34–1.66). After adjusting for age, gender, hypertension, diabetes, hyperlipidemia, alcohol-related diseases, stroke, chronic obstructive pulmonary disease, asthma, gallstones, anxiety, depression, chronic kidney disease, and cirrhosis, GERD patients had a higher risk of IHD (aHR = 1.49, 95% CI = 1.34–1.66). On the other hand, the impact of cardiac pathology on GERD is diverse, including reduced regional blood flow and esophageal hypoxia due to endothelial dysfunction of arteries, as well as dysmotility of the upper gastrointestinal tract in IHD. The negative effects of IHD medications such as calcium channel blockers, nitrates, beta-blockers, and antiplatelet drugs on the lower esophageal sphincter tone were noted. Proton pump inhibitor (PPI) therapy improves GERD symptoms and may indirectly improve IHD outcomes through esophagocardiac reflex. However, prolonged PPI use has been associated with an increased risk of atherosclerosis and may exacerbate cardiac contractile dysfunction [3].

Peptic ulcer disease (PUD) is a common condition, affecting 11–14% of men and 8–11% of women during their lifetime. A case-control study has shown an increased risk of PUD in patients with ischemic heart disease (IHD), largely due to shared risk factors such as smoking and poor dietary habits. Peptic ulcers in IHD patients are often associated with the use of antiplatelet agents, particularly low-dose aspirin, as part of standard therapy. Prolonged aspirin use has been linked to a two- to fourfold increase in upper gastrointestinal complications. Importantly, up to two-thirds of endoscopically confirmed PUD cases are asymptomatic. In the UK and the US, NSAID-associated ulcer bleeding causes over 20,000 and 16,500 deaths annually, respectively. Despite this, many patients take antiplatelet agents for years without adverse events. Data from two large-scale cohort studies — the UK Biobank (N=213,598) and the German ESTHER study (N=7,737) — with follow-up periods over 10 years, assessed the relationship between low-dose aspirin use and PUD. Short-term use (<1 year) was associated with a significantly higher risk: hazard ratios were 1.82 [1.58–2.11] and 1.66 [1.36–2.04] in the Biobank study, and 2.83 [1.40–5.71] and 3.89 [1.46–10.42] in ESTHER. Long-term aspirin use (>1 year) showed a weaker association with gastroduodenal ulcers: 1.27 [1.07–1.51] in Biobank and 1.33 [0.54–3.29] in ESTHER [4].

The combined use of aspirin and proton pump inhibitors (PPIs) reduces the risk of peptic ulcer disease (PUD) and may also decrease the frequency of cardiovascular disease (CVD) exacerbations. This is likely due to a reduction in gastrointestinal (GI) symptoms, potentially improving patient

adherence to long-term therapy. However, antiplatelet therapy is not the sole trigger of ulceration and gastrointestinal bleeding (GIB). A prospective study involving approximately 1,000 patients with stable ischemic heart disease—most of whom (76%) had undergone elective percutaneous coronary intervention (PCI) and had no contraindications to antithrombotic therapy—revealed signs of gastric mucosal injury, including erosions and peptic ulcers. Notably, these lesions were also observed in patients receiving PPI therapy. Independent contributors to GIB include mucosal ischemia in the context of widespread atherosclerosis, adverse effects of PPIs, and *Helicobacter pylori* infection. The REGATA-1 study found *H. pylori* infection in 87.5% of patients with severe gastrointestinal bleeding, highlighting its significant role as an etiological factor. [5,6]

Viral and bacterial pathogens are increasingly being recognized as potential contributors to the pathogenesis of ischemic heart disease (IHD). In recent years, growing evidence has highlighted the possible involvement of *Helicobacter pylori* in the development of atherothrombosis. Clinical studies have shown that patients testing positive for *H. pylori* have a significantly higher prevalence of clinically relevant coronary stenosis compared to *H. pylori*-negative individuals (7.6% vs. 2.9%, P = 0.01).Several hypotheses have been proposed to explain this association, including *H. pylori*-induced systemic inflammation leading to endothelial dysfunction, increased oxidative stress, dysregulation of lipid metabolism, enhanced platelet aggregation, and secondary hyperhomocysteinemia. Although a unified consensus has not yet been reached regarding the precise role of *H. pylori* in the onset and progression of IHD, eradication therapy in *H. pylori*-infected patients has been shown to improve clinical outcomes. These include reduced angina episodes, decreased need for antianginal medications, and improved exercise tolerance [7]. In light of the above, routine *Helicobacter pylori* screening followed by eradication therapy should be considered essential for patients with ischemic heart disease receiving long-term antiplatelet therapy, in addition to prolonged proton pump inhibitor use [8].

Inflammatory bowel disease (IBD) is a systemic disorder that affects multiple organ systems. The association between IBD and cardiovascular pathology has been the subject of increasing research interest. A meta-analysis of nine clinical studies demonstrated that patients with IBD have a 95% higher risk of developing ischemic heart disease (IHD) compared to the general population (OR = 1.35; 95% CI: 1.19–1.52). Chronic systemic inflammation is a key pathogenic mechanism in both IHD and IBD. It is associated with increased intestinal epithelial permeability, resulting in abnormal absorption of bacterial toxins, inflammatory mediators, and proinflammatory cytokines. These factors can induce the expression of adhesion molecules on vascular endothelial cells, facilitating leukocyte adhesion and diapedesis. Overproduction of C-reactive protein, interleukins (IL-1, IL-6), and tumor necrosis factor (TNF) observed in IBD contributes to atherogenesis [9, 10, 11].

Inflammatory bowel disease (IBD) increases not only the risk of atherosclerosis but also predisposes to both arterial and venous thrombosis. Persistent systemic inflammation contributes to a prothrombotic state and widespread endothelial dysfunction via multiple pathophysiological mechanisms, thereby promoting the development of thrombosis and thromboembolic events. Numerous studies have demonstrated elevated levels of several coagulation factors in IBD patients, including factors V and VIII, von Willebrand factor, and fibrinogen, as well as markers of thrombin and fibrin generation such as fibrinopeptide A, prothrombin fragment 1+2, thrombin–antithrombin complexes, and D-dimers. Additionally, markers of endothelial activation, including von Willebrand factor and thrombomodulin, are also significantly elevated in individuals with active IBD [13, 14, 15].

In patients with inflammatory bowel disease (IBD), the composition of the gut microbiota is significantly altered compared to healthy individuals, characterized by a marked loss of microbial diversity. The potential role of gut microbiota modulation in regulating immune responses is currently under active discussion. The gut microbiota is also implicated in lipid metabolism, primarily through the deconjugation of bile acids by bacterial genera such as *Bacteroides* and *Bifidobacterium*, which are key producers of short-chain fatty acids (SCFAs). A deficiency of SCFAs, commonly observed in IBD, may contribute to the development of atherosclerosis [16].

The management of thrombotic complications in patients with comorbid ischemic heart disease (IHD) and inflammatory bowel disease (IBD) remains particularly challenging due to the elevated risk of bleeding, which peaks during active phases of IBD. Major gastrointestinal bleeding occurs in up to 6% of IBD cases. Nevertheless, overly cautious use of antithrombotic therapy in patients with IBD and coexisting cardiovascular disease (CVD) may increase the risk of adverse cardiovascular events. Striking an optimal balance between ischemic and bleeding risks in patients with both IBD and IHD is

difficult. Importantly, comprehensive data on bleeding risk in IBD patients undergoing antithrombotic treatment remain limited [17, 18].

The standard therapy for inflammatory bowel disease (IBD) includes 5-aminosalicylic acid (5-ASA) preparations, glucocorticoids (GCs), immunomodulators, and biologic agents. A decrease in the risk of ischemic heart disease (IHD) has been observed in IBD patients receiving 5-ASA (OR = 1.16; 95% CI 1.06–1.26), compared to those not using 5-ASA (OR = 1.36; 95% CI 1.22–1.51), including among users of oral corticosteroids (CS). Corticosteroid therapy may provoke gastroduodenal ulcers and increase intestinal permeability. Excess cortisol contributes to the increased permeability of the intestinal barrier. Prolonged use of GCs in IBD exacerbates the consumption and activation of several coagulation factors, reduces prostacyclin synthesis by the vascular endothelium, and enhances platelet adhesive-aggregation functions [19].

TNF antagonists (anti-TNF), which have proven anti-inflammatory effects, have a controversial impact on cardiovascular disease (CVD) risks**.** Data on the relationship between anti-TNF therapy and CVD were analyzed in a nationwide cohort study**,** which included 50,756 patients with inflammatory bowel disease (IBD), of whom 3,109 received anti-TNF therapy from 1999 to 2010. Ischemic heart disease (IHD) developed in 31 patients receiving anti-TNF therapy and 2,641 patients not receiving this therapy. The adjusted risk was 0.85 (95% CI; 0.59–1.24), while the risk of stroke associated with anti-TNF therapy was 1.42 (95% CI; 0.82–2.45)**.** The authors concluded that anti-TNF therapy had a protective effect on IHD, but also noted that it might pose a potential risk factor for stroke [20].

Conclusion

The complex relationship between acid-dependent gastrointestinal diseases—such as GERD, PUD, and IBD—and ischemic heart disease (IHD) demands an individualized, multidisciplinary approach. GERD can exacerbate myocardial ischemia via esophagocardiac reflexes and is often worsened by cardiac medications. PUD complicates antiplatelet therapy, highlighting the need for risk stratification and PPI co-therapy. IBD increases cardiovascular risk through chronic inflammation, endothelial dysfunction, and hypercoagulability. Managing thrombosis versus bleeding, especially during flares, remains difficult. While 5-ASA may offer mild cardioprotection, corticosteroids can worsen both GI and vascular risks. Anti-TNF agents show promise in reducing IHD risk, though more research is needed. An integrated management strategy—including H. pylori screening, cautious antithrombotic use, and tailored anti-inflammatory therapy—is essential. Future research should refine treatment algorithms to reduce both GI and cardiovascular complications in multimorbid patients.

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