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The Impact of Nonsteroidal Anti-Inflammatory Drugs on the Gastrointestinal Tract and Strategies for Preventing Associated Adverse Effects

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Abstract

Introduction. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used because of their broad range of therapeutic applications. However, their use, regardless of treatment duration, is associated with the risk of adverse effects, predominantly involving the gastrointestinal (GI) tract.

Aim. The aim of this paper is to review the potential GI adverse effects associated with NSAIDs and discuss methods for their prevention.

Material and methods. The study was prepared based on a review of literature retrieved from the Google Scholar, PubMed, and Scopus databases from recent years. The literature was filtered by keywords: 'nonsteroidal anti-inflammatory drugs', 'gastrointestinal', 'upper tract', 'adverse effects', proton pump inhibitor', 'small bowel'.

Results. NSAIDs-related complications involve both the upper and lower GI tract, however their pathogenesis appears to be distinct. The main mechanism of upper GI tract injury involves weakening of the mucosal barrier and its subsequent damage by gastric acid and digestive enzymes, whereas in case of lower GI tract, studies report the direct harmful effects of NSAIDs on the intestinal mucosa, mitochondrial damage, and alterations in the gut microbiota. Key strategies for the prevention of upper GI side effects involve either co-therapy with NSAIDs and PPIs or selective COX-2 inhibitor use. In contrast, due to a different pathogenesis, probiotics, mucoprotective agents, mesalazine and COX-2 inhibitors used as monotherapy may be beneficial in the treatment and prevention of lower GI complications.

Conclusions. Each patient should be individually assessed for complications related to a specific part of the GI tract, with treatment adjusted appropriately.

Keywords: nonsteroidal anti-inflammatory drugs, gastrointestinal, upper tract, adverse effects, proton pump inhibitor, small bowel

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications.Their popularity stems from their effectiveness in alleviating pain and inflammation. In addition to their analgesic, anti-pyretic and anti-inflammatory activities, aspirin is an example of a drug used in the treatment of atherosclerosis. Studies also indicate the multifaceted anti-cancer effects of NSAIDs [1]. Chronic inflammation is now recognized as a factor in carcinogenesis. Consequently, the administration of anti-inflammatory agents, either in monotherapy or combined with chemotherapy, is considered important in both the prevention and treatment of cancer [2]. Despite their extensive therapeutic applications, NSAIDs are associated with a variety of serious adverse effects, including gastrointestinal (GI), renal, hepatic or cardiovascular complications, hypertension, and other less significant disorders [1]. Due to its frequency and seriousness, GI toxicity is regarded as a major complication correlated with NSAIDs use. Both short and long-term NSAIDs therapy may result in damage to the upper and lower GI tract, specifically in predisposed individuals [3]. Particular caution is required during the treatment of elderly patients. The high prevalence of multimorbidity in this group, and consequently the use of multiple medications, increase the chance of harmful interactions.The risk of GI bleeding may be elevated by the simultaneous use of pharmaceuticals that regulate hemostasis, including acetylsalicylic acid, clopidogrel, rivaroxaban and warfarin [4].

NSAIDs are inhibitors of the cyclooxygenase (COX) enzyme which participates in conversion of arachidonic acid into prostanoids (prostaglandins, prostacyclins and thromboxanes). At least two isoforms of this enzyme can be distinguished: COX-1 and COX-2. Medications may be categorized based on their activity against each form of enzyme. The COX-1 enzyme, regarded as a constitutively expressed enzyme, is the prevalent form. It contributes in the maintenance of physiological homeostasis by protection of the GI tract, especially the stomach, as well as activity in renal epithelial cells, the vascular endothelium and blood platelets. In contrast, COX-2 is classified as an inducible isoform, since its baseline expression is relatively limited and its activity is mainly increased in response to inflammatory mediators [5].

2. Research material and methods

The study was prepared based on a review of literature retrieved from the Google Scholar, PubMed, and Scopus databases from recent years. The literature was filtered by keywords:

‘nonsteroidal anti-inflammatory drugs’, ‘gastrointestinal’, ‘adverse effect’, 'proton pump inhibitor’, ‘small bowel’.

3. Results

3.1 Side effects on the gastrointestinal tract

The side effects of NSAIDs on the gastric and duodenal mucosa have been thoroughly studied. Endoscopic lesions located in the upper digestive tract such as erosions, ulcerations, and subepithelial hemorrhage are found in around 30–50% of NSAIDs users, most commonly situated in the gastric antrum [6]. Changes frequently remain undetected due to the lack of symptoms and the first manifestation may be complications of ulcer disease. On the other hand, some patients report GI complaints without any endoscopic identifiable lesions [7]. The most frequently observed symptoms are gastroesophageal reflux including heartburn or regurgitation and dyspeptic symptoms such as bloating, belching, epigastric discomfort or nausea [6].

In contrast to upper tract, lower GI NSAIDs-related bleeding is still poorly characterized in terms of prevalence, risk factors, pathogenesis, and preventive strategies.The complications can affect both the small and large intestine and may present as perforation, bleeding, stenosis or protein-losing enteropathy [8]. In cases of suspected bleeding where gastroscopy and colonoscopy do not reveal any bleeding lesions, small bowel ulcerative injury should be taken into account. Endoscopy and upper GI imaging allow relatively simple detection of complications in the stomach and duodenum, while diagnosing abnormalities in the small intestine is considerably more challenging [9]. The manifestations of NSAIDs-induced lower GI toxicity are frequently asymptomatic and difficult to identify. Patients may describe dyspepsia, nausea, diarrhea, constipation and abdominal discomfort [3]. Advances in endoscopic techniques such as capsule endoscopy and double-balloon endoscopy allowed previously unrecognized lesions to be visualized, showing that they are more common than earlier assumed [10].

The main mechanism underlying GI bleeding is the inhibition of COX-enzymes, especially COX-1 which are involved in producing protective prostaglandins in the GI tract. The integrity of the mucosal barrier becomes weakened, making it more exposed to damage from gastric acid and digestive enzymes. As a result, structural damage can occur, potentially leading to bleeding [11]. However, the pathogenesis of NSAIDs-related enteropathy appears to be more complex. Side effects are related to the high local concentration of NSAIDs in the intestinal lumen and

their enterohepatic circulation, rather than to the inhibition of COX-enzymes. Evidence suggests that NSAIDs contribute to direct detrimental effects on the intestinal mucosa, mitochondrial damage, and oxidative stress, thereby increasing permeability of epithelium. Disruption of barrier function predisposes to small bowel inflammation accompanied by blood and protein loss. Additionally, NSAIDs have been reported to disturb the normal intestinal microbiome which is associated with excessive growth of Gram-negative and anaerobic bacteria [12].

3.2 How to prevent gastrointestinal side effects?

Over the years, a variety of preventive strategies have been developed to minimize adverse effects associated with NSAIDs therapy, including prescribing COX-2–selective inhibitors and co-therapy with gastroprotective medications such as proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs) or misoprostol [13].

In this paper, we aim to discuss these methods and evaluate their effectiveness in relation to both the upper and lower GI tract.

3.2.1 Upper gastrointestinal tract

Concomitant treatment with PPIs is a well-established and frequently recommended strategy for reducing the risk of peptic ulcers and upper GI complications in patients receiving long-term NSAIDs therapy who are at increased risk [14]. PPIs exhibit protective effects against NSAIDs-induced gastroduodenal damage due to their ability to suppress gastric acid secretion [15]. They act by inhibiting the hydrogen-potassium dependent (H^+/K^+) ATPase enzyme in gastric parietal cells, thereby decreasing gastric acid secretion and increasing intragastric pH [15-16]. Yang et al. conducted meta-analysis to assess the efficacy of PPIs in preventing ulcer-related complications, examine the influence of potential modifying factors on treatment outcomes, and compare the effectiveness of different PPIs in reducing NSAIDs-related GI toxicity. Multiple factors are believed to modify the risk of NSAIDs-induced ulcer formation, particularly age, previous peptic ulcer disease, and *Helicobacter pylori* infection. According to analyses, PPIs significantly reduced the occurrence of endoscopic peptic ulcers compared with both placebo and H2RAs therapy, while PPIs and high-dose misoprostol showed comparable efficacy. No significant differences were observed among esomeprazole, omeprazole, lansoprazole, and rabeprazole in preventing ulcer complications. However, esomeprazole was

substantially more effective than pantoprazole. Subgroup findings suggested that efficacy was independent of NSAIDs class, ulcer risk factors, history of peptic ulcer disease, *Helicobacter pylori* infection and age [17]. Scally et al. also evaluated the role of PPIs, prostaglandin analogues or H2RAs in the prevention and treatment of gastric ulcer disease. Gastroprotective medications decreased the occurrence of endoscopic and symptomatic ulcers as well as upper GI bleeding, although no significant reduction in mortality was observed. Nevertheless, compared with other gastroprotective drugs, PPIs showed greater effectiveness in reducing the risk of upper GI bleeding and promoting the healing of existing lesions [18].

Non-selective NSAIDs such as naproxen or ibuprofen inhibit both isoforms COX-1 and COX-2, while selective NSAIDs such as celecoxib, etoricoxib inhibit COX-2 [15]. Studies showed that COX-2–selective NSAIDs may be related to a lower incidence of both symptomatic and endoscopically identified ulcers compared with non-selective NSAIDs [19]. Jarupongprapa et al. compared GI side effects between COX-2 inhibitors and non-selective NSAIDs administered with PPIs. Monotherapy with selective COX-2 inhibitors was found to be more effective in reducing the incidence of perforation, obstruction, bleeding, diarrhoea, and discontinuation due to adverse events. The observed benefit, however, was confined to patients with an elevated risk of GI complications and to long-term users. NSAIDs co-administered with PPIs showed an advantage in the prevention of dyspepsia [20]. Lee et al. compared combination treatment with aceclofenac and ilaprazole against celecoxib alone in terms of effectiveness and safety for managing NSAIDs-related dyspepsia. The analysis did not reveal any significant differences. However, authors emphasized that findings from recent studies suggests that selective COX-2 inhibitors, such as celecoxib, may be linked to a higher incidence of cardiovascular complications. The use of celecoxib was found to be associated with a dose-dependent increase in cardiovascular mortality. Consequently, special attention should be paid to patients with a history of cardiovascular disease. In such patients, celecoxib is not typically administered [21].

Yuan et al. selected randomized controlled trials evaluating two or more of the following therapeutic approaches: non-selective NSAIDs, selective COX-2 inhibitors, non-selective NSAIDs with PPIs, non-selective NSAIDs with misoprostol, non-selective NSAIDs with H2RAs, selective COX-2 inhibitors with PPIs and selective COX-2 inhibitors with misoprostol. Among the evaluated strategies, the combination of selective COX-2 inhibitors plus PPIs offered the strongest GI protection, followed by COX-2 inhibitors alone, and subsequently non-

selective NSAIDs with PPIs [13]. Based on the trial results, Chan et al. suggests that combination therapy with a COX-2 inhibitor and a PPI is recommended for patients at very high risk of recurrent ulcer bleeding who require continuation of NSAIDs treatment [22].

Conversely, in a cohort study Lin et al. observed that COX-2 selective inhibitors users demonstrated increased risk of developing upper GI bleeding. The authors concluded, according to comparisons with other studies, that the differences in outcomes resulted from the inclusion of elderly patients and individuals with comorbidities in the analyzed group. Factors independently associated with upper GI bleeding in COX-2 selective inhibitors users include age, male sex, history of previous peptic ulcer disease, Helicobacter pylori infection, coexisting diseases and polypharmacy [23]. Similarly, in meta-analysis, the combined use of COX-2 selective inhibitors and warfarin was associated with substantially elevated risk of GI bleeding in comparison with warfarin monotherapy [24].

3.2.2 Lower gastrointestinal tract

PPIs offer little benefit for lower GI mucosal protection, since the mechanisms underlying lower GI lesions are unrelated to acid secretion. Moreover, concerns have recently been raised regarding this approach because of its potential association with small-bowel injury. The links between these factors are not yet completely understood [25].

The meta-analysis of randomized controlled trials revealed an increased prevalence of endoscopy-detected small bowel mucosal damage among individuals treated with both PPIs and NSAIDs. Findings from two randomized studies indicated that concomitant PPI use was associated with a greater decrease in hemoglobin level. According to subgroup analyses, co-treatment with PPIs significantly increased the occurrence of small bowel injury in patients receiving either non-selective NSAIDs and COX-2 inhibitors compared to treatment with COX-2 inhibitors alone. Interestingly, statistical significance was demonstrated in randomized studies but not in observational trials. These data support the hypothesis that PPIs may contribute to small-bowel damage in NSAIDs users, although further studies are required to clarify the clinical importance of this effect [14]. The impact on small bowel mucosal injury was assessed by comparing co-therapy PPIs with non-selective NSAIDs and selective COX-2 inhibitors administered alone. Goldstein et al. randomized patients into three groups: treated with celecoxib, ibuprofen plus omeprazole and placebo. Then, Fujimori et al. randomly assigned individuals to celecoxib or loxoprofen plus lansoprazole groups. The results were verified by

capsule endoscopy in both cases, which indicated a lower incidence of small intestinal mucosal breaks among subjects receiving a COX-2–selective NSAIDs in monotherapy [26-27]. In the conducted meta-analysis, Jung et al. observed that patients receiving both NSAIDs and PPIs are more prone to lower GI bleeding, with a special emphasis on small bowel bleeding. Authors recommended careful evaluation of potential upper GI comorbidities in patients with lower GI bleeding. If upper GI risk is excluded, PPI therapy should be discontinued [25].

A growing number of studies suggest that PPIs may promote dysbiosis of the intestinal microbiome and small intestinal bacterial overgrowth (SIBO). It may aggravate NSAIDs-associated enteropathy through elevated ileal reabsorption of NSAIDs and greater bile acid toxicity [25]. Tsujimoto et al. noticed the addition of PPIs resulted in an increased proportion of Lactobacillales within the microbiota of patients taking low-dose aspirin. Throughout the study, measurements of serum gastrin, hemoglobin and hematocrit levels were performed. Based on the observed positive correlation between gastrin levels and the proportion of Lactobacillales, it was concluded that suppression of gastric acid secretion influences changes in the intestinal microbiota. In terms of hemoglobin and hematocrit levels, no significant reduction was observed [28]. The reduction of gastric acidity facilitates the passage of bacteria into the intestinal tract by weakening the stomach's natural antimicrobial barrier. Analysis of fecal samples showed that PPIs reduce microbial diversity and increase proportion of bacteria originating from the upper GI tract [29].

Experimental data suggest that the composition of the gut microbiome is an important determinant of NSAIDs-related enteropathy. Dysbiosis is a disturbance in the composition of the microbiota involving a decline in health-promoting bacterial populations and an expansion of pathogenic bacteria typically found in small numbers [30]. Although some antibiotics are effective in preventing small bowel damage caused by NSAIDs, their long-term use is problematic, as NSAIDs are commonly prescribed for chronic conditions requiring extended treatment. Prolonged antibiotic exposure may contribute to development of multidrug-resistant bacteria and intestinal inflammation resulting from changes in the microbial community. Prebiotic and probiotic supplementation may provide protection against intestinal mucosal injury in patients who continue treatment with NSAIDs and PPIs [30-31]. In a randomized controlled study, Endo et al. assessed the effect of the probiotic *Lactobacillus casei* supplementation in patients treated with low-dose aspirin in combination with omeprazole. Three months of probiotic therapy resulted in a significant decrease in the number of small

intestinal mucosal breaks compared to the control group [32]. Similar outcomes were observed in the study by Chen et al. Patients presenting with aspirin-induced small bowel mucosal injuries were randomized equally to either combination therapy with enteric-coated aspirin and a probiotic capsule containing *Lactobacillus rhamnosus* I and II and *Enterococcus faecium*, or enteric-coated aspirin monotherapy for 2 months. In comparison with the control group, the probiotics group demonstrated a significantly greater reduction in mucosal injury scores of the small intestine from baseline to post-intervention [33].

In addition, mucoprotective agents and prostaglandin analogues have proven effective in the treatment of small-intestinal injury caused by NSAIDs [34]. Prophylactic use of mucoprotective medications lowered the frequency of mucosal erosions and significantly diminished the likelihood of post-treatment mucosal damage. Furthermore, mucoprotective therapy enhanced the rate of complete mucosal recovery. Rebamipide, geranylgeranylacetone, misoprostol, isinglass and ecabet sodium increase prostaglandin concentrations in both the serum and small-intestinal mucosa, leading to improved mucosal blood flow and enhanced secretion of mucus and bicarbonate, thereby strengthening mucosal protection [35]. The phase III randomized trial conducted by Taha et al. confirmed the effectiveness of misoprostol in the treatment of small bowel lesions in patients using low-dose aspirin and other NSAIDs. However, in some patients misoprostol therapy was associated with GI adverse events, particularly abdominal pain, nausea, vomiting, and diarrhoea [36].

Rácz et al. evaluated the addition of mesalazine granules to concomitant naproxen and omeprazole therapy over 4 weeks. Patients receiving combined therapy with naproxen and mesalazine granules demonstrated a marked reduction in enteropathy scores compared with periods when naproxen was administered alone. Mesalazine significantly alleviated naproxen-induced mucosal damage in individuals with moderate-to-severe enteropathy. However, several limitations should be considered when interpreting the results. The trial involved only a small number of patients, and no control group was available to determine the mucosal impact of NSAIDs in the absence of mesalazine. Therefore, additional studies are needed to verify the beneficial effects of mesalazine granules [37].

4. Discussion

NSAIDs-related adverse effects may involve both the upper and lower GI tract, however, their pathogenesis appears to be different. A better understanding of the mechanisms underlying

lesion development and the associated risk factors may enable the implementation of more effective treatment regimens. Upper GI tract complications are mainly attributed to the damaging effects of gastric acid and digestive enzymes on weakened mucosal barrier, whereas the pathogenesis of lower GI tract injury involves direct NSAIDs-induced toxicity, mitochondrial damage, and disturbances in the gut microbiota. Researchers have conducted studies comparing different approaches for preventing GI adverse effects. The main preventive strategies for upper GI complications consist of co-administration of NSAIDs with PPIs or the use of selective COX-2 inhibitors. In contrast, due to the distinct mechanisms involved in lower GI tract injury, evidence suggests benefits from probiotics, mucoprotective agents, prostaglandin analogues, mesalazine granules, and selective COX-2 inhibitor monotherapy. It is crucial to evaluate each patient individually for complications in a specific segment of the GI tract, with subsequent optimization of therapy.

Conclusions

1) Gastrointestinal complications are the predominant adverse effects associated with the use of NSAIDs.
2) Although complications can occur in both the upper and lower GI tract, their pathogenesis appears to be different.
3) Upper GI tract damage is primarily connected with weakening of the mucosal barrier and the harmful effects of gastric acid and digestive enzymes.
4) According to studies, damage to the lower GI tract is multifactorial in origin. Direct harmful effects of NSAIDs on the intestinal mucosa, disruption of the gut microbiota or mitochondrial damage are considered**.**
5) Combination therapy non-selective NSAIDs with PPIs or monotherapy with selective COX-2 inhibitors appears to be the main strategies for protecting the upper GI tract.
6) Evidence suggests that PPIs may not alleviate NSAIDs-related side effects in the lower GI tract and may even contribute to small-bowel injuries.
7) Potential approaches to the prevention and treatment of lower GI complications include probiotics, mucoprotective drugs, prostaglandin analogues and selective COX-2 inhibitors.

Disclosure

Author’s contribution

Conceptualization: PM, PB, KC, and JB; methodology: PM, PB, and KC; software: JB; check: JB, KC; formal analysis: PM and PB; investigation: PM, and KC; resources: PM, JB; data curation: JB, and PB; writing - rough preparation: PM, PB, KC, and JB; writing - review and editing: PM, PB, KC, and JB, supervision: PM, project administration: PM

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References

[1] Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol*. 2020;180:114147. https://doi.org/10.1016/j.bcp.2020.114147

[2] Zappavigna S, Cossu AM, Grimaldi A, et al. Anti-Inflammatory Drugs as Anticancer Agents. *Int J Mol Sci*. 2020;21(7):2605. Published 2020 Apr 9. https://doi.org/10.3390/ijms21072605

[3] Maseda D, Ricciotti E. NSAID-Gut Microbiota Interactions. *Front Pharmacol*. 2020;11:1153. Published 2020 Aug 7. https://doi.org/10.3389/fphar.2020.01153

[4] Monteiro C, Silvestre S, Duarte AP, Alves G. Safety of Non-Steroidal Anti-Inflammatory Drugs in the Elderly: An Analysis of Published Literature and Reports Sent to the Portuguese Pharmacovigilance System. *Int J Environ Res Public Health*. 2022;19(6):3541. Published 2022 Mar 16. https://doi.org/10.3390/ijerph19063541

[5] Drożdżal S, Lechowicz K, Szostak B, et al. Kidney damage from nonsteroidal anti-inflammatory drugs-Myth or truth? Review of selected literature. *Pharmacol Res Perspect*. 2021;9(4):e00817. https://doi.org/10.1002/prp2.817

[6] Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther*. 2013;15 Suppl 3(Suppl 3):S3. https://doi.org/10.1186/ar4175

[7] Hijos-Mallada G, Sostres C, Gomollón F. NSAIDs, gastrointestinal toxicity and inflammatory bowel disease. AINE, toxicidad gastrointestinal y enfermedad inflamatoria intestinal. *Gastroenterol Hepatol*. 2022;45(3):215-222. https://doi.org/10.1016/j.gastrohep.2021.06.003

[8] Chan FK. NSAID-associated lower gastrointestinal bleeding: where do we stand?. *Clin Gastroenterol Hepatol*. 2012;10(10):1060-1061. https://doi.org/10.1016/j.cgh.2012.08.001

[9] Park SC, Chun HJ, Kang CD, Sul D. Prevention and management of non-steroidal anti-inflammatory drugs-induced small intestinal injury. *World J Gastroenterol*. 2011;17(42):4647-4653. https://doi.org/10.3748/wjg.v17.i42.4647

[10] Takeuchi K, Satoh H. NSAID-induced small intestinal damage--roles of various pathogenic factors. *Digestion*. 2015;91(3):218-232. https://doi.org/10.1159/000374106

[11] Tawfik AG, Gomez-Lumbreras A, Del Fiol G, et al. Nonsteroidal Anti-Inflammatory Drugs and Risk of Gastrointestinal Bleeding: A Systematic Review and Meta-Analysis. *Clin Pharmacol Ther*. 2026;119(1):46-62. https://doi.org/10.1002/cpt.70054

[12] Utzeri E, Usai P. Role of non-steroidal anti-inflammatory drugs on intestinal permeability and nonalcoholic fatty liver disease. *World J Gastroenterol*. 2017;23(22):3954-3963. https://doi.org/10.3748/wjg.v23.i22.3954

[13] Yuan JQ, Tsoi KK, Yang M, et al. Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. *Aliment Pharmacol Ther*. 2016;43(12):1262-1275. https://doi.org/10.1111/apt.13642

[14] Zhang X, Xiao X, Chen PR, Li YN, Lv XH, Yang JL. Proton Pump Inhibitors Increase the Risk of Nonsteroidal Anti-inflammatory Drug-Related Small-Bowel Injury: A Systematic Review With Meta-analysis. *Clin Transl Gastroenterol*. 2023;14(6):e00588. Published 2023 Jun 1. https://doi.org/10.14309/ctg.0000000000000588

[15] Garegnani L, Oltra G, Burgos MA, et al. Proton pump inhibitors for the prevention of non-steroidal anti-inflammatory drug-induced ulcers and dyspepsia. *Cochrane Database Syst Rev*. 2025;5(5):CD014585. Published 2025 May 8. https://doi.org/10.1002/14651858.CD014585.pub2

[16] Drygała Z, et al. "The Consequences of Long-Term Therapy With Proton Pump Inhibitors". *Journal of Education, Health and Sport*, vol. 53, Jan. 2024, pp. 44-59, https://doi.org/10.12775/JEHS.2024.53.004

[17] Yang M, He M, Zhao M, et al. Proton pump inhibitors for preventing non-steroidal anti-inflammatory drug induced gastrointestinal toxicity: a systematic review. *Curr Med Res Opin*. 2017;33(6):973-980. https://doi.org/10.1080/03007995.2017.1281110

[18] Scally B, Emberson JR, Spata E, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. *Lancet Gastroenterol Hepatol*. 2018;3(4):231-241. https://doi.org/10.1016/S2468-1253(18)30037-2

[19] Ghosh S. Metabolomic Studies for Metabolic Alterations Induced by Non-Steroidal Anti-Inflammatory Drugs: Mini Review. *Biomolecules*. 2021;11(10):1456. Published 2021 Oct 4. https://doi.org/10.3390/biom11101456

[20] Jarupongprapa S, Ussavasodhi P, Katchamart W. Comparison of gastrointestinal adverse effects between cyclooxygenase-2 inhibitors and non-selective, non-steroidal anti-inflammatory drugs plus proton pump inhibitors: a systematic review and meta-analysis. *J Gastroenterol*. 2013;48(7):830-838. https://doi.org/10.1007/s00535-012-0717-6

[21] Lee S, Kim JG, Kim HJ. Efficacy of Aceclofenac and Ilaprazole Combination Therapy versus Celecoxib Monotherapy for Treating NSAID-Induced Dyspepsia in Lumbar Spinal Stenosis Patients. *Medicina (Kaunas)*. 2023;59(7):1307. Published 2023 Jul 14. https://doi.org/10.3390/medicina59071307

[22] Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-

blind, randomised trial. *Lancet*. 2007;369(9573):1621-1626. https://doi.org/10.1016/S0140-6736(07)60749-1

[23] Lin XH, Young SH, Luo JC, et al. Risk Factors for Upper Gastrointestinal Bleeding in Patients Taking Selective COX-2 Inhibitors: A Nationwide Population-Based Cohort Study. *Pain Med*. 2018;19(2):225-231. https://doi.org/10.1093/pm/pnx097

[24] Villa Zapata L, Hansten PD, Panic J, et al. Risk of Bleeding with Exposure to Warfarin and Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review and Meta-Analysis. *Thromb Haemost*. 2020;120(7):1066-1074. https://doi.org/10.1055/s-0040-1710592

[25] Jung YS, Park JH, Park CH. Impact of proton pump inhibitors on the risk of small bowel or colorectal bleeding: A systematic review and meta-analysis. *United European Gastroenterol J*. 2023;11(9):861-873. https://doi.org/10.1002/ueg2.12448

[26] Goldstein JL, Eisen GM, Lewis B, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. *Aliment Pharmacol Ther*. 2007;25(10):1211-1222. https://doi.org/10.1111/j.1365-2036.2007.03312.x

[27] Fujimori S, Hanada R, Hayashida M, Sakurai T, Ikushima I, Sakamoto C. Celecoxib Monotherapy Maintained Small Intestinal Mucosa Better Compared With Loxoprofen Plus Lansoprazole Treatment: A Double-blind, Randomized, Controlled Trial. *J Clin Gastroenterol*. 2016;50(3):218-226. https://doi.org/10.1097/MCG.0000000000000372

[28] Tsujimoto H, Hirata Y, Ueda Y, et al. Effect of a proton-pump inhibitor on intestinal microbiota in patients taking low-dose aspirin. *Eur J Clin Pharmacol*. 2021;77(11):1639-1648. https://doi.org/10.1007/s00228-021-03167-0

[29] Kiecka A, Szczepanik M. Proton pump inhibitor-induced gut dysbiosis and immunomodulation: current knowledge and potential restoration by probiotics. *Pharmacol Rep*. 2023;75(4):791-804. https://doi.org/10.1007/s43440-023-00489-x

[30] Otani K, Tanigawa T, Watanabe T, et al. Microbiota Plays a Key Role in Non-Steroidal Anti-Inflammatory Drug-Induced Small Intestinal Damage. *Digestion*. 2017;95(1):22-28. https://doi.org/10.1159/000452356

[31] Marlicz W, Loniewski I, Grimes DS, Quigley EM. Nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and gastrointestinal injury: contrasting interactions in the stomach and small intestine. *Mayo Clin Proc*. 2014;89(12):1699-1709. https://doi.org/10.1016/j.mayocp.2014.07.015

[32] Endo H, Higurashi T, Hosono K, et al. Efficacy of Lactobacillus casei treatment on small bowel injury in chronic low-dose aspirin users: a pilot randomized controlled study. *J Gastroenterol*. 2011;46(7):894-905. https://doi.org/10.1007/s00535-011-0410-1

[33] Chen X, Gao F, Zhang J. *Lactobacillus* complex capsules ameliorate aspirin-related small intestinal mucosal injury: a prospective, randomized, controlled clinical trial. *Scand J Gastroenterol*. 2022;57(10):1195-1201. https://doi.org/10.1080/00365521.2022.2073184

[34] Edogawa S, Takeuchi T, Kojima Y, et al. Current Topics of Strategy of NSAID-Induced Small Intestinal Lesions. *Digestion*. 2015;92(2):99-107. https://doi.org/10.1159/000437395

[35] Teutsch B, Boros E, Váncsa S, et al. Mucoprotective drugs can prevent and treat nonsteroidal anti-inflammatory drug-induced small bowel enteropathy: a systematic review and meta-analysis of randomized controlled trials. *Ther Adv Gastroenterol*. 2021;14:17562848211038772. Published 2021 Sep 30. https://doi.org/10.1177/17562848211038772

[36] Taha AS, McCloskey C, McSkimming P, McConnachie A. Misoprostol for small bowel ulcers in patients with obscure bleeding taking aspirin and non-steroidal anti-inflammatory drugs (MASTERS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2018;3(7):469-476. https://doi.org/10.1016/S2468-1253(18)30119-5

[37] Rácz I, Szalai M, Kovács V, Regőczi H, Kiss G, Horváth Z. Mucosal healing effect of mesalazine granules in naproxen-induced small bowel enteropathy. *World J Gastroenterol*. 2013;19(6):889-896.https://doi.org/10.3748/wjg.v19.i6.889