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LETTER TO THE EDITOR

Critical analysis of the effects of proton pump inhibitors on inflammatory bowel disease: An updated review

Omesh Goyal, Manjeet Kumar Goyal

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Abstract

This letter critically evaluates the effects of proton pump inhibitors (PPIs) on inflammatory bowel disease, particularly focusing on Crohn's disease (CD) and ulcerative colitis (UC), as discussed in Liang *et al*'s recent review. While the review provides significant insights, it relies heavily on cross-sectional and observational studies, which limits the ability to draw causal inferences. The heterogeneous study populations and inconsistent definitions of long-term PPI use further complicate the findings. This letter also highlights the need for rigorous control of confounding factors and considers the potential publication bias in the existing literature. The implications of these issues are discussed in the context of both CD and UC, and future research directions are proposed to address these shortcomings.

Key Words: Proton pump inhibitors; Inflammatory bowel disease; Gut microbiota; Intestinal mucosal barrier; Immune cell function

Core Tip: This letter critically analyzes the review by Liang *et al* on the effects of proton pump inhibitors (PPIs) on inflammatory bowel disease (IBD), highlighting several methodological flaws. Reliance on cross-sectional and observational studies limits causal inference, and heterogeneous study populations complicate result interpretation. Furthermore, inconsistent definitions of long-term PPI use, inadequate control for confounding factors, and potential publication bias necessitate cautious interpretation. Future research should prioritize large-scale, prospective cohort studies with rigorous control for confounders, standardized outcome measures, and transparent study selection criteria. Addressing these issues is essential for guiding clinical practice effectively and improving outcomes in IBD management.

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TO THE EDITOR

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), represents a significant clinical challenge due to its chronic and relapsing nature. The role of proton pump inhibitors (PPIs) in influencing the course of IBD has garnered attention, as highlighted in the recent review by Liang *et al*[1]. This letter aims to provide a critical analysis of the conclusions drawn by Liang *et al*[1], emphasizing the methodological limitations of the studies included in their review and the implications for clinical practice particularly.

Liang *et al*[1] discuss the potential role of PPIs in exacerbating IBD extensively, with a particular focus on how these medications might affect the gastrointestinal microbiota. Their review suggests that PPI-induced changes in gastric pH could foster an environment conducive to the growth of pathogenic bacteria, which may, in turn, influence the inflammatory processes characteristic of IBD. However, the review predominantly relies on cross-sectional and observational studies, which inherently limits the ability to establish causal relationships. The absence of longitudinal data in many of the studies reviewed makes it difficult to determine whether PPI use is a contributing factor to the onset or worsening of IBD or merely a correlate of other underlying conditions that predispose individuals to these diseases.

One of the major limitations of Liang *et al*'s review is the lack of distinction between CD and UC in their analysis[1]. CD and UC, while both falling under the umbrella of IBD, have distinct pathophysiological mechanisms and clinical manifestations. The review's broad approach to IBD overlooks these differences, potentially obscuring the nuanced effects that PPIs might have on each condition. For instance, the role of the gut microbiota in CD, which often affects the entire gastrointestinal tract, may differ significantly from its role in UC, which is typically confined to the colon. A more granular analysis that separately considers the impact of PPIs on CD and UC would provide clearer insights and better guidance for clinical decision-making.

Further complicating the interpretation of Liang *et al*'s findings is the heterogeneity of the study populations included in their review[1]. The studies they critique involve diverse patient groups with varying degrees of disease severity, PPI dosages, and durations of use. This variability makes it challenging to draw definitive conclusions about the relationship between PPI use and IBD outcomes. For example, in the context of UC, the cohort study by Fossmark *et al*[2] offers a more rigorous approach. This study included over 10000 newly diagnosed UC patients in Norway and found that PPI use was associated with an increased risk of starting advanced therapies or systemic glucocorticoids, or undergoing colectomy[3]. These findings suggest a potentially significant impact of PPIs on the disease course in UC, a nuance that is not fully captured in Liang *et al*'s broader review[1].

Moreover, the methodological shortcomings of the studies included in Liang *et al*'s review are not adequately addressed[1]. For instance, while the review references the meta-analysis by Shastri *et al*[4], it fails to provide sufficient detail on the research methods or data sources of that meta-analysis. Shastri *et al*[4] had conducted a comprehensive statistical evaluation, incorporating data from eight observational studies with a total of 157758 participants. Their analysis found a significant association between PPI use and an increased risk of IBD, with substantial heterogeneity across the included studies. However, the connection between this meta-analysis and Liang *et al*'s conclusions remains underexplored, particularly in how the findings from Shastri *et al*[3] either support or challenge the original review's assertions[1].

The implications of these methodological issues are significant. Without a clear understanding of the study designs and populations involved, it is difficult to assess the reliability of the conclusions drawn by Liang *et al*[1]. Furthermore, the potential for publication bias—where studies showing a significant association between PPI use and IBD are more likely to be published—adds another layer of complexity. This bias could lead to an overestimation of the risks associated with PPI use in IBD patients, further complicating clinical decision-making.

Looking forward, it is clear that more robust research is needed to clarify the relationship between PPIs and IBD. Future studies should prioritize longitudinal designs that can better establish causality and should focus on large, homogeneous patient cohorts to reduce variability in the findings. It is also essential that future research distinguishes between CD and UC in its analysis, given the differences in disease mechanisms and responses to treatment. Such studies should also implement rigorous control for confounding factors, such as concurrent medication use and underlying health conditions, which could independently influence IBD outcomes.

In conclusion, while Liang *et al*[1] provide valuable insights into the potential risks associated with PPI use in IBD patients, their conclusions are limited by significant methodological flaws. The reliance on heterogeneous study populations and inconsistent definitions of PPI use, combined with the lack of distinction between CD and UC, limit the applicability of their findings. Future research should focus on addressing these limitations through more rigorous study designs, which are essential to better understand the relationship between PPIs and IBD and to guide clinical practice effectively[5].

FOOTNOTES

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