A Systematic Literature Review of the Effect of Proton-Pump Inhibitors on Gallbladder Function

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Abstract

Objective: The objective of the study was to determine the association between proton-pump inhibitors (PPIs) and gallbladder (GB) function. **Methods:** A systematic search of Medline, EMBASE, and CENTRAL (inception to April 2020) was conducted to capture the relevant studies. A comprehensive inclusion-exclusion criterion was developed and implemented to screen the titles and abstracts. Full texts of the selected abstracts were then appraised to establish their inclusion or exclusion in our review. The primary outcome was GB ejection fraction. We intended to extract study data from eligible studies into a data extraction form and evaluate the quality of the included studies using the best available guidelines for each study design outlined in the library for health research reporting. We, however, found no eligible studies. **Results:** The systematic search identified 38 unique articles for title and abstract screening. Of which, five were included as potentially relevant studies. However, upon full-text screening, none of them met our inclusion criteria. This review is, therefore, an empty systematic review. **Conclusion:** There are no good quality studies determining the effect of PPIs on GB function. Given the common use of PPIs and their potential impact on GB function, there is an urgent need for conducting clinical studies to address this gap in the evidence.

Keywords: Gallbladder ejection fraction, Gallbladder emptying rate, Gallbladder function, Proton-pump inhibitors

Introduction

Gallbladder (GB) disease is one of the most common illnesses of the digestive system around the globe and is a significant source of the economic drain in many nations.[1] Patients with intermittent right upper quadrant (RUQ) abdominal pain generally undergo an ultrasound to rule out gallstones. However, hepatobiliary iminodiacetic acid scan (HIDA) with cholecystokinin stimulation is used to assess the function of the GB and biliary tree, if the diagnosis could not be formed by ultrasound. HIDA scan measures GB emptying rate also called ejection fraction of the GB (GBEF). An accepted normal functioning GBEF is >35% and typically ranges between 35% and 65%. However, an ejection fraction below 35% indicates GB motility disorder called biliary dyskinesia or hypokinesia of the GB.[2]

The human liver produces at least 1000 ml of bile per day, but standard bile duct flow rates are low during fasting (0.5–1.0 ml/min), they increase after a meal to between 2 and 3 ml/min.[3] The inability of GB to release bile into the small intestine not only affects fats digestion but also irritates GB walls. This irritation results in inflammation which causes a majority of GB diseases, including cholecystitis and gallstones.[4] Hence, GBEF is one of the primary tests to understand GB disorders.

Health practitioners use various tests to form the diagnosis. The widely accepted diagnosis of biliary dyskinesia is comprised of vague RUQ pain in the absence of gallstones or with GB wall thickening and an abnormally low GBEF on HIDA scan. This scan shows the movement of the bile through the bile duct system and measures the GB emptying rate.[5]

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Medkrux

Proton-pump inhibitors (PPIs) are a group of medications that reduce the production of stomach acid. PPIs are largely used to treat symptoms of gastroesophageal reflux disease (GERD) and are considered the most effective treatment of GERD.[6] Morton *et al*. (2002) conducted a study to compare pre- and post-operative GB function in patients undergoing fundoplication to understand the association between GERD or its therapies and GB function. The authors unexpectedly found that approximately 60% of patients with pre-operative GER had abnormally low GB function. More surprisingly, 86% of these patients had normalized GB function after fundoplication.[7] This discovery led Cahan *et al*. (2006) to conduct a trial to determine whether GB function is reduced by chronic PPI therapy. Although the authors found some evidence to support their hypothesis, this evidence alone may be insufficient to determine the direct associations between PPIs and GB function. There is no systematic review to summarize the evidence on the association between GB function and PPIs. We are, therefore, conducting this systematic review to identify the studies indicating the association PPIs and GB function.

Objectives

There were two objectives of this systematic review:

- To determine the association between PPIs and GB function
- To highlight the gap in the evidence.

Methods

This systematic review was conducted to summarize the evidence describing the effect of PPIs on GB function. We followed PRISMA reporting guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for this systematic literature review.[8] We aimed to apply a rigorous and transparent methodology to reduce bias in the selection of relevant studies.

Criteria for considering studies for this review

Eligibility criteria

Eligibility criteria for including studies for this systematic literature review were as follows:

Type of studies

All published randomized and non-randomized clinical trials, including cluster and cross-over trials, were eligible for inclusion in this systematic review. In addition to this, analytical observational studies including prospective and retrospective cohort studies, prospective and retrospective case–control studies, cross-sectional studies, controlled before-and-after studies, and systematic reviews were also eligible for inclusion. Systematic reviews were included for cross-referencing. We, however, excluded single-arm studies, letters to the editor, narrative reviews, editorials, expert opinions, case studies, and case series.

Minimum study duration

Studies of any duration were eligible for inclusion in this systematic review.

Publication language

Studies published in English language were eligible for inclusion in this review.

Types of participants

Studies conducted in any population were included in this review without any restrictions.
No age limits were applied.

Types of interventions

Studies comparing the effect of PPIs and placebo or any other intervention on GBEF and GB function were included in this systematic review.

Outcomes

The primary outcome was GBEF. The secondary outcomes were any abnormal functioning of GB due to the effect of PPIs.

Data sources and search strategy

We systematically searched three databases; Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) for this review. Medline and EMBASE were searched through ProQuest while CENTRAL was searched through Cochrane library. All three databases were searched from inception to April 2020 to retrieve the relevant literature. Our core search strategy was based on the keywords extracted from relevant articles, Medical Subject Headings, and the controlled vocabulary used by each database. The search strategy used for Medline, EMBASE, and Cochrane is reported in the Supplementary Materials [Table 1] and was constructed from

Table 1: Search strategy for Medline and EMBASE

Set#	Searched for	Databases	Results
S1	(MESH.EXACT.EXPLODE("Gallbladder Emptying"))	MEDLINE®	717°
S2	(ti,ab("gallbladder ejection fraction" or "GBEF" or "gallbladder function" or "gallbladder motor dysfunction" or "gallbladder motor function" or "gallbladder disorder" or "gallbladder disorders" or "gallbladder disease" or "gallbladder problem" or "gallbladder emptying" or "gallbladder"))	MEDLINE®	32145*
S3	(MESH.EXACT.EXPLODE("Biliary Dyskinesia"))	MEDLINE®	**1240**°
S4	(ti,ab("biliary dyskinesia" or "gallbladder spasm" or "chronic acalculous cholecystitis"))	MEDLINE®	**541**°
S5	S4 OR S3 OR S2 OR S1	MEDLINE®	32256*
S6	((MESH.EXACT.EXPLODE("Proton-Pump Inhibitors")))	MEDLINE®	18623*
S7	(ti,ab("omeprazole" or "Prilosec" or "Prilosec OTC" or "aspirin and omeprazole" or "Yosprala" or "lansoprazole" or "Prevacid" or "Prevacid IV" or "Prevacid 24-h" or "dexlansoprazole" or "Dexilent" or "Dexilent Solutab" or "rabeprazole" or "Aciphex" or "Aciphex Sprinkle" or "pantoprazole" or "Protonix" or "esomeprazole" or "Nexium" or "Nexium IV" or "Nexium 24 HR" or "esomeprazole magnesium" or "naproxen" or "Vimovo" or "omeprazole" or "sodium bicarbonate" or "Zegerid" or "Zegerid OTC" or "proton-pump inhibitor" or "proton-pump inhibitors" or "PPI" or "PPIs" or "antisecretory agents" or "antisecretory"))	MEDLINE®	50012*
S8	S7 OR S6	MEDLINE®	53972*
S9	((MESH.EXACT("clinical trial (topic)") OR MESH.EXACT("controlled clinical trial") OR MESH.EXACT("clinical trial") OR MESH.EXACT("controlled clinical trial (topic)") OR MESH.EXACT("cohort analysis") OR MESH.EXACT("population-based case–control study") OR MESH.EXACT("hospital-based case–control study") OR MESH.EXACT("case–control study") OR MESH.EXACT("multicenter study (topic)") OR MESH.EXACT("multicenter study") OR MESH.EXACT("retrospective study") OR MESH.EXACT("systematic review (topic)") OR MESH.EXACT("systematic review") OR MESH.EXACT("meta-analysis") OR MESH.EXACT("meta-analysis (topic)") OR MESH.EXACT("prospective study")) OR (ti,ab("randomized controlled trial" or "randomized controlled trial" or "randomization" or "randomization" or "randomized control*" or "rct" or "single blind*" or "double blind*") or ti,ab((single OR double OR treb$ OR tripl$) NEAR/2 (blind* OR mask)) or ti,ab("phase 1 clinical trial" or "phase 2 clinical trial" or "phase 3 clinical trial" or "phase 4 clinical trial") or ti,ab("phase 1" or "phase 1" or "phase ii" or "phase 2" or "phase iii" or "phase 3" or "phase iv" or "phase 4") or ti,ab(allocat* NEAR/3 random*) or ti,ab(random* NEAR/4 (trial* OR stud*)) or ti,ab("clinical trial" or "meta-analysis" or "multicenter study" or "multicenter study" or "prospective study"))) NOT ((MESH.EXACT("case study")) OR MESH.EXACT("letter") OR MESH.EXACT("editorial") OR (ti,ab("case study" or "letter" or "editorial")))	MEDLINE®	1016780*
S10	(S8 AND S9 AND S5) and (human(yes)) and (la.exact("English"))	MEDLINE®	7°
S11	((EMB.EXACT.EXPLODE("gallbladder emptying")))	EMBASE®	837°
S12	((ti,ab("gallbladder ejection fraction" or "GBEF" or "gallbladder function" or "gallbladder motor dysfunction" or "gallbladder motor function" or "gallbladder disorder" or "gallbladder disorders" or "gallbladder disease" or "gallbladder problem" or "gallbladder emptying" or "gallbladder")))	EMBASE®	44790*
S13	(EMB.EXACT.EXPLODE("Biliary Dyskinesia"))	EMBASE®	4°
S14	(ti,ab("biliary dyskinesia" or "gallbladder spasm" or "chronic acalculous cholecystitis"))	EMBASE®	747°

(Contd...)

Table 1:*(Continued)*

Set#	Searched for	Databases	Results
S15	S11 OR S12 OR S13 OR S14	EMBASE®	45400*
S16	((EMB.EXACT.EXPLODE("proton-pump inhibitor")))	EMBASE®	78283*
S17	(((ti,ab("omeprazole" or "Prilosec" or "Prilosec OTC" or "aspirin and omeprazole" or "Yosprala" or "lansoprazole" or "Prevacid" or "Prevacid IV" or "Prevacid 24-h" or "dexlansoprazole" or "Dexilent" or "Dexilent Solutab" or "rabeprazole" or "Aciphex" or "Aciphex Sprinkle" or "pantoprazole" or "Protonix" or "esomeprazole" or "Nexium" or "Nexium IV" or "Nexium 24 HR" or "esomeprazole magnesium" or "naproxen" or "Vimovo" or "omeprazole" or "sodium bicarbonate" or "Zegerid" or "Zegerid OTC" or "proton-pump inhibitor" or "proton-pump inhibitors" or "PPI" or "PPIs" or "antisecretory agents" or "antisecretory"))))	EMBASE®	77510*
S18	S17 OR S16	EMBASE®	118411*
S19	(EMB.EXACT("clinical trial (topic)") OR EMB.EXACT("controlled clinical trial") OR EMB.EXACT("clinical trial") OR EMB.EXACT("controlled clinical trial (topic)") OR EMB.EXACT("cohort analysis") OR EMB.EXACT("population-based case–control study") OR EMB.EXACT("hospital-based case–control study") OR EMB.EXACT("case–control study") OR EMB.EXACT("multicenter study (topic)") OR EMB.EXACT("multicenter study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("systematic review (topic)") OR EMB.EXACT("systematic review") OR EMB.EXACT("meta-analysis") OR EMB.EXACT("meta-analysis (topic)") OR EMB.EXACT("prospective study")) OR (ti,ab("randomized controlled trial" or "randomized controlled trial" or "randomization" or "randomization" or "randomized control*" or "rct" or "single blind*" or "double blind*") or ti,ab((single OR double OR treb$ OR tripl$) NEAR/2 (blind* OR mask)) or ti,ab("phase 1 clinical trial" or "phase 2 clinical trial" or "phase 3 clinical trial" or "phase 4 clinical trial") or ti,ab("phase 1" or "phase i" or "phase ii" or "phase 2" or "phase iii" or "phase 3" or "phase iv" or "phase 4") or ti,ab(allocat* NEAR/3 random*) or ti,ab(random* NEAR/4 (trial* OR stud*)) or ti,ab("clinical trial" or "meta-analysis" or "multicenter study" or "multicenter study" or "prospective study")) NOT ((EMB.EXACT("case study")) OR EMB.EXACT("letter") OR EMB.EXACT("editorial") OR (ti,ab("case study" or "letter" or "editorial")))	EMBASE®	4070093*
S20	(S15 AND S18 AND S19) and (human(yes)) and (la.exact("English"))	EMBASE®	32°
S21	S20 OR S10	EMBASE®, MEDLINE® These databases are searched for part of your query	34°

*Duplicates are removed from the search, but included in the result count. °Duplicates are removed from the search and from the result count. With duplicates=41

search terms relating to GB function to PPIs. The search was narrowed by applying filters to limit the studies only to the English language and human. The bibliographies of relevant studies were also screened to identify other relevant studies. The search results were downloaded and imported in reference management software "Zotero."

Study selection

The studies were screened in abstract screening software "Rayyan QCRI"[9] by two researchers by title and abstracts, and discrepancies were resolved through discussion. Primary research studies and systematic reviews relevant to PPIs and GB function, reporting the effects of anti-secretary drugs on GB

motility and published in English, were included in our research. The inclusion and exclusion criteria are reported in full in Table 2 in Supplementary Materials.

The full texts were retrieved for all studies that met the inclusion criteria for the title and abstract screening. Full texts were screened using the same inclusion criteria as abstract screening but focused on identifying studies with clinically relevant outcomes. Two researchers independently conducted full-text screening and resolved the disagreements through discussion.

Data extraction

We planned to extract the relevant data into a pre-agreed Microsoft Excel template and resolve any disagreements by discussion. Where available, we planned to extract the following data for each eligible study:

1. Study details: Study name, study design, year of publication, study duration, study setting, country, recruitment method, number of study centers, and inclusion and exclusion criteria
2. Participants characteristics: Age, sex, ethnicity, body weight, concomitant diseases, and the number of subjects in the intervention and control group
3. Interventions: Description of intervention and control treatment, dosage, regimen, and any concomitant medications
4. Outcomes: Primary and secondary outcomes specified and collected, time points reported, number of subjects with follow-up data, statistical analyses data, and adverse effects data.

We planned to evaluate the methodological quality of the included studies using the best available guidelines for each study design outlined in the library for health research reporting.[10] We planned to conduct a descriptive analysis from the included studies and synthesize the results narratively to identify common themes and gaps in the evidence.

Results

The database search of EMBASE, Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) identified 44 citations, of which 6 were duplicates, leaving 38 unique citations for screening [Table 3]. Two independent reviewers (MJ and MST) screened the titles and abstracts against the eligibility criteria shown in Table 2. Discrepancies were resolved through discussion. We assessed five full-text articles for eligibility using the same inclusion and exclusion criteria but found none to be eligible for inclusion into our review [Figure 1]. The reasons for exclusion are provided in the PRISMA flow diagram. Articles excluded based on full-text screening are listed in Table 4.

Table 2: Identification and inclusion/exclusion of studies

Description	Inclusion	Exclusion
Patient population	• Adult and/or pediatric patients with poor GBEF (reduced gallbladder function)	• Patients with other diseases • Animal/*in vitro* studies
Intervention	PPIs	All other interventions
Comparator	Any or none	N/A
Outcomes	• Gallbladder ejection function • Biliary-type pain • Blood tests, including serum alanine aminotransferase, aspartate aminotransferase, conjugated and unconjugated bilirubin, alkaline phosphatase, amylase, and lipase	
Study design	• Randomized controlled trials • Non-randomized studies • Cohort studies • Case–control studies • Cross-sectional studies • SLRs/NMAs[a]	• Editorials • Case studies • Letters
Limits	English language only; human only	
Timespan	No limits; all databases were searched from inception to April 30, 2020.	

[a]Relevant SLRs and NMAs will be ordered and included study lists will be reviewed, to identify any additional relevant publications

Discussion

This is an empty systematic review as none of the studies met the eligibility criteria for inclusion in this review. However, we did identify one study single-arm study conducted in 2006 to determine the effect of chronic PPI therapy on GB function.[11] The authors enrolled 21 healthy subjects for a 30 days trial by advertising in the newspaper and a university campus. Nineteen subjects completed the study. The investigators measured GBEF of each subject before commencing 40 mg once daily omeprazole. The GBEF was measured again on day 30. The authors concluded that PPI therapy was associated with reduced GB motility in healthy volunteers. Although this study provides some indication of the association between PPI and GB dysfunction, this study is subjected to high risk of bias and has several flaws including small sample size, no comparison group, short study duration, no randomization, and no blinding. In addition to the above, the study subjects were selected by advertising in the newspaper and on campus, which make this population less representative of the target population.

GB motility is vital for the health of the digestive system. Low GBEF causes irritation and inflammation of the GB walls, which, in turn, can lead to serious diseases including GB cancer. Hence, it is essential to maintain the GB health. PPIs are commonly used to treat GERD. There is significant

Table 3: Total number of studies identified from database searches

Source	Number of hits	Total after deduplication
Medline	7	38
EMBASE	32	
Central	5	

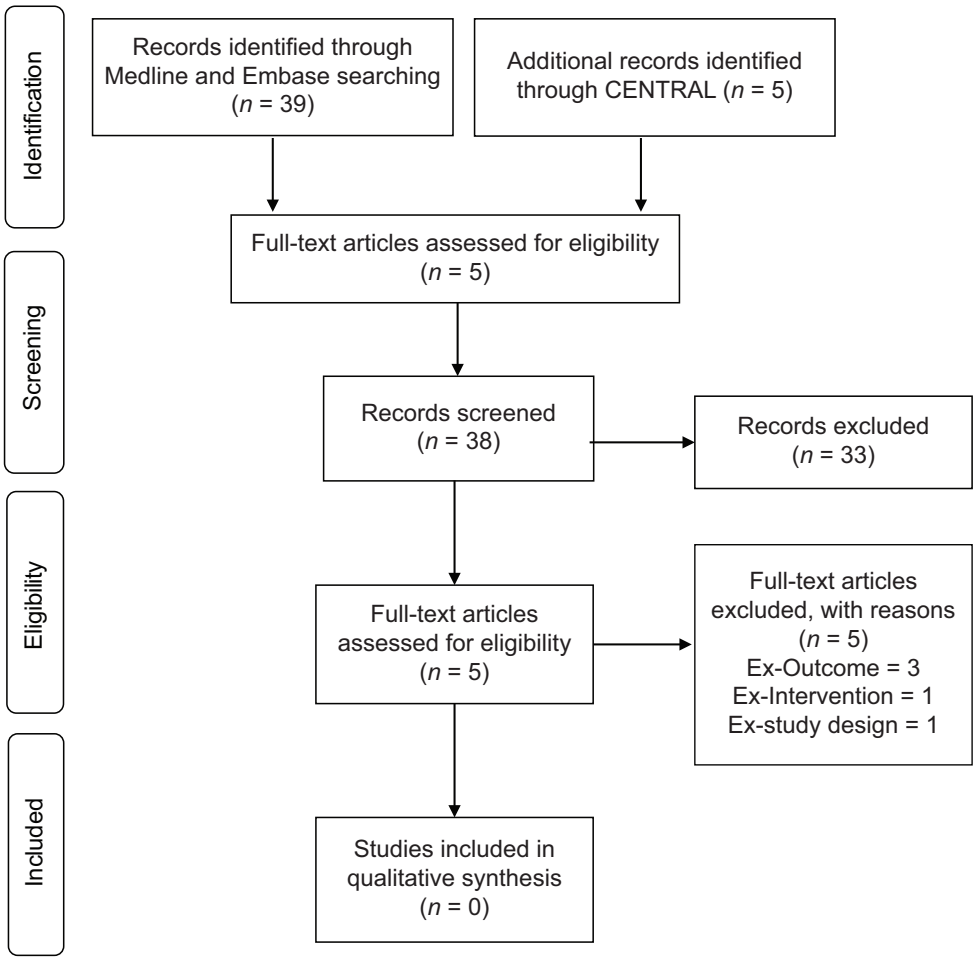

Figure 1: PRISMA flow diagram

Table 4: Articles excluded based on full text with reasons

Reference	Reason for exclusion
Cahan MA, Balduf L, Colton K, Palacioz B, McCartney W, Farrell TM. Proton pump inhibitors reduce gallbladder function. Surg Endosc 2006;20:1364-7.	Study design out of scope
Xiong J, Wang Y, Chen G, Jin L. Proton pump inhibitors and the risk of gallbladder cancer: A hospital-based case-control study. Gut 2020;69:2265-7.	Outcome out of scope
Rasmussen L, Qvist N, Oster-Jorgensen E, Rehfeld JF, Holst JJ, Pedersen SA. A double-blind placebo-controlled study on the effects of omeprazole on gut hormone secretion and gastric emptying rate. Scand J Gastroenterol 1997;32:900-5.	Outcome out of scope
Kapicioglu S, Baki AH, Arslan M, Cetiner M, Cihanyurdu N. Effect of omeprazole on gallbladder contraction in humans. Hepatogastroenterology 2000;47:346-8.	Intervention out of scope
Santucci N, Hussain SZ, Harmon CM, Hyman PE. Biliary dyskinesia in children: A systematic review. J Pediatr Gastroenterol Nutr 2016;63:S95-6.	Outcome out of scope

evidence that change in lifestyle can improve GERD symptoms.[12] However, the patients who require PPIs should receive the lowest effective dose[13] and that combining lifestyle interventions with PPIs provide better results.[14] Evidence suggests that most patients receiving twice-daily PPI therapy for GERD could be maintained on once-daily PPI or no acid suppression for 12 months of follow-up.[15] In addition to this, the use of right PPI for specific symptoms would not only treat GERD more efficiently but will also reduce the economic burden on national health care. For instance, Javed *et al*. (2020)[6] reported that omeprazole lowered intragastric pH faster and the results lasted longer compared to lansoprazole.[16] The results were statistically significant; hence, it is advisable to administer omeprazole to GERD patients if the objective is to lower intragastric pH unless recommended otherwise by the physician.

We are confident that our search strategy was comprehensive, and we identified all the relevant literature. We did not apply any age limits and incorporated a variety of study designs in a bid to retrieve all relevant publications; however, none of the studies met the inclusion criteria. Far less research has been carried out to understand the effect of PPIs on GB function. Hence, there is an urgent need to design and conduct high-quality clinical studies to determine the association of various PPIs and GBEF.

Conclusion

There are no good quality studies determining the effect of PPIs on GB function. Given the common use of PPIs and their potential impact on GB function, there is an urgent need of conducting clinical studies to fill this gap in the literature.

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Supplementary Material

Search terms for Cochrane Library were “gallbladder” AND “proton-pump inhibitor*” retrieved 5 articles. All three databases were searched from inception to April 30, 2020.