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IMPACT OF LONG-TERM USE OF PROTON PUMP INHIBITOR ON GLYCEMIC CONTROL IN ADULT PATIENT WITH T2DM WHO SUFFER FROM HEARTBURNING: SYSTEMIC REVIEW

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) and gastroesophageal reflux disease frequently coexist, leading to prolonged proton pump inhibitor (PPI) use. However, the impact of long-term PPI therapy on glycemic control remains unclear due to conflicting evidence. This systematic review aimed to evaluate the effect of long-term PPI use on glycemic control in adult T2DM patients with heartburn.
Methods: A systematic review was conducted following PRISMA guidelines. A comprehensive literature search was performed in PubMed and reference lists up to 2024. Eligible studies included observational designs (cohort, case-control, cross-sectional) and randomized controlled trials (RCTs) involving adults with T2DM and heartburn, comparing long-term PPI use (≥12 weeks) versus no or short-term use. Outcomes included HbA1c, fasting plasma glucose (FPG), and diabetes incidence. Two independent reviewers performed study selection, data extraction, and risk of bias assessment using the Newcastle-Ottawa Scale and JBI checklists. A narrative synthesis was conducted.
Results: Ten studies (approximately 145,000 patients) met the inclusion criteria. Short-term PPI use (≤6 months), particularly pantoprazole, was associated with modest HbA1c reductions (0.2%–0.8%). However, five studies (50%) reported no significant glycemic changes with long-term use (>1 year). Notably, prolonged PPI use (>2 years) was associated with a 24% increased risk of new-onset diabetes (OR 1.24; 95% CI 1.15–1.34) in one large case-control study. Overall, the evidence indicated that PPIs produce no clinically significant or sustained glycemic improvement, with long-term use showing neutral to potentially adverse metabolic effects.
Conclusion: Long-term PPI use does not provide consistent or clinically meaningful improvements in glycemic control in T2DM patients with heartburn. While short-term therapy may yield transient, modest benefits, prolonged use offers no sustained advantage and may carry metabolic risks. PPIs should be prescribed based on gastrointestinal indications, not for glycemic management.

KEYWORDS: Proton pump inhibitors, glycemic control, type 2 diabetes mellitus, heartburn, gastroesophageal reflux disease, HbA1c, long-term use

BACKGROUND

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to persistent hyperglycemia. It represents a major global health burden due to its increasing prevalence and its association with serious complications affecting multiple organ systems. Effective glycemic control remains the cornerstone of diabetes management to reduce the risk of both microvascular and macrovascular complications (Ciardullo et al., 2022).
In addition to metabolic disturbances, patients with T2DM frequently present with gastrointestinal disorders, particularly symptoms related to acid reflux and heartburn. These symptoms are commonly linked to gastroesophageal reflux disease, which has been observed to occur more frequently among diabetic individuals due to autonomic neuropathy, delayed gastric emptying, and altered gastrointestinal motility (Trang et al., 2021).
Proton pump inhibitors (PPIs) are among the most widely prescribed medications for the management of acid-related disorders, including heartburn and gastroesophageal reflux disease. They act by irreversibly inhibiting the hydrogen-potassium ATPase enzyme system in gastric parietal cells, leading to a significant reduction in gastric acid secretion.

Their effectiveness and relatively favorable safety profile have contributed to their widespread and often long-term use (Lv et al., 2024).

Long-term use of PPIs has become increasingly common, particularly in patients with chronic gastrointestinal symptoms. However, concerns have emerged regarding the potential systemic effects of prolonged PPI therapy. These concerns include nutrient malabsorption, alterations in gut microbiota, and possible metabolic consequences that may extend beyond the gastrointestinal tract (Saboo et al., 2023).

Emerging evidence suggests that PPIs may influence glucose metabolism through several potential mechanisms. One proposed mechanism involves the elevation of serum gastrin levels, which may stimulate pancreatic beta-cell activity and insulin secretion. This interaction raises the possibility that PPIs could have a modulatory effect on glycemic control in patients with T2DM (Villegas et al., 2019).

Conversely, other studies have suggested that long-term PPI use may be associated with adverse metabolic outcomes, potentially contributing to worsened glycemic control. These conflicting findings highlight the complexity of the relationship between PPI use and glucose homeostasis, and they underscore the need for a comprehensive evaluation of the available evidence (Sattaru et al., 2025).

Patients with T2DM who suffer from heartburn represent a unique subgroup in which both conditions frequently coexist, leading to prolonged exposure to PPIs. In such patients, understanding the impact of chronic PPI use on glycemic control is particularly important, as it may influence therapeutic decisions and long-term disease management strategies (Kumar et al., 2024).

Despite the growing body of literature, the evidence regarding the effect of long-term PPI use on glycemic control remains inconsistent and fragmented. Differences in study design, population characteristics, duration of PPI use, and outcome measures have contributed to variability in findings, making it difficult to draw definitive conclusions (Burmeister et al., 2023).

Systematic reviews play a crucial role in synthesizing existing evidence and identifying patterns, gaps, and inconsistencies in research findings. By systematically collecting and analyzing data from multiple studies, a more comprehensive understanding of the relationship between PPI use and glycemic control can be achieved (Herdiana, 2023).

Given the high prevalence of both T2DM and heartburn, and the widespread use of PPIs, it is essential to clarify whether long-term PPI therapy has a beneficial, neutral, or detrimental effect on glycemic control. Such insights could have important clinical implications for optimizing treatment strategies in this patient population (Rajput et al., 2020).

This research aimed to systematically evaluate the impact of long-term use of proton pump inhibitors on glycemic control in adult patients with Type 2 Diabetes Mellitus who suffer from heartburn.

METHODOLOGY

Study Design

This study was conducted as a systematic review aimed at evaluating the impact of long-term use of proton pump inhibitors (PPIs) on glycemic control in adult patients with Type 2 Diabetes Mellitus who suffer from heartburn. A structured and transparent approach was followed to identify, select, and critically appraise relevant studies, ensuring a comprehensive synthesis of the available evidence.

Review Protocol and Reporting Guidelines

The methodology of this systematic review was developed in accordance with established guidelines for systematic reviews. The review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure clarity, transparency, and reproducibility in reporting. A predefined protocol guided all stages of the review process, including study selection, data extraction, and data synthesis.

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies included observational designs such as cohort studies, case-control studies, and cross-sectional studies that investigated adult patients aged 18 years or older diagnosed with Type 2 Diabetes Mellitus and experiencing heartburn symptoms.

Studies were included if they assessed long-term use of proton pump inhibitors, defined as continuous use for at least 12 weeks or as specified by individual studies. The comparison group consisted of patients not using PPIs or those using PPIs for a short duration of less than 12 weeks. Included studies were required to report outcomes related to glycemic control, such as HbA1c levels, fasting blood glucose, or other relevant indicators.

Studies were excluded if they involved patients with Type 1 Diabetes Mellitus, gestational diabetes, or pediatric populations. Randomized controlled trials, systematic reviews, meta-analyses, case reports, editorials, letters, animal studies, and in vitro studies were also excluded. Additionally, non-English publications and studies lacking relevant glycemic outcomes were not considered.

Information Sources

A comprehensive literature search was conducted using electronic databases. PubMed was used as the primary database to identify relevant studies. In addition, manual searches of the reference lists of included articles were performed to ensure that all relevant studies were captured.

Search Strategy

A structured search strategy was developed using a combination of keywords and Medical Subject Headings (MeSH) terms related to proton pump inhibitors, glycemic control, Type 2 Diabetes Mellitus, and heartburn or gastroesophageal reflux disease. Boolean operators such as AND and OR were used to combine search terms effectively.

The search strategy included terms related to proton pump inhibitors such as omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, and dexlansoprazole. Terms related to glycemic control included HbA1c, fasting blood glucose, and blood glucose levels. Additional terms included heartburn, gastroesophageal reflux disease, and long-term or chronic use.

Study Selection

All identified records were imported into reference management software, and duplicate studies were removed. The selection process was conducted in two stages. In the first stage, titles and abstracts were screened independently by two reviewers based on the eligibility criteria. In the second stage, full-text articles of potentially relevant studies were retrieved and assessed for inclusion.

Disagreements between reviewers were resolved through discussion, and when necessary, consultation with a third reviewer was undertaken to reach consensus.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted data included study characteristics such as author, year of publication, country, and study design. Participant characteristics, including sample size, age, gender, duration of diabetes, and severity of heartburn, were also recorded.

Details regarding PPI use, including type, dosage, and duration of therapy, were collected. Outcome measures related to glycemic control, such as HbA1c levels, fasting blood glucose, and any reported changes from baseline, were documented. Information on potential confounding factors, including concurrent medications, lifestyle factors, and comorbid conditions, was also extracted.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were assessed using validated tools. Cohort and case-control studies were evaluated using the Newcastle-Ottawa Scale, while cross-sectional studies were assessed using the Joanna Briggs Institute critical appraisal checklist.

Two reviewers independently performed the risk of bias assessment, and discrepancies were resolved through discussion or by involving a third reviewer. The overall quality of evidence was considered during data interpretation.

Data Synthesis

A narrative synthesis of the findings was conducted to summarize and interpret the results of the included studies. Studies were grouped based on similarities in study design, population characteristics, duration of PPI use, and outcome measures.

Where sufficient homogeneity existed among studies in terms of design and outcomes, quantitative synthesis in the form of meta-analysis was considered. Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test. When meta-analysis was not feasible, findings were presented descriptively.

Assessment of Heterogeneity

Heterogeneity among studies was evaluated based on clinical, methodological, and statistical differences. Variations in participant characteristics, duration of PPI exposure, and outcome measurement methods were carefully examined. Statistical heterogeneity was quantified using appropriate statistical methods, and potential sources of heterogeneity were explored.

Ethical Considerations

As this study involved the analysis of previously published data, ethical approval was not required. However, the review was conducted in accordance with ethical standards for research, ensuring accurate reporting, transparency, and proper acknowledgment of original sources.

Dissemination of Findings

The findings of this systematic review were prepared for publication in a peer-reviewed scientific journal and may be presented at relevant academic conferences. The results contribute to improving understanding of the impact of long-term PPI use on glycemic control and may inform clinical practice and future research.

RESULTS

Overview

A total of 10 eligible studies published between 2010 and 2024 met the inclusion criteria after screening 127 records. These studies included eight observational designs (six cohort and two case–control studies) and two randomized

controlled trials (RCTs). The total study population comprised approximately 145,000 adult patients with Type 2 Diabetes Mellitus (T2DM), of whom nearly 28% had documented long-term proton pump inhibitor (PPI) use (≥12 weeks).

The included studies were conducted across multiple countries, including the United States, Germany, China, Denmark, Italy, Canada, Mexico, and India. The most frequently investigated PPIs were omeprazole, pantoprazole, and esomeprazole. Glycemic outcomes primarily included glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG), while a subset of studies also evaluated insulin resistance (HOMA-IR) and the incidence of diabetes.

Table 1: Summary of Included Studies

Author (Year)	Country / Study Design	Population (n)	Type / Duration of PPI	Comparison Group	Main Glycemic Outcomes	Key Findings
Trang et al. (2021)	USA / Retrospective cohort	14,602 T2DM (non-insulin)	Mixed PPI (≥1 year)	No PPI use	HbA1c	No significant effect; HbA1c slightly higher with PPI (Δ +0.08)
Ciardullo et al. (2022)	Italy / Case–control	26,744 T2DM	Various PPIs (>2 years)	No/short-term PPI	Diabetes incidence	24% increased risk of T2DM (OR 1.24; 95% CI 1.15–1.34)
Villegas et al. (2019)	USA / Cross-sectional	1,157 T2DM	PPI ≥6 months	No PPI	HbA1c, FPG	Lower HbA1c in PPI users (6.9 vs 7.2, p=0.02)
Gómez-Izquierdo & Yu (2017)	Canada / Meta-analysis	320 patients	Various PPIs	Placebo/control	HbA1c	Overall neutral (WMD −0.36, p=0.17); pantoprazole subgroup improved
Sánchez-García et al. (2020)	Mexico / Meta-analysis (RCTs)	580 patients	PPIs (12 weeks–6 months)	Placebo	HbA1c, FPG	No significant difference in HbA1c or FPG
Hove et al. (2013)	Denmark / RCT	62 T2DM	Pantoprazole (12 weeks)	Placebo	HbA1c, FPG	HbA1c decreased (−0.3%) but not significant
Singh et al. (2012)	India / Randomized double-blind trial	50 T2DM	Pantoprazole (3 months)	Placebo	HbA1c, FPG	Significant HbA1c reduction (−0.8%) and FPG decrease
Hove et al. (2010)	Denmark / Retrospective	370 T2DM	PPI ≥6 months	Non-PPI	HbA1c	Lower HbA1c in PPI users (7.06 vs 7.38, p<0.05)
Lu et al. (2024)	China / Meta-analysis	~3,600	PPIs in GERD + T2DM	Control	HbA1c, FPG	HbA1c reduced (−0.18%, p=0.03)
Foresta et al. (2024)	Italy / Cohort	91,006 elderly T2DM	Long-term PPI (>12 months)	No PPI	HbA1c, CV outcomes	HbA1c unchanged; increased cardiovascular mortality

Magnitude and Direction of Effects

Among the 10 included studies, four studies (40%) demonstrated mild improvement in glycemic control, including reductions in HbA1c or fasting plasma glucose. These improvements were observed in studies such as Singh et al. (2012), Hove et al. (2010), Villegas et al. (2019), and Lu et al. (2024).

Five studies (50%) reported no statistically significant changes in glycemic outcomes, including Trang et al. (2021), Gómez-Izquierdo and Yu (2017), Sánchez-García et al. (2020), and Foresta et al. (2024). One study (10%), conducted by Ciardullo et al. (2022), identified an increased risk of developing diabetes associated with prolonged PPI use, particularly in non-diabetic populations.

Dose and Duration Effects

Short-term or moderate PPI use (≤6 months), particularly in randomized controlled trials, was associated with modest reductions in HbA1c ranging from 0.2% to 0.8%. In contrast, long-term use (>1 year), primarily assessed in observational cohort studies, demonstrated largely neutral or slightly adverse effects. This suggests that any initial glycemic benefit may diminish with prolonged exposure.

Drug-Type Differences

Pantoprazole showed the most consistent, although modest, improvement in glycemic control across studies, with HbA1c reductions ranging from approximately 0.3% to 0.9%. In contrast, other PPIs such as omeprazole and esomeprazole were generally associated with neutral effects on glycemic outcomes.

Mechanistic Insights

Several studies proposed that PPIs may influence glucose metabolism through increased gastrin secretion, which can stimulate pancreatic beta-cell activity and enhance insulin secretion. However, prolonged hypergastrinemia may lead to beta-cell desensitization over time, potentially explaining the reduced effectiveness of long-term PPI therapy on glycemic control.

Adverse Metabolic Associations

Evidence from long-term observational studies suggests that chronic PPI use exceeding two years may be associated with an increased risk of developing T2DM and adverse metabolic outcomes. These effects may be mediated through alterations in gut microbiota, impaired nutrient absorption, and metabolic dysregulation.

Table 2: Quantitative Summary

Outcome Measure	Range Across Studies	Direction of Effect	Interpretation
HbA1c change	−0.9% to +0.1%	Mixed	Mild short-term benefit; no sustained effect
Fasting glucose	−12 to +4 mg/dL	Slight reduction	Likely transient effect
Diabetes incidence	OR 0.76–1.24	Slight increase (long-term)	Possible risk with prolonged use
HOMA-IR	−0.16 to +0.20	Neutral	No significant effect on insulin resistance

Synthesis

The overall body of evidence indicates that proton pump inhibitors do not produce a clinically significant or sustained improvement in glycemic control among patients with Type 2 Diabetes Mellitus. While short-term use, particularly with pantoprazole, may result in modest reductions in HbA1c (<1.0%), these effects are not consistently maintained over longer durations.

Furthermore, prolonged PPI use exceeding two years may be associated with an increased risk of developing diabetes and other adverse metabolic outcomes. Therefore, the use of PPIs in diabetic patients should remain guided by gastrointestinal indications, such as gastroesophageal reflux disease, rather than for glycemic control.

The effect of proton pump inhibitors on glycemic parameters is **neutral to mildly beneficial in the short term**, but **neutral to potentially adverse with long-term use**, with no strong evidence supporting their role in improving glycemic control in clinical practice.

DISCUSSION

The present systematic review evaluated the impact of long-term proton pump inhibitor (PPI) use on glycemic control in adult patients with Type 2 Diabetes Mellitus (T2DM) who experience heartburn. Overall, the findings demonstrate that the relationship between PPI therapy and glycemic outcomes is complex and heterogeneous. While some studies reported modest improvements in glycemic parameters, others found neutral or even potentially adverse metabolic effects. The synthesis of evidence from the ten included studies suggests that PPIs are unlikely to produce a clinically meaningful or sustained improvement in glycemic control when used for prolonged periods. These findings are

consistent with previous research emphasizing the multifactorial nature of glucose homeostasis in T2DM (Ciardullo et al., 2022).

One of the most notable observations in this review was that several studies reported mild improvements in glycemic parameters, particularly HbA1c and fasting plasma glucose, during short-term PPI therapy. Randomized trials such as those conducted by Singh et al. (2012) demonstrated a significant reduction in HbA1c levels following three months of pantoprazole therapy, suggesting a potential pharmacological interaction between gastric acid suppression and glucose metabolism. Similarly, retrospective findings by Hove et al. (2010) indicated lower HbA1c levels among diabetic patients receiving PPIs compared with non-users. These findings support the hypothesis that PPIs may exert a modest beneficial effect on glycemic control under certain conditions.

The potential mechanism behind this improvement is thought to involve the hormone gastrin. PPIs suppress gastric acid secretion by inhibiting the hydrogen-potassium ATPase pump in parietal cells, which results in compensatory hypergastrinemia. Elevated gastrin levels have been shown to stimulate pancreatic beta-cell proliferation and insulin secretion, thereby potentially improving glycemic regulation (Villegas et al., 2019). This biological pathway provides a plausible explanation for the reductions in HbA1c observed in several clinical studies included in this review.

However, despite these potential mechanisms, the majority of studies in the current review reported neutral effects of PPI therapy on glycemic control. Large observational cohort studies, including the work of Trang et al. (2021), found no statistically significant difference in HbA1c levels between PPI users and non-users among patients with T2DM. Similarly, meta-analytic evidence from Gómez-Izquierdo and Yu (2017) demonstrated that the overall pooled effect of PPI therapy on HbA1c reduction was not statistically significant. These findings suggest that any initial metabolic benefits associated with PPIs may be small and inconsistent across populations.

Another important observation from the included studies is that the duration of PPI therapy appears to influence metabolic outcomes. Short-term treatment lasting less than six months was more frequently associated with modest improvements in glycemic markers. For instance, the randomized controlled trial conducted by Singh et al. (2012) demonstrated significant reductions in both HbA1c and fasting plasma glucose during a three-month treatment period. In contrast, studies evaluating long-term PPI exposure exceeding one year generally reported neutral outcomes, indicating that the glycemic benefits observed initially may diminish over time.

The decline in glycemic benefits with prolonged therapy may be related to adaptive physiological mechanisms. Chronic hypergastrinemia caused by long-term PPI use may eventually lead to beta-cell desensitization or reduced responsiveness of insulin-secreting cells. Such physiological adaptation could explain why early improvements in glycemic control are not sustained during prolonged treatment. This interpretation is supported by experimental findings discussed in previous metabolic studies of PPI therapy (Sánchez-García et al., 2020).

Beyond neutral metabolic effects, some observational studies have raised concerns regarding potential adverse outcomes associated with chronic PPI use. Ciardullo et al. (2022) reported that prolonged PPI therapy was associated with a 24% increased risk of developing T2DM in non-diabetic populations. Although the causal relationship remains uncertain, this finding suggests that long-term exposure to PPIs may contribute to metabolic dysregulation in susceptible individuals.

One possible explanation for these adverse metabolic associations involves alterations in gut microbiota. Long-term gastric acid suppression can modify the intestinal microbial environment by allowing greater survival of ingested bacteria. Such dysbiosis has been associated with metabolic disturbances, insulin resistance, and obesity-related inflammation (Burmeister et al., 2023). Therefore, microbial changes induced by chronic PPI therapy may partially contribute to impaired glucose metabolism.

Another mechanism that has been proposed involves nutrient malabsorption. PPIs can interfere with the absorption of essential micronutrients such as magnesium, vitamin B12, and calcium, all of which play roles in metabolic regulation and cellular function. Deficiencies in these nutrients have been linked to impaired insulin sensitivity and increased risk of metabolic disorders (Saboo et al., 2023). Over time, these nutritional disturbances may offset any early metabolic benefits associated with gastrin stimulation.

Differences between specific PPI agents were also observed in the included studies. Pantoprazole appeared to demonstrate the most consistent improvements in glycemic markers, particularly in randomized clinical trials. Studies such as those conducted by Singh et al. (2012) and Hove et al. (2013) reported reductions in HbA1c levels among patients treated with pantoprazole. In contrast, other PPIs such as omeprazole and esomeprazole were generally associated with neutral metabolic outcomes. These findings suggest that pharmacological differences between PPIs may influence their metabolic effects.

The variability of findings across studies may also be attributed to differences in study design and population characteristics. Observational cohort studies typically involve larger sample sizes but may be subject to confounding factors such as comorbidities, medication adherence, and lifestyle variables. Randomized controlled trials, on the other hand, provide stronger causal inference but often include smaller participant groups and shorter follow-up periods. This methodological diversity contributes to the inconsistency observed in the literature (Lv et al., 2024).

Another factor influencing glycemic outcomes may be the presence of gastroesophageal reflux disease (GERD) itself. Patients with T2DM frequently experience gastrointestinal complications due to autonomic neuropathy and delayed gastric emptying. The coexistence of GERD and diabetes may complicate metabolic regulation through alterations in gastrointestinal motility and hormonal signaling pathways (Kumar et al., 2024). As a result, it is difficult to isolate the metabolic effects of PPI therapy from those of the underlying gastrointestinal condition.

Furthermore, the interaction between diabetes and gastrointestinal disorders may influence treatment patterns and medication use. Patients with chronic heartburn often require prolonged PPI therapy, which increases cumulative drug exposure. Understanding how this prolonged exposure affects metabolic regulation is essential for optimizing clinical management in diabetic populations (Sattaru et al., 2025).

The findings of this review also highlight the importance of evaluating long-term safety outcomes associated with PPI therapy. Foresta et al. (2024) reported that prolonged PPI use among elderly diabetic patients was associated with increased cardiovascular mortality, although glycemic parameters remained largely unchanged. These findings emphasize that the metabolic implications of chronic PPI use may extend beyond glycemic control and involve broader systemic effects.

Taken together, the evidence synthesized in this systematic review indicates that proton pump inhibitors should not be considered a therapeutic strategy for improving glycemic control in patients with Type 2 Diabetes Mellitus. Although modest short-term reductions in HbA1c may occur, particularly with pantoprazole, these improvements are generally small and not consistently maintained during long-term therapy. Clinical decisions regarding PPI use should therefore remain focused on gastrointestinal indications rather than metabolic outcomes (Rajput et al., 2020).

CONCLUSION

In conclusion, the findings of this systematic review indicate that long-term use of proton pump inhibitors in adult patients with Type 2 Diabetes Mellitus who suffer from heartburn does not produce a consistent or clinically significant improvement in glycemic control. While short-term therapy may lead to modest reductions in HbA1c or fasting glucose levels, these benefits are generally transient and not sustained during prolonged use. Furthermore, evidence from observational studies suggests that extended PPI exposure may be associated with potential metabolic and cardiovascular risks. Therefore, PPIs should continue to be prescribed primarily for appropriate gastrointestinal indications rather than for the purpose of improving glycemic outcomes in patients with diabetes.

REFERENCES

1. Burmeister, M. A., Smith, T. E., Fincher, T. K., & Weldon, A. J. (2023). Evidence for proton-pump inhibitor (PPI)-associated dysbiosis in metabolically unhealthy obesity. *Frontiers in endocrinology*, *14*, 1205490. https://doi.org/10.3389/fendo.2023.1205490
2. Ciardullo, S., Rea, F., Savaré, L., Morabito, G., Perseghin, G., & Corrao, G. (2022). Prolonged Use of Proton Pump Inhibitors and Risk of Type 2 Diabetes: Results From a Large Population-Based Nested Case-Control Study. *The Journal of Clinical Endocrinology & Metabolism*, *107*(7), e2671-e2679. https://doi.org/10.1210/clinem/dgac231
3. Foresta, A., Fernandez, L. O., Torrigiani, G., Schena, S., Roncaglioni, M. C., Nobili, A., Tettamanti, M., Franchi, C., Fortino, I., Succurro, E., Sesti, G., & Baviera, M. (2024). Proton Pump Inhibitor Use and the Risk of Cardiovascular Complications and Death in Older Adults with Diabetes: A Population-Based Cohort Study. *Drugs & aging*, *41*(3), 239–249. https://doi.org/10.1007/s40266-024-01097-x
4. Gómez-Izquierdo, J. C., & Yu, O. H. Y. (2017). The Influence of Proton-Pump Inhibitors on Glycemic Control: A Systematic Review of the Literature and a Meta-Analysis. *Canadian Journal of Diabetes*, *41*(4), 351-361. https://doi.org/10.1016/j.jcjd.2016.11.004
5. Herdiana Y. (2023). Functional Food in Relation to Gastroesophageal Reflux Disease (GERD). *Nutrients*, *15*(16), 3583. https://doi.org/10.3390/nu15163583
6. Hove, K. D., Færch, K., Bödvarsdóttir, T. B., Karlsen, A. E., Petersen, J. S., & Vaag, A. (2010). Treatment with a proton pump inhibitor improves glycaemic control in type 2 diabetic patients - a retrospective analysis. *Diabetes research and clinical practice*, *90*(3), e72–e74. https://doi.org/10.1016/j.diabres.2010.09.007
7. Hove, K.D., Brøns, C., Færch, K. et al. Effects of 12 weeks' treatment with a proton pump inhibitor on insulin secretion, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: a randomised double-blind prospective placebo-controlled study. Diabetologia 56, 22–30 (2013). https://doi.org/10.1007/s00125-012-2714-y
8. Kumar, K., Bhawana, F., Vandna, F., Pirya, F., Kumari, P., Sawlani, A., Sara, S., Simran, F., Kumar, A., Deepa, F., & Gul, A. (2024). Interactions Between Gastroesophageal Reflux Disease and Diabetes Mellitus: A Systematic Review of Pathophysiological Insights and Clinical Management Strategies. *Cureus*, *16*(8), e66525. https://doi.org/10.7759/cureus.66525

9. Lv, N., Li, N., & Qi, C. H. (2024). Efficacy and safety of proton pump inhibitors for diabetes mellitus in patients with gastroesophageal reflux disease: a meta-analysis. *Archives of medical science : AMS*, *21*(5), 1956–1964. https://doi.org/10.5114/aoms/192052
10. Rajput, M. A., Ali, F., Zehra, T., Zafar, S., & Kumar, G. (2020). The effect of proton pump inhibitors on glycaemic control in diabetic patients. *Journal of Taibah University Medical Sciences*, *15*(3), 218–223. https://doi.org/10.1016/j.jtumed.2020.03.003
11. Saboo, B., Mulwani, N., Petare, A. U., Veligandla, K. C., Pinto, C. S., Mane, A., Rathod, R., & Kotak, B. (2023). A real-world retrospective study of omeprazole-domperidone combination in managing acid peptic disease with PRoton-pump Inhibitors in patients with type 2 DiabEtes mellitus (PRIDE-2). *Drugs in context*, *12*, 2022-10-3. https://doi.org/10.7573/dic.2022-10-3
12. Sánchez-García, A., Simental-Mendía, M., & Simental-Mendía, L. E. (2020). Effect of Proton-Pump Inhibitors on Glucose and Insulin Metabolism on Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Current pharmaceutical design*, *26*(32), 4007–4013. https://doi.org/10.2174/1381612826666200523170718
13. Sattaru, K., Thipani Madhu, M., Kumar Singh, J., Kandi, V., Gupta, A., Ca, J., Balaji, O., Sridhar, N., & Talla, V. (2025). A Comprehensive Review of the Effects of Diabetes Mellitus on the Gastrointestinal System. *Cureus*, *17*(1), e77845. https://doi.org/10.7759/cureus.77845
14. Singh, P. K., Hota, D., Dutta, P., Sachdeva, N., Chakrabarti, A., Srinivasan, A., Singh, I., & Bhansali, A. (2012). Pantoprazole Improves Glycemic Control in Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial. *The Journal of Clinical Endocrinology & Metabolism*, *97*(11), E2105-E2108. https://doi.org/10.1210/jc.2012-1720
15. Trang, A., Bushman, J., & Halalau, A. (2021). Effect of Long-Term Proton Pump Inhibitor Use on Glycemic Control in Patients with Type Two Diabetes Mellitus. *Journal of diabetes research*, *2021*, 5578265. https://doi.org/10.1155/2021/5578265
16. Villegas, K., Meier, J. L., Long, M., Lopez, J., & Swislocki, A. (2019). The Effect of Proton Pump Inhibitors on Glycemic Control in Patients with Type 2 Diabetes. *Metabolic Syndrome and Related Disorders*. https://doi.org/10.1089_met.2018.0138