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Review Article

The impact of drug-drug interactions between proton pump inhibitors and metformin: A systematic review of clinical evidence

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Abstract

Metformin, a substrate of the organic cation transporters, is commonly co-prescribed with proton pump inhibitors, which inhibits these transporters. However, the clinical significance of this potential drug-drug interaction remains unclear. This systematic review aimed to assess the potential and clinical relevance of the interaction between proton pump inhibitors and metformin based on published clinical evidence. PubMed and Embase were searched for studies reporting the effects of this interaction in adults (≥18 years old), published up to January 2024. Data on pharmacokinetic and pharmacodynamic effects were collected and analyzed. The study protocol is registered in PROSPERO (CRD42023456957). A total of 14 studies were included, comprising five experimental and nine observational studies. Experimental pharmacokinetic studies indicated minimal changes in metformin AUC when combined with proton pump inhibitors, with reported changes ranging from a slight decrease (-5.46%) to a moderate increase (up to +17%). Pharmacodynamic data from both experimental and observational studies supported these findings, showing minimal clinically relevant changes in HbA1c levels. However, some studies reported decreased vitamin B12 levels in patients with type 2 diabetes mellitus using both proton pump inhibitors and metformin. Based on the current clinical evidence, the impact of drug-drug interaction between proton pump inhibitors and metformin is minimal. However, regular monitoring of glucose and vitamin B12 levels is advised for high-risk populations and those on long-term metformin and proton pump inhibitor therapy.

Keywords

drug-drug interactions, proton pump inhibitors, metformin, vitamin B12, glycemic control

Introduction

Diabetes mellitus (DM) is a type of metabolic disorder characterized by hyperglycemia attributed to impaired insulin secretion, insulin action, or both (Holt and Flyvbjerg 2024). Type 2 DM (T2DM) is the most common, with a prevalence estimated at 80% in low-income and middle-income countries (Tinajero and Malik 2021). Metformin is recommended by the European Society of Cardiology (ESC) as the first-line monotherapy of choice for T2DM patients (Cosentino et al. 2020). This drug effectively improves glycemic control while maintaining a good safety profile, with a low risk of hypoglycemia and a reduced cardiovascular risk. It is safe for use in obese patients, af-

fordable, and widely available (Foretz et al. 2023). However, metformin also has a major side effect, namely gastrointestinal intolerance, which may lead to symptoms such as 'diarrhea, nausea, flatulence, indigestion, vomiting, and abdominal discomfort' (Bonnet and Scheen 2017).

Approximately 2% to 63% of patients taking metformin are reported to experience gastrointestinal side effects (Bolen et al. 2007). These side effects can reduce the quality of life and contribute to non-compliance with treatment (Florez et al. 2010). The gastrointestinal side effects of metformin may result from impaired transport of serotonin or histamine, increased exposure to bile acids in the colon, and alterations in the gut microbiome (McCreight et al. 2016).

A commonly used treatment strategy to prevent gastrointestinal side effects is the co-administration of metformin with proton pump inhibitors (PPIs) (Ferguson and DeVault 2007; Ding et al. 2013). PPIs are widely recognized as the treatment of choice for managing gastrointestinal disorders, owing to their highly favorable efficacy profile (Gyawali and Fass 2018). Their use is prevalent among both inpatient and outpatient populations (Hálfdánarson et al. 2018; Sattayalertyanyong et al. 2020; Shanika et al. 2023). However, potential long-term adverse effects associated with the use of PPIs have been reported (Schoenfeld and Grady 2016; Yibirin et al. 2021).

Metformin is a substrate of organic cation transporter (OCT) 1, 2, and 3 (Tzvetkov et al. 2009; Graham et al. 2011). These transporters facilitate its distribution to body tissues, including the intestine, liver, and kidneys (Gong et al. 2012). In the liver, metformin inhibits gluconeogenesis, thereby reducing glucose production (Flory and Lipska 2019). Its uptake into the liver is primarily mediated by OCT1, with a potential contribution from OCT3 (Graham et al. 2011). Both OCT1 and OCT3 are expressed on the basolateral membrane of hepatocytes (Nies et al. 2009). In contrast, OCT2, which is predominantly expressed on the basolateral membrane of renal tubules, facilitates the transfer of metformin from the bloodstream into renal epithelial cells (Graham et al. 2011; Rena et al. 2012). Metformin is not metabolized by the liver and is excreted in unchanged form through the urine (Gong et al. 2012; Graham et al. 2011). Consequently, DDIs involving the inhibition of OCTs may have significant clinical implications (Ben Ghezala et al. 2022).

PPIs are potent OCT inhibitors. Nies et al. demonstrated that PPIs at therapeutic concentrations can inhibit the uptake of metformin into cells via OCT1, OCT2, and OCT3 (Nies et al. 2011). Consequently, the concurrent administration of PPIs and metformin may theoretically lead to pharmacokinetic drug-drug interactions (DDIs), where PPIs inhibit metformin uptake into key target tissues, such as hepatocytes, and impede its renal excretion. Two randomized controlled trials (RCTs) conducted in healthy subjects reported that co-administration of PPIs with metformin increased the maximum plasma concentration (Cmax) of metformin by approximately 15–22%, depending on the specific PPI used (Ding et al. 2013; Kim et al. 2014).

Although pharmacologically relevant DDIs between metformin and PPIs are possible, most DDI databases classify this combination as having no significant interaction potential. However, considering the frequent co-prescription of these medications, it is essential to understand the clinical implications of these potential interactions. This review, therefore, aims to evaluate the potential and clinical relevance of DDIs between metformin and PPIs.

Methods

This study was structured following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Page et al. 2021). The protocol was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/) under registration number CRD42023456957. This systematic review included only experimental and observational studies conducted in adults (≥18 years). Articles considered for inclusion were those that examined combinations and reported results of drug-drug interactions (DDIs) between proton pump inhibitors (PPIs) and metformin. Conversely, articles in the form of editorials, letters, correspondence, conference abstracts, expert opinions, commentaries, reviews, as well as in silico, in vitro, and in vivo studies were excluded.

The evaluation of drug interactions was conducted using pharmacokinetic parameters, specifically the percentage change in the area under the curve (AUC) value of metformin, with and without interaction with PPI drugs, categorized based on the criteria outlined by Bahar et al. (Bahar et al. 2017). Additionally, pharmacodynamic parameters were assessed using the clinical impact categorization proposed by Jansman et al. (Jansman et al. 2011). Detailed descriptions of both standards are provided in Suppl. material 1.

Search strategy

A systematic search was conducted using PubMed and Embase to identify articles published before 1 January 2024. The search terms included pharmacokinetic parameters (e.g., AUC values), pharmacodynamic parameters (e.g., HbA1c values, current blood glucose levels, fasting blood glucose levels, 2-hour postprandial blood glucose levels), and other relevant clinical outcomes. The complete search strategies are provided in Suppl. material 2.

Study article selection

Articles retrieved from the search were imported into Rayyan® QCRI (https://rayyan.qcri.org/welcome) (Ouzzani et al. 2016) and then, the duplicates were removed. Two independent reviewers (RAA and IYK) performed title and abstract screening to identify eligible articles. In case of disagreement, a discussion to reach a consensus was initiated, and when necessary, a third reviewer (MAB) was involved. After initial screening, the full text of eligible articles was also evaluated independently by RAA and IYK to arrive at the final selection. The level of inter-rater agreement was assessed using the percentage agreement and reliability Kappa Cohen (κ) statistic (McHugh 2012).

Data extraction

Data extraction was conducted independently by two reviewers (RAA and IYK) to minimize errors in data collection. Collected data included study year, country, population, study design, drug types, doses of PPIs and metformin, and study duration. Outcomes related to DDIs were categorized into pharmacokinetic data (AUC values), pharmacodynamic data (HbA1c and vitamin B12 values), and other relevant clinical outcomes.

Result

A systematic literature search conducted in PubMed and Embase identified 190 and 1,497 articles, respectively (Fig. 1). After removing 85 duplicates, 1,602 articles proceeded to the title and abstract screening stage. During the first screening stage, 1,564 articles were excluded for not meeting the inclusion criteria, such as incorrect study designs, review articles, or irrelevant topics. The percentage agreement between the two reviewers for the title and abstract (TIAB) screening was 99.9%, with a Kappa value of 0.98, indicating excellent agreement.

In the second screening stage (full-text screening), 14 articles met the eligibility criteria, consisting of five experimental and nine observational studies. At this stage, 24 articles were excluded for various reasons: lack of discussion on interactions and clinical outcomes of metformin and PPIs (n = 5), absence of clinical data (n = 2), and being limited to abstracts without full text, commentaries, or reviews (n = 17). The percentage agreement between the two reviewers for the full-text screening was 100%, with a Kappa value of 1, also indicating excellent agreement.

Study characteristics

Experimental studies

Five experimental studies were identified. Three studies were conducted on healthy volunteers using a randomized, double-blind, crossover, placebo-controlled design (Al-Bachaji et al. 2019). The remaining two studies focused on patients and employed a randomized trial design (Thirumurugu et al. 2010; Rajput et al. 2020). The characteristics of each study are shown in Table 1.

Observational studies

One case-control study compared the use of metformin and metformin combined with PPIs in diabetic patients (Al-Bachaji et al. 2019). Five cohort studies investigated patients treated with metformin monotherapy and those receiving a combination of metformin and PPIs, each involving a different number of participants (Crouch et al. 2012; Inci et al. 2014; Flory et al. 2015; Han et al. 2015; Chen et al. 2016). Additionally, three cross-sectional studies focused on patients receiving metformin and/or PPIs, with vitamin B12 deficiency identified as the primary outcome (Damião et al. 2016; Hansen et al. 2017; Chappell et al. 2020). The detailed characteristics of each study are presented in Table 1.

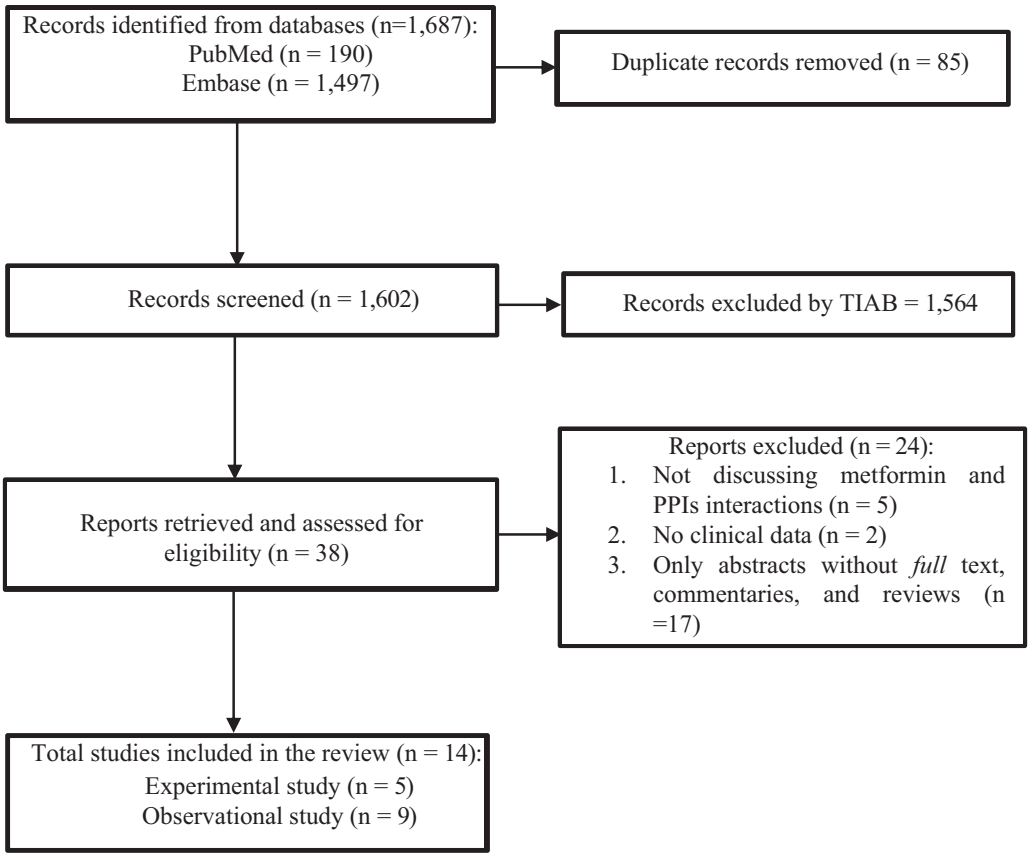

Figure 1. Flow chart of systematic review result.

Table 1. Study characteristics.

Reference	Study Design	Number of Patients		Patient type	Age (year)			Co-medication with other drugs	Metformin Dosage	PPI	PPI Dosage	Duration of study
		Size (n)			Mean	Median	Range					
Ding et al. (2013)	Randomized, double-blind, two-way crossover, placebo-controlled trial	20	Metformin+Placebo = 20 Metformin + Lansoprazole = 20	Healthy volunteers	34.7 ± 2.3	–	–	NA	Single dose 1000 mg first day, single dose 750 mg second day, 12-hour interval	Lansoprazole	30 mg	2 days
Kim et al. (2014)	Randomized, six-sequence, three-period crossover study	24	Metformin monotherapy = 24 Metformin+Pantoprazole = 24 Metformin+Rabeprazole = 24	Healthy volunteers	25.9 ± 5.1	–	30–60	NA	750 mg (8 pm), 500 mg (8 am)	Pantoprazole, Rabeprazole	40 mg, 20 mg	9 days
Liu et al. (2016)	Randomized, two-crossover study with a 14-day washout period.	15	Metformin+Plasebo = 15 Metformin + Rabeprazole = 15	Healthy volunteers	25.3 ± 6.5	–	–	NA	Single dose of 1000 mg on the first day, single dose of 750 mg on the second day	Rabeprazole	20 mg	7 days
Thirumurugu et al. (2010)	Randomized cross-over study in two phases with a washout period of 4 weeks	10	Monotherapy Metformin = 10 Metformin+Pantoprazole = 10	Patient	–	–	21–30	NA	500 mg	Pantoprazole	20 mg	1 day
Rajput et al. (2020)	Randomized open-label trial	80	Metformin + Glimepiride = 40 Metformin+Glimepiride+Omeprazole = 40	Patient	–	–	30–60	Glimepiride 1 mg	500 mg	Omeprazole	20 mg	12 weeks
Al-Bachaji et al. (2019)	Case-control study	60	Metformin monotherapy = 30 Metformin+PPI = 30	Patient	54.98 ± 4.2	–	40–62	Amlodipine, metoprolol, statins, fenofibrate, clopidogrel	850 g/day	Omeprazole, Pantoprazole, Lansoprazole	NA	4 months
Han et al. (2015)	Cohort study	9	Metformin = 9 Metformin+PPI = 9	Patient	63.81 ± 10.73	–	34–80	NA	NA	Esomeprazole, Pantopazole Rabeprazole, Lansoprazole, Ilaprazole	NA	Mean duration: 80 days
Crouch et al. (2012)	Cohort study	16	Metformin = 16 Metformin+PPI = 16	Patient	62.6	–	32–87	NA	NA	NA	NA	NA
Flory et al. (2014)	Cohort study	35.373	Metformin monotherapy = 30,954 Metformin+PPI = 4,419	Patient	–	–	60–67	Statins, calcium channel blockers, beta-adrenoceptor blockers, ACEI-ARB, thiazide, steroids, antipsychotics	NA	Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole	NA	3–9 months
Chen et al. (2016)	Cohort study	86.343	Ever exposed to metformin = 86,343 Ever exposed to metformin + PPI = 13,746	Patient	53.68 ± 0.06	–	–	ACEI-ARB, sulfonylureas, thiazolidinedione, insulin, statins, beta-blockers, dihydropyridine CCB, nondihydropyridine CCB, nitrates, diuretics, anticoagulants, antiplatelets	NA	NA	NA	90 days
Inci et al. (2014)	Cohort study	41	Metfromin+pantoprazole = 41	Patients	47.9 ± 17	–	18–73	NA	NA	Pantoprazole	40 mg	12 weeks
Chappell et al. (2020)	Cross-sectional study	103	Metformin+omeprazole = 71 Metformin+pantoprazole = 32	Patient	53	–	20–69	NA	1000 mg	Omeprazole, Pantoprazole	40 mg, 20 mg	Majority: 1 to 4 years
Damiao et al. (2016)	Cross-sectional study	128	Metformin+PPI/H2RA = 58 PPI/H2RA = 70	Patient	–	–	54–69	H2RA	NA	NA	NA	NA
Hansen et al. (2017)	Cross-sectional study	469	Metformin and/or PPI = 469	Patient	59 ± 11.6	–	20–80	NA	NA	NA	NA	NA

Pharmacokinetic data

Experimental studies

Four experimental studies reported changes in the AUC values of metformin when combined with PPIs such as lansoprazole, pantoprazole, and rabeprazole, ranging from -5% to 17% (Thirumurugu et al. 2010; Ding et al. 2013; Kim et al. 2014; Liu et al. 2016). Overall, these pharmacokinetic interactions were minimal. Ding et al. observed a 17% increase in metformin AUC with lansoprazole (Ding et al. 2013). Kim et al. reported increases of 15% and 16% with pantoprazole and rabeprazole, respectively (Kim et al. 2014), while Liu et al. found a 14.5% increase with rabeprazole (Liu et al. 2016). In contrast, Thirumurugu et al. reported a 5.46% decrease in metformin AUC when combined with pantoprazole (Thirumurugu et al. 2010). The results are displayed in Table 2.

Pharmacodynamic data

Experimental study

The pharmacodynamic effects of this combination showed no substantial changes in blood glucose levels. Ding et al. and Kim et al. reported that the combination of metformin with lansoprazole or rabeprazole did not significantly alter the pharmacodynamics of metformin ($p > 0.05$) (Ding et al. 2013; Kim et al. 2014). Similarly, Liu et al. also found no significant change in blood glucose levels ($p = 0.824$) (Liu et al. 2016). Thirumurugu et al. reported that the glycemic effect of metformin remained unchanged when combined with pantoprazole (Thirumurugu et al. 2010). Rajput et al. observed that changes in HbA1c levels were minimal (Rajput et al. 2020). The outcomes are summarized in Table 2.

Observational studies

In nine observational studies, only pharmacodynamic data were reported, with no pharmacokinetic data available (Table 2). Two studies observed a significant reduction in HbA1c values (Inci et al. 2014; Al-Bachaji et al. 2019). In contrast, one study reported a slight increase in HbA1c values after combination (Han et al. 2015). Two studies reported no clinically relevant changes in HbA1c values (Crouch et al. 2012; Flory et al. 2015).

Three cross-sectional studies reported vitamin B12 status as an outcome (Table 2). Chappell et al. found no relevant vitamin B12 deficiency, while Damiao et al. and Hansen et al. reported decreased levels that may cause temporary discomfort (category B) (Damião et al. 2016; Hansen et al. 2017; Chappell et al. 2020).

Other clinical outcomes

Chen et al. reported that the use of metformin and PPIs increased the risk of hospitalization or death (adjusted HR = 1.55; 95% CI: 1.46–1.64). However, this effect was probably due to a worse prognosis in metformin and PPI users compared to metformin-only users at the beginning of the cohort (Chen et al. 2016). This study lacked information on the pharmacokinetic and pharmacodynamic parameters of metformin.

Discussion

This review investigated the clinical impact of drug interactions between proton pump inhibitors (PPIs) and metformin. All experimental pharmacokinetic studies indicated minimal changes in metformin AUC when combined with PPIs. Reported changes in metformin AUC ranged from a slight decrease (-5.46%) to a moderate increase (up to +17%). These AUC variations are unlikely to be clinically relevant due to metformin's wide therapeutic index (Kajbaf et al. 2016) and its non-linear pharmacokinetics-pharmacodynamics (PK-PD) profile (Chung et al. 2018).

The variability in AUC changes may depend on the type of PPI used. For example, pantoprazole caused both a minor increase (15%) and a drop (-5.46%) in AUC values (Kim et al. 2014; Thirumurugu et al. 2010), while lansoprazole produced a 17% increase in metformin AUC (Ding et al. 2013). Rabeprazole also showed increases ranging from 14.5% to 16%. These observed differences might be due to the variabilities in the pharmacological properties of PPIs, such as their inhibitory potency and selectivity for OCTs (Nies et al. 2011; Hacker et al. 2015). To confirm these results, further studies exploring the effects of specific PPIs on metformin are needed. For the majority of patients, the interaction is less likely to require dose modifications in spite of these pharmacokinetic differences. However, individuals with a high risk of lactic acidosis, such as those with impaired renal function or elderly patients, may require closer monitoring (Sambol et al. 1995; Lalau 2010; Jain et al. 2024).

The mechanism underlying these pharmacokinetic changes is likely related to the inhibition of OCT1, OCT2, and OCT3 transporters by PPIs (Nies et al. 2011). PPIs inhibit metformin uptake into liver tissue mediated by OCT1 and OCT3. Consequently, the inhibition of metformin distribution to the liver is presumed to increase plasma concentrations (Ding et al. 2013). PPIs may inhibit metformin excretion through the kidney by inhibiting OCT2, which facilitates the transfer from the blood circulation into renal epithelial cells. Inhibition of OCT2 by PPIs could potentially increase the systemic disposition of metformin by reducing renal clearance (Ding et al. 2013; Song et al. 2008).

The experimental pharmacokinetic study results were confirmed by the pharmacodynamic effects. In all experimental trials, there were no clinically relevant changes in HbA1c levels as a result of DDIs between PPIs and metformin (Thirumurugu et al. 2010; Ding et al. 2013; Kim et al. 2014; Liu et al. 2016; Rajput et al. 2020). HbA1c was shown to have significantly decreased in two of the observational studies and to have slightly increased in one (Inci et al. 2014; Han et al. 2015; Al-Bachaji et al. 2019). These findings might be due to uncontrolled confounding factors, such as differences in baseline characteristics (age, duration of T2DM), the use of other drugs, the presence

Table 2. Overview of clinical outcomes.

Reference	Clinical outcome interactions			Clinical Implications	
	Pharmacokinetics	Pharmacodynamics	Other results	Pharmacokinetics	Pharmacodynamics
Ding et al. (2013)	The AUC value of metformin increased by 17%	Maximum glucose concentration value of metformin+placebo combination = 28 mg/dl and metformin+lansoprazole = 26 mg/dl (p > 0.05).	NA	Minimal drug interaction category	There was no significant change in blood glucose levels (category A = clinically irrelevant effect).
Kim et al. (2014)	Metformin+pantoprazole combination = metformin AUC value increased by 15%. Metformin+rabeprazole combination = metformin AUC value increased by 16%.	The difference in blood glucose concentration between metformin+pantoprazole = 0.09 mg/dl (95% CI: -4.58 - 2.77); metformin+rabeprazole = 3.55 mg/dl (95% CI: -0.13 - 7.22), p > 0.05.	NA	Minimal drug interaction category	There was no significant change in blood glucose levels (category A = clinically irrelevant effect).
Liu et al. (2016)	The AUC value of metformin increased by 14.5%	The maximum glucose concentration of metformin+placebo combination= 7.21 ± 1.13, and metformin+rabeprazole= 7.26 ± 1.01, p = 0.824.	NA	Minimal drug interaction category	There was no significant change in blood glucose levels (category A = clinically irrelevant effect).
Thirumurugu et al. (2010)	The AUC value of metformin decreased by 5.46%	The glycemic effect of metformin does not change after a combination with pantoprazole.	NA	Minimal drug interaction category	There was no significant change in blood glucose levels (category A = clinically irrelevant effect).
Radjput et al. (2020)	NA	HbA1c metformin= 7.47% ± 0.04 and metformin + PPI = 7.29% ± 0.07 (p = 0.03).	NA	–	The resulting change in HbA1c is minimal (category A = clinically irrelevant effect).
Al-Bachaji et al. (2019)	NA	HbA1c metformin= 8.15 ± 3.44% and metformin + PPI = 6.01 ± 2.19% (p = 0.0022).	NA	–	PPIs reduce the glycemic index of T2DM patients with metformin.
Han et al. (2015)	NA	HbA1c metformin= 6.97 ± 1.05% and metformin + PPI= 7.34 ± 1.22% (p = 0.035).	NA	–	Slight increase in HbA1c (category A = clinically irrelevant effect).
Crouch et al. (2012)	NA	HbA1c metformin= 7.10% and metformin + PPI= 6.80% (p = 0.25).	NA	–	No significant change in HbA1c (category A = clinically irrelevant effect).
Flory et al. (2014)	NA	There was a decrease in HbA1c values by 0.06% [95% CI: -0.10-(-0.01), p = 0.01].	NA	–	The resulting change in blood glucose level is small (category A = clinically irrelevant effect).
Chen et al. (2016)	NA	NA	Metformin + PPI users had an increased risk of hospitalization or death (adjusted HR=1.55; 95% CI, 1.46–1.64).	–	Category A = clinically irrelevant effect. The observed clinical effect was probably not due to drug interaction effects but because metformin + PPI users had a worse prognosis than metformin users at the beginning of the cohort.
Inci et al. (2014)	NA	HbA1c metformin= 7.2±1.3% and metformin + PPI= 6.8±1.0% (p = 0.007).	NA	–	Pantoprazole improved HbA1c levels in patients. However, the resulting reduction in HbA1c values was small (category A = clinically irrelevant effect).
Chappell et al. (2020)	NA	No vitamin B12 deficiency	NA	–	Clinically irrelevant effects (category A)
Damiao et al. (2016)	NA	Metformin + H2RA/PPI: 20.7% without vitamin B12 deficiency vs. 40.4% with vitamin B12 deficiency, P = 0.004.	NA	–	The clinical combination of metformin with H2RA/PPI lowers vitamin B12 level (category B = may cause temporary discomfort (<24–48 hours).
Hansen et al. (2017)	NA	Serum vitamin B12 levels were lower in patients on metformin+PPI compared to patients not treated with either drug. Serum vitamin B12 levels (p < 0.001): PPI monotherapy = 235.5 pmol/l (IQR 189.0; 314.0)	NA	–	The clinical combination of metformin with PPIs lowers vitamin B12 levels (category B = may cause temporary discomfort (<24–48 hours).
		Metformin monotherapy= 280.0 pmol/l (IQR 207.0; 363.0)			
		Metformin + PPI = 262.0 pmol/l (IQR 213.0; 365.0)			
		Without metformin + PPI = 368.5 pmol/l (IQR 274.0; 460.0)			

NA = Not Available

of concomitant disease(s), the number of patients, the duration of comedication, etc. No clinically relevant changes in glycemic control were identified by two other studies, confirming that any pharmacodynamic interaction is likely minimal in most patients.

Chen et al. reported that the combination of metformin and PPIs is associated with an increased risk of hospitalization or death (Chen et al. 2009). However, this increased risk may be due to poorer health conditions among patients using combination therapy, rather than a causal effect of interaction between the drugs (Chen et al. 2009). Since the study has no pharmacokinetic or pharmacodynamic data, it is difficult to draw definitive conclusions. Future studies with more robust designs (randomized controlled trials) are needed to investigate the causal relationship.

The combination of metformin and PPIs is also associated with a higher incidence of vitamin B12 deficiency (Damião et al. 2016; Hansen et al. 2017). The risk of vitamin B12 deficiency increases with the use of high doses and long duration of metformin drugs (Jager et al. 2010; Kibirige and Mwebaze 2013). In metformin therapy, several mechanisms have been proposed to cause vitamin B12 deficiency, such as impaired enterohepatic circulation of vitamin B12, increased hepatic storage, reduced intrinsic factor (IF) production, decreased intestinal motility with bacterial overgrowth, and calcium interference hindering the binding of the IF-vitamin B12 complex to ileal receptors, thereby reducing vitamin B12 absorption (Sayedali et al. 2023). Long-term therapy using of PPIs could also lead to vitamin B12 deficiency (Mumtaz et al. 2022). PPIs alter gastric acid, which is important for the digestion and absorption of vitamin B12 from food sources (Miller 2018). This leads to pharmacodynamic interactions, particularly additive interactions between the two drugs. Consequently, the concurrent use of metformin and PPIs, particularly over extended periods, increases the risk of vitamin B12 insufficiency due to their combined effects. This problem is particularly concerning in T2DM patients, who may already be at a higher risk of neuropathy (Gupta et al. 2018) and anemia since vitamin B12 deficiency could exacerbate these conditions, potentially leading to neurological complications (Hansen et al. 2017). Therefore, vitamin B12 levels should be regularly checked, especially for high-risk populations like the elderly or those receiving long-term treatment.

Despite the comprehensive approach of this review, several limitations should be acknowledged. First, the included studies exhibited significant heterogeneity in study designs, populations, types of PPIs, and duration of combination use, which may have contributed to inconsistent results. Second, most experimental studies were conducted in healthy volunteers, limiting their generalizability to T2DM patients, who may have altered drug metabolism or comorbid conditions. Third, while observational studies provided valuable real-world insights, they were subject to potential confounders, such as baseline differences in health status, co-medications, and disease severity. Fourth, the lack of detailed pharmacokinetic data in observational studies hindered the ability to directly link pharmacodynamic outcomes to pharmacokinetic interactions. Fifth, although this review assessed the pharmacokinetic effects of various PPIs, plasma PPI concentrations were not measured, limiting conclusions about dose-dependent interactions. Sixth, most experimental studies focused on short-term outcomes, making it difficult to evaluate the long-term implications of PPI-metformin co-administration. Seventh, the relatively short duration of experimental studies may have resulted in drug concentrations that did not accurately reflect those observed in patients who attain steady-state levels. Eighth, none of the studies considered genetic variations in OCTs and the CYP2C19 enzyme, which may be associated with differences in metformin and PPI pharmacokinetics, respectively. Lastly, only a subset of studies examined the impact on vitamin B12 levels, potentially underestimating its clinical significance, particularly in high-risk populations or those undergoing long-term therapy. Therefore, future studies with a robust design should address these limitations to provide a clearer understanding of the long-term impact of the PPI-metformin combination.

In real-world settings, the concurrent use of metformin and PPIs may be safe for most T2DM patients. However, routine monitoring of glucose levels and vitamin B12 status is essential for patients on long-term therapy or those at higher risk of complications. Personalized approaches, such as patient education and risk stratification, may enhance the safe and effective use of these medications.

Conclusion

This review concludes that pharmacokinetic interactions between PPIs and metformin result in minor variations in metformin AUC, ranging from -5.46% to +17%, which are not clinically relevant. Pharmacodynamic effects also show no substantial impact on glycemic control. However, concurrent use of both drugs increases the risk of vitamin B12 deficiency.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

Conceptualization: RAA, MAB; methodology, formal analysis, software: RAA, IYK; data collection and investigation: RAA, IYK; data curation and validation: RAA, IYK, MAB; writing – original draft preparation: RAA, IYK; writing – review and editing: MM, MAB; and funding acquisition: MM, MAB. All authors have read and approved the final version of the manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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Supplementary material 1

Supplementary data

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Data type: docx

Explanation note: **table S1.** The estimation of clinical impact of pharmacokinetic interactions (Bahar et al. 2017); **table S2.** Categories of clinical effects of pharmacodynamic drug interactions (Jansman et al. 2011).

Link: https://doi.org/10.3897/pharmacia.72.e142999.suppl1

Supplementary material 2

The complete search strategies

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Data type: docx

Link: https://doi.org/10.3897/pharmacia.72.e142999.suppl2