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Original Research

The Influence of Proton-Pump Inhibitors on Glycemic Control: A Systematic Review of the Literature and a Meta-Analysis

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ABSTRACT

Objectives: Proton-pump inhibitors (PPIs) have shown antihyperglycemic effects by stimulating insulin secretion. The aim of this study was to analyze the effect of PPIs on glucose metabolism in general and any potential antidiabetes effects in patients with type 2 diabetes.
Methods: A systematic search was conducted in MEDLINE, Embase, Cochrane and PubMed. Studies using PPIs as interventions and reporting glucose levels, glycated hemoglobin (A1C) levels and insulin levels were selected. Weighted-mean differences (WMDs) were calculated for all outcomes. A random-effects model was used for moderate and high heterogeneity and a fixed-effects model for low heterogeneity data.
Results: The research included 9 studies have involving 320 patients in total. Among patients with type 2 diabetes, those exposed to PPIs did not see significant reductions in A1C levels; WMD –0.36, 95% confidence interval (CI) –0.87, 0.15; p=0.17. Pantoprazole resulted in a statistically significant reduction in A1C levels in patients with type 2 diabetes when compared to control interventions; WMD –0.93, 95% CI –1.49, –0.37; p=0.001. There was no statistically significant difference in other outcomes (p≥0.05).
Conclusions: This meta-analysis demonstrates that PPIs, in general, do not decrease A1C levels in patients with type 2 diabetes. However, pantoprazole produced significant reductions in A1C levels in patients with type 2 diabetes. Given the limitations and the presence of bias in the primary studies, larger and better-quality studies are warranted.

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RÉSUMÉ

Objectifs : Les inhibiteurs de la pompe à protons (IPP) ont montré des effets antihyperglycémiques en stimulant la sécrétion d'insuline. Le but de la présente étude était d'analyser l'effet des IPP sur le métabolisme du glucose en général et tous les effets antidiabétiques potentiels chez les patients atteints du diabète de type 2.
Méthodes : Nous avons mené une recherche systématique dans MEDLINE, Embase, Cochrane et PubMed. Nous avons sélectionné les études ayant eu recours à l'utilisation des IPP comme interventions et ayant rapporté des concentrations de glucose, des concentrations d'hémoglobine glyquée (A1c) et des concentrations d'insuline. Nous avons calculé les différences des moyennes pondérées (DMP) pour tous les résultats cliniques. Nous avons utilisé un modèle à effets aléatoires en présence d'hétérogénéité modérée et d'hétérogénéité élevée, et un modèle à effets fixes en présence de faible hétérogénéité.
Résultats : La recherche a porté sur 9 études qui regroupaient 320 patients au total. Parmi les patients atteints du diabète de type 2, ceux exposés aux IPP n'ont pas constaté de réductions significatives des concentrations d'A1c; DPM –0,36, intervalle de confiance (IC) à 95 % –0,87, 0,15; p=0,17. Comparativement aux interventions auprès des groupes témoins, le pantoprazole a entraîné une réduction statistiquement significative des concentrations d'A1c chez les patients atteints du diabète de type 2; DPM –0,93, IC à 95 % –1,49, –0,37; p=0,001. Nous n'avons observé aucune différence statistiquement significative dans les autres résultats cliniques (p≥0,05).
Conclusions : Cette méta-analyse démontre qu'en général les IPP ne diminuent pas les concentrations d'A1c chez les patients atteints du diabète de type 2. Toutefois, le pantoprazole a généré des réductions

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significatives des concentrations d'A1c chez les patients atteints du diabète de type 2. Étant donné les limites et la présence de biais des études originales, des études de plus grande envergure et de qualité supérieure sont justifiées.

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Introduction

Gastroesophageal reflux disease (GERD) and its complications, for example, Barrett metaplasia and epithelial dysplasia, are conditions that have higher prevalence in patients with type 2 diabetes (1). In fact, the risk for developing GERD increases over time in patients with type 2 diabetes (1). Furthermore, some oral antidiabetes medications can cause dyspepsia (2), which is a symptom commonly treated with proton-pump inhibitors (PPIs). As a result, the use of PPIs is common among patients with diabetes.

Although PPIs have been shown to be safe and effective for treating GERD, studies have shown that PPIs may affect glycemic control in patients with diabetes. PPIs were found to have antihyperglycemic effects in experimental animal models (3) and in humans in observational studies (4). The proposed mechanism through which PPIs could improve metabolic control in patients with diabetes is via suppression of acid production in the stomach which, in turn, gives positive feedback to the parietal cells to secrete gastrin (5). Gastrin is known to have a stimulating effect on the beta cells of the pancreas, causing an increase in insulin secretion (5). The mechanism by which PPIs affect glucose metabolism via the gastrin pathway is similar to that of dipeptidyl peptidase-4 inhibitors (6).

Furthermore, PPIs have been shown to interfere with the metabolism of metformin, the first-line antidiabetes agent recommended in the treatment of type 2 diabetes (7). PPIs can have potential interactions with metformin that can result in reduced glucose levels by slowing the elimination of metformin by inhibiting kidney clearance of this medication through their effect on the organic cation transporter 2 in the proximal tubule (8). Clinical studies have shown that PPIs could also improve the absorption of metformin in the gastrointestinal system due to increases in stomach pH (9). Yet in vitro studies have demonstrated that PPIs could interfere with the uptake of metformin by the liver (7). Overall, the effects of PPIs on metformin metabolism may result in a modest decrease in glucose levels (10).

Considering that PPIs are commonly used in patients with diabetes and can have interactions with antidiabetes medications, potentially resulting in antihyperglycemic effects, further studies to investigate the effects of PPIs on glycemic control are warranted. The aim of this study was to analyze the effects of PPIs on glucose metabolism in general and any potential antihyperglycemic effects in patients with type 2 diabetes.

Methods

Primary objective

The goal of this study was to analyze the effects of PPIs compared to oral antidiabetes agents or placebo on glycemic control, defined by glycated hemoglobin (A1C) levels and fasting glucose levels in patients with type 2 diabetes. We performed a systematic review of the literature and made a meta-analysis.

Secondary objectives

The secondary objectives of this study were to test the effects of PPIs on glucose metabolism in humans, more precisely, on fasting glucose levels and maximum glucose levels (Gmax) (defined as the maximum serum glucose level displayed in a curve after a glucose challenge); the influence of PPIs on gastrin levels, because this is the suggested mechanism for improving glucose levels; and whether PPIs increase insulin secretion.

Systematic search and databases

The search strategy included medical subject headings (MeSH) terms related to diabetes, diabetes medication combined with PPI molecule names, gastrointestinal pathologies and conditions that constitute indications for treatment with PPIs (Appendix 1). It was conducted in 4 different databases: MEDLINE, Embase, Cochrane and PubMed, the most widely used databases in medicine. No language limits were applied, and the search strategy was conducted through April 30, 2016. The search strategy was restricted to clinical trials and studies in humans.

Study selection and data extraction

Any article discussing the use of PPIs in patients with diabetes or testing the effects of PPIs on glucose metabolism was extracted. Studies using PPIs as intervention and reporting outcomes related to glucose metabolism—more precisely, glucose, A1C and insulin levels—were selected for quality analysis and data synthesis (meta-analysis). Data extraction was performed using a previously prepared standard electronic format that included first author, year of publication, sample size, trial design, diabetes information, population of patients, intervention, control intervention and results. Studies' eligibility standards and risk for bias were assessed by the first author of this study (JG).

Statistical analysis

The methods used for this study followed the Cochrane (11) Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (12) guidelines for systematic reviews and meta-analyses. Risk for bias in randomized trials was also evaluated using the Cochrane collaboration's tool, PRISMA (11). Risk for publication bias was assessed using funnel plots. After data extraction, results were plotted using the Cochrane Review Manager software, v. 5.2. Results were reported as weighted mean differences (WMDs) because all the outcomes were continuous variables. The method described by Hozo (13) was used to extrapolate means or standard deviation from the reported results in the original studies, when necessary. When results were not reported in the results section of the studies but were displayed in graphics, data were extracted using the GraphClick beta software (Arizona Software, Phoenix, Arizona, United States), which is a valid method of data extraction in meta-analysis (14). Some studies analyzed the effects of medication on glucose metabolism by displaying the concentration of glucose and insulin in curves (15–17), especially when a glucose challenge was involved (a meal or an oral glucose test). From these graphics, the maximum level displayed in the curve (the highest point of the curve) for Gmax and insulin level was taken for analyses. A1C levels were reported as percentages; gastrin and insulin levels in $pmol^{-1}$ $litre^{-1}$; and fasting glucose and Gmax in $mmol^{-1}$ $litre^{-1}$. Unit conversions were performed when necessary. Heterogeneity was tested using the I^2 statistic considering low heterogeneity (<25%), moderate heterogeneity (25% to 50%) and high heterogeneity (>50%). Low heterogeneity data were analyzed using a fixed-effects model; moderate and high heterogeneity data were analyzed using a random-effects model, as recommended by the Cochrane Handbook for Systematic Reviews (11).

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