REVIEW

Proton pump inhibitors: impact on glucose metabolism

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Abstract Diabetes mellitus is a complex chronic disease associated with an absolute insulin deficiency in type 1 diabetes (T1D) and a progressive deterioration of β-cell function in type 2 diabetes (T2D). T2D pathophysiology has numerous defects including incretin deficiency/resistance. Gastrin has demonstrated to be an islet growth factor (like glucagon-like peptide-1, epidermal growth factor, transforming growth factor-α,...) and be able to restore a functional β-cell mass in diabetic animals. This hormone is likely to stimulate insulin secretion during an ordinary protein-rich meal, this is, to have an incretin-like effect. Proton pump inhibitors (PPIs) can raise serum gastrin concentration significantly and therefore, affect to glucose metabolism through promoting β-cell regeneration/expansion and also enhancing insulin secretion. The present paper aims to review studies concerning the effect of PPIs on glucose metabolism. Several research groups have recently explored the potential role of this class of drugs on glycemic control, mainly in T2D. The results show antidiabetic properties for the PPIs with a global glucose-lowering power around 0.6–0.7 % points of HbA1c, but the level of evidence for the available literature is still not high. If these data start to become demonstrated in the ongoing clinical trials, PPIs could become a new antidiabetic agent with a good and safe profile for T2D and even useful for T1D, particularly in the area of islet transplantation to preserve β-cell mass.

Keywords Proton pump inhibitors · Diabetes · Treatment · Incretins

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Introduction

The prevalence of diabetes mellitus is 366 million globally (8.3 %), by 2030 this will have risen to 552 million (9.9 %), nearly 95 % of the cases will be type 2 diabetes (T2D) [1]. These predictions indicate a growing burden of diabetes, particularly in developing countries [2]. We face a worldwide epidemic.

T2D is a complex disease, pathophysiology of which includes not only the classical *triumvirate*—insulin resistance in muscle and liver and progressive β-cell failure—but at least the ominous octet [3]: accelerated lipolysis, incretin deficiency/resistance, hyperglucagonemia, renal increased glucose reabsorption, and brain insulin resistance. At the end, hyperglycemia in both type 1 diabetes (T1D) and T2D results from an absolute or relative deficit in the pancreatic β-cell mass; therefore, β-cell regeneration is an area under active investigation.

The natural history of T2D implies that more than one medication will be necessary for most patients over time and effective treatment requires multiple drugs used in combination to correct multiple pathophysiological defects. Choices of therapies are usually made according to efficacy, safety, tolerability, cost of medications, simplicity, and anticipated degree of patient adherence. Furthermore, it should be noted that some associations have proven safe, but others are not recommended, and other long-term safety is unknown [4], so the therapeutic arsenal is not as broad as it seems and any new therapeutic strategy that takes into account the above features would be welcomed.

Gastrin is the major endocrine regulator of the acid secretory response to a protein meal [5] and has been said to have trophic effects on β-cell mass [6–8]. There is a negative feedback loop between gastric acid and gastrin release.

Proton pump inhibitors (PPIs) are drugs used to treat symptoms of acid-related disorders and for primary prevention of gastroduodenal toxicity [9]. They decrease secretion of acid and therefore produce a modest hypergastrinemia [10], so this effect could be associated with better glycemic control. Based on this hypothesis, a few groups [11–13] have analyzed whether treatment with PPIs is associated with better glycemic control in T2D with positive and similar results in different clinical contexts.

This review examines the in vitro and in vivo evidence of PPIs on glucose metabolism.

Proton pump inhibitors. How they act?

The introduction of PPIs in the late 1980s optimized the medical treatment of acid-related disorders, mainly gastroesophageal reflux disease. Other indicated uses include the treatment and prevention of upper gastrointestinal tract ulcers from nonsteroidal antiinflammatory drugs, as part of therapeutic regimens for eradication of *Helicobacter pylori* infection, in the management of patients with bleeding peptic ulcer and in the management of functional dyspepsia [14].

Gastric acid secretion is a complex process regulated by at least three types of receptors on the parietal cell: histamine, gastrin, and acetylcholine [15]. Release of histamine by gastrin from enterochromaffin-like (ECL) cell appears to be the major physiologic mechanism [16], although parietal cells also have gastrin receptors. In addition, the ECL cells integrate stimulatory messages from cholinergic nerves and inhibition by locally released somatostatin (Fig. 1).

Hydrogen ions are actively secreted in exchange for potassium ions by means of an H–K–ATPase, the so-called proton pump located on the apical surface of the parietal cell. H–K–ATPase comprises the final pathway that has been triggered by the stimulation of one or more receptors, by which HCl is secreted into the gastric lumen. There gastric acid serves both to hydrolyze dietary protein and maintain a sterile environment.

PPIs inhibit the final step of acid secretion, the proton pump. All PPIs are prodrugs, and have to be protected against acid degradation. After oral administration of PPIs peak plasma concentrations are achieved within 2–4 h. When PPIs reach the acidic environment of the parietal cells they are entrapped and form an irreversible bond with the hydrogen potassium ATPase, inhibiting its action [17]. Because of the amount of H–K–ATPase present in the parietal cell is greatest after a prolonged fast, PPIs should be administered before the first meal of the day. In most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition.

There are currently six PPIs available on the market: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole. They share a similar core structure, but they differ according to the chemical stability under acidic and neutral pH. Rabeprazole possesses a slightly faster onset of action, while pantoprazole is often touted as being the most "gastro-specific." However, whether these differences in chemical structure translate into differences in clinical efficiency is matter of debate [18].

PPIs are metabolized via hepatic cytochrome P450 enzymes, with CYP2C19 having the dominant role. Pantoprazole has the lowest potential for P450 metabolism and drug interactions. Interactions are uncommon, except for PPIs and clopidrogrel—omeprazole specially—but the recent literature has suggested that there may not be a clinically meaningful interaction [19].

The long-term safety of these drugs has been best established with omeprazole, since it was the first to become available clinically. These data suggest that its use for more than 15 years is safe, although some risks have been described [20]. Hypochlorhydria is of concern because may predispose to infections and malabsorption. Chronic PPI therapy has been associated with *Clostridium difficile* infection, community-acquired pneumonia, and calcium malabsorption resulting in osteoporosis and increased fracture risk, but with reservations in some aspects because of lack of good methodological studies [21]. There is a risk of hypomagnesemia in patients who have been on PPIs long-term [22] and long-term therapy with omeprazole has been associated with vitamin B12 malabsorption [23].

The secondary hypergastrinemia induced by PPIs created a concern about gastric carcinoid tumors. However, long-term omeprazole therapy (up to 11 years) has shown to be safe [24], but because of this consequence of acid suppression there is a possibility of rebound acid hypersecretion when stopping PPIs after prolonged use [14]. A small risk of atrophic gastritis has been reported [20].

The hormone gastrin was an early incretin candidate

The main production site of gastrin is the antral G-cells, where is synthesized as gatrin-17 (the predominant form) and gastrin-34, also other gastrins are synthesized but in small quantities, in response to a number of luminal stimuli, including the presence of amino acids and dietary amines [25, 26].

Fetal and neonatal G-cells in pancreatic islets produce only sulphated gastrin-17 [27].

The gastrin receptor is the predominant receptor for gastrin and cholecystokinin (CCK) peptides in the central nervous system. It is abundantly expressed on ECL-cells in the stomach [28]. There are data consistent with the view that growth control by gastrin and expression of gastrin/
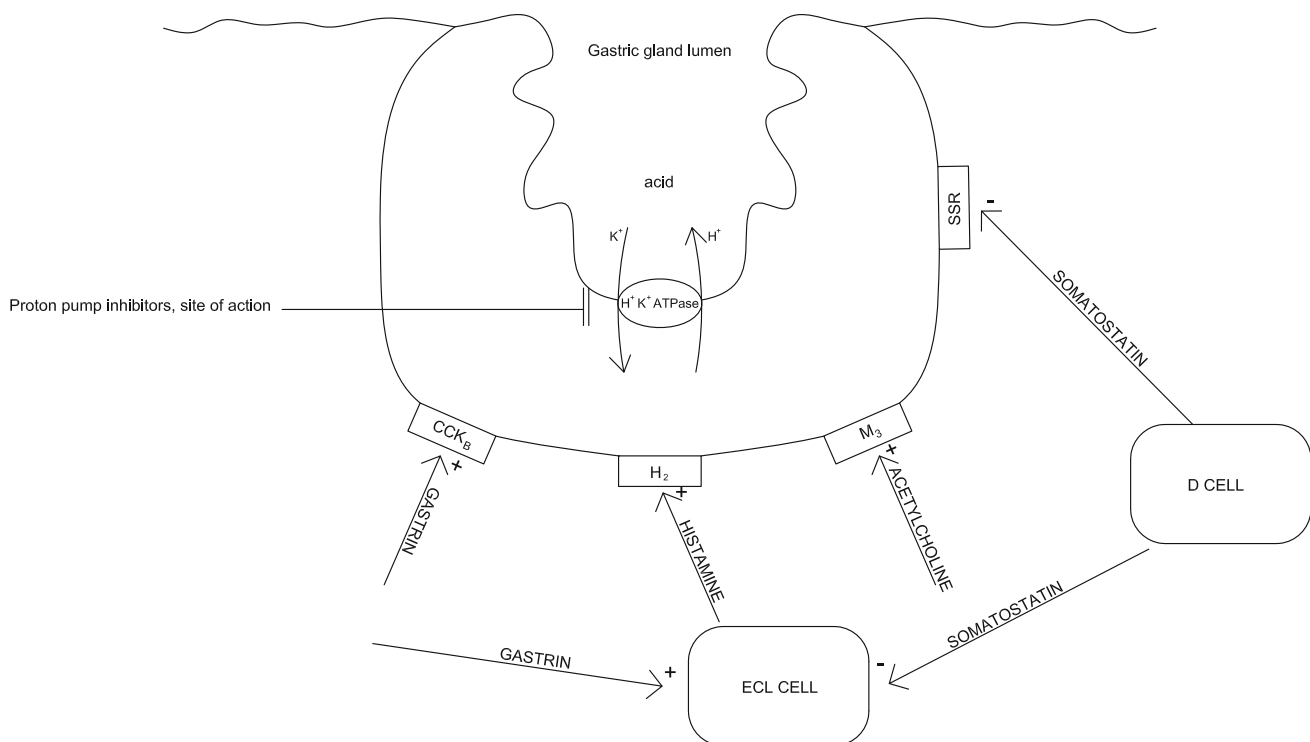
Fig. 1 Schematic diagram of acid secretion by the gastric parietal cell

CCK-B receptors is present in fetal and regenerating pancreas [29, 30]. But the expression of this receptor in the pancreas is species-specific [31]; there is an abundant islet cell expression in man and pig, whereas CCK receptor is more abundant in rodents and dogs. Therefore, results on CCK and gastrin obtained from rodents and dogs do not necessarily apply to humans.

Gastrin was an early incretin candidate [32–34], since it was released by oral glucose and potentiates the glucose-induced insulin secretion [35]. However, the amounts of gastrin released by oral glucose were too low to stimulate β-cell secretion significantly, and the interest of gastrin in incretin research decreased for decades until recent studies have shown that interaction between gut hormones, including gastrin, is able to restore normoglycemia in diabetic mice.

But gastrin had shown their effect on insulin secretion several times in old studies [31]. Exogenous gastrin-17 is a potent insulin-releaser together with intravenous glucose and during an ordinary protein-rich meal is likely to stimulate the secretion of insulin significantly. Moreover, studies in endogenous hypergastrinemia support an incretin effect of gastrin in man.

The lack of consideration for the incretin effect of this hormone during decades was motivated by overlooking at least two problems [31]: (1) oral overload of glucose is unphysiological, meals are mixtures of many components that release more than a hundred hormonal bioactive intestinal peptides, (in addition to glucose-dependent insulinotropic peptide—GIP—and glucagon-like peptide-1—GLP-1), while gastrin is mainly delivered by proteins; (2) incretins often have multiple targets, this mean multiple functions, and may have important interactive effects. For instance, GLP-1 in high doses is without effect on pancreatic islet-cell and hyperglycemia in NOD mice. However, when GLP-1 is combined with small doses of gastrin, the β cells grow, insulin is secreted, and the mice become normoglycemic [36].

Gastrin stimulates β-cell neogenesis: evidence from basic research

In the area of pancreatic islet transplantation and regenerative medicine, mechanisms that regulate the pancreatic β-cell mass require deep understanding. Many stimuli influence β-cell neogenesis from pancreatic duct cells in vitro and in vivo. These include growth factors, such as transforming growth factor-α (TGF-α), epidermal growth factor (EGF), and keratinocyte growth factor [37–40]. Gastrointestinal peptides, such as GLP-1 [41] and gastrin [6] can also stimulate β-cell neogenesis.

Rooman et al. [6] reported that a 3-day continuous intravenous gastrin administration further increases expansion of

the β-cell mass in the ligated pancreas of the rat and this occurs by the process of neogenesis. In the model of pancreatic duct ligation, no histological changes occur in the unligated part; in the ligated part, exocrine acinar lobules are replaced by ductal complexes and new β-cells are generated from the latter [42]. Duct-like cells start to express TGF-α, gastrin [43], and the high-affinity gastrin/CCK-B receptor, which is not expressed on β-cells [30]. Cells in these ductal complexes proliferate and can differentiate into endocrine cells [42]. Infusion of gastrin from day 7–10 postligation resulted in doubling of the β-cell mass in the ligated part as measured by morphometry. This robust hyperplasia cannot be accounted for by β-cell self-replication, as the fraction of β-cells being engaged in the cell cycle remains very low. This means that gastrin extends the process of neogenesis that was already induced by the procedure of duct ligation. Administration of a selective CCK-B gastrin receptor antagonist completely prevents the duct ligation-induced increase in β-cell mass [44], so gastrin is a crucial factor in the regulation of β-cell neogenesis during regeneration.

Xu et al. [45] reported endocrine differentiation as a result of endogenous hypergastrinemia in a model of subtotal pancreatectomy.

Interesting information concerning regenerative expansion of β-cells has been obtained from various transgenic mouse models. TGF-α overexpressing transgenic mice develop metaplastic acinoductal complexes in the pancreas and show signs of tissue inflammation [46]. When these mice are crossed with transgenic mice overexpressing gastrin hormone under control of the insulin promoter, the double transgenic TGF-α/gastrin mice were found to contain significantly more β-cells (approximately twice over the control group) [47].

Combination therapy with EGF and gastrin increases β-cell mass and reduces hyperglycemia in streptozotocin–diabetic rats [48] and induces islet regeneration and restores normoglycemia in mice treated with alloxan [49]. In this last model, a β-cell growth rate of 30 % per day was observed. Although there was no complete regeneration of the original β-cell number after subtotal destruction, regenerative growth induced by the gastrin and EGF treatment led to the restoration of 30–40 % of the normal β-cell mass within 7 days. The treatment had no effect on β-cell replication, cell size, or apoptosis, and therefore, the regenerative effect could be attributed to neogenesis from precursor cells.

The combination of these two growth factors, EGF and gastrin, also induces neogenesis of adult human islet β-cells from pancreatic duct cells and an increase in functional β-cell mass [8]. EGF stimulated the proliferation of CK19-positive duct cells, whereas gastrin induced the expression of the transcription factor PDX-1 in these duct cells and their differentiation into insulin-positive β-cells. The findings are consonant with the different roles that EGF and gastrin have in islet development.

The gastrointestinal incretin hormone GLP-1 has been repeatedly reported to affect β-cell function, replication, apoptosis, and neogenesis [50, 51]. Suarez-Pinzon et al. [52] demonstrated that combination therapy with GLP-1 and gastrin expands the β-cell mass in human islets implanted in immunodeficient diabetic mice, largely from pancreatic duct cells associated with the islets, and this was sufficient to ameliorate hyperglycemia in the mice. Correction of hyperglycemia was accompanied by increased insulin content in the human pancreatic cell grafts as well as by increased plasma levels of human C-peptide. Immunocytochemical examination revealed a fourfold increase in insulin-positive cells in the human pancreatic cell grafts in mice treated with GLP-1 and gastrin, and most of this increase was accounted for the appearance of CK19-positive pancreatic duct cells expressing insulin.

Finally, specific treatment with a PPI to raise endogenous levels of gastrin in several animal models has shown an improvement in glycemic control.

Suarez-Pinzon et al. [53] demonstrated that combination therapy with a DPP-4 inhibitor to raise endogenous levels of GLP-1, together with a PPI could reverse diabetes in the NOD mouse model of T1D. Treatment with DPP-4 inhibitor restored normoglycemia in 38 % of mice, PPI in 33 %, and combination of DPP-4 inhibitor and PPI in 75 % of animals. Treatments with a single agent did not significantly increase plasma C-peptide or pancreatic insulin content, whereas combined treatment significantly did.

This combination drug therapy, specifically sitagliptin and pantoprazole, induces β-cell neogenesis in adult human pancreatic cells implanted in NOD-severe combined immunodeficient mice. The increased β-cell mass appears to be derived from pancreatic exocrine duct cells [54].

PPIs have also demonstrated a positive effect on glycemic control in a model of type 2 diabetes—*Psammomys obesus* [55].

In summary, gastrin can be considered as an important regulator of β-cell neogenesis. Neogenesis by the process of transdifferentiation and/or stem cells appears to be activated only after severe injury to endocrine or exocrine pancreatic tissue, or when strong additional stimuli like GLP-1 and/or gastrin are provided. β-Cell self-replication can also be increased by certain stimuli like glucose and other nutrients, insulin and several growth factors, but it apparently cannot lead to an efficient regeneration [56]. Clinical interpretation of β-cell regenerative therapies is limited because of these studies have been almost carried out in rodent models of diabetes or under in vitro conditions.

Somatostatin, proton pump inhibitors and diabetes relationship

Somatostatin (SST) is an inhibitory hormone that regulates numerous biological processes, including insulin and glucagon secretion. SST secretion from islet δ-cells is stimulated by increased extracellular glucose, although the threshold concentration for δ-cells to respond to glucose is lower than for β-cells [57].

Several studies seem to show that administration of omeprazole decreased the antral SST content [58, 59]. In healthy men, administration of omeprazole 40 mg/day increased the antral gastrin content and decrease the antral somatostatin content significantly [58].

In a small interventional study with five healthy volunteers, who were given a single oral administration of omeprazole 20 mg, plasma somatostatin significantly increased after drug ingestion [60]. However, Stoschus et al. [61] found that treatment with omeprazole led to an increase in fasting and postprandial plasma concentrations of xenin, gastrin, and pepsinogens A and C, whereas somatostatin plasma levels remained unchanged.

Studies with animals, specifically in sheep, showed that gastrin can stimulate somatostatin independently of changes in gastric acidity [62] and omeprazole administration had no effect on plasma somatostatin, but antral somatostatin increased significantly [63]. Again species-specific receptor may be the key.

On the one hand, the rare somatostatinoma [64] and somatostatin analogs (SSA) used in acromegaly are followed sometimes by a glucose metabolism imbalance [65]. A recent meta analysis of acromegaly studies [66] shows that SSA decrease fasting serum insulin levels without consistent effects on glucose homeostasis. In most included studies, SSA did not induce any significant change in glucose metabolism, and only a few studies reported an increase in serum HbA1c and glucose during OGTT, whereas fasting plasma glucose was not significantly affected, so the clinical importance may be minor. In fact, current guidelines suggest that the reduction in GH levels usually achieved with SSA tends to outweigh any effect on β-cell function and leads to an overall improvement in insulin resistance [67].

On the other hand, further areas for development of SSA therapy include obesity and diabetes mellitus [68]. The most developed thus far is the use of octreotide in hyperinsulinemic forms of obesity [69], SSA can retard weight gain in children with hypothalamic obesity and induce a small amount of weight loss in some adults with hyperinsulinemic obesity. The therapeutic potential of somatostatin receptor ligands to control the excess of pro-angiogenic factors in diabetes-associated retinal complications has also been tested [70]. Nevertheless, for the treatment of T2D, use of somatostatin per se would be counterproductive due to its broad spectrum of inhibitory actions, including, of course, inhibition of insulin secretion [71]. Considerable effort has been put forth over the years in identifying the receptor subtypes responsible for the various inhibitory actions of somatostatin, and some subtype-selective analogs have been identified [72]. However, there appears to be species-specific receptor and receptor subtype overlap. For instance, somatostatin receptor subtype 2 (SSTR2) appears to mediate the effects of somatostatin on GH [72] and inhibits the release of glucagon, but not that of insulin, via SSTR2 [73]. In isolated perfused human pancreas, infusion of SSTR2 agonist into the isolated perfused human pancreas resulted in a significant inhibition of insulin and C-peptide secretion [74].

It can be said based on these papers that the relationship between SST and PPIs is not clear at all, but some kind of relationship with the pancreas activity exists that needs necessarily further investigation.

Proton pump inhibitors delay gastric emptying: underlying mechanism?

The delayed emptying of solids due to PPI therapy may have clinical implications in the management of gastro-esophageal reflux disease, functional dyspepsia, as well as diabetes. Sanaka et al. [75] reviewed several studies (from 1979 to 2009) that investigated the rate of gastric emptying in PPIs users. The underlying mechanisms for this effect remain mostly hypothetic. Gastric emptying of solids involves a process of peptic hydrolysis. PPIs impair the hydrolytic digestion by inhibiting acid-dependent peptic activity, thereby delaying the solid emptying. Gastric emptying of liquids largely depends on volume and energy density of intragastric contents. These medications variably modify the volume and the energy density by reducing gastric fluid secretion.

Hypergastrinemia has also been considered to delay gastric emptying, but it seems of minor importance.

Treatment with proton pump inhibitors improves glycemic control in humans: a retrospective look

There are few data about the effect of PPIs on glucose metabolism in humans. Below we are going to review them (Table 1).

First, Mefford et al. [11] compared HbA1c levels from type 2 diabetic patients taking a PPI (7.0 %) and type 2 diabetic patients not taking (7.6 %), obtaining significant differences. Then, they performed a sub-analysis based on diabetes treatment being aware of the risk the treatment

Table 1 Effect of proton pump inhibitors on glucose metabolism in diabetic patients

Authors (references)	Study design	Type of diabetes (additional comment)	Clinical care context	Drug	Number of subjects	Consumption ratio PPI/no PPI	HbA1c (%) with PPI vs. HbA1c (%) without PPI
Mefford et al. [11]	Cross-sectional	T2D	Primary	Not restricted	347	65/282	7.0 vs. 7.6*
Boj-Carceller et al. [88]	Cross-sectional	T2D and T1D (poor glycemic control)	Hospital	Not restricted	72	33/39	8.8 vs. 9.5
Hove et al. [13]	Case–control	T2D (on insulin treatment)	Diabetes Center	Esomeprazole	42	21/21	−0.7 vs. −0.2* (difference HbA1c after-before treatment)
Boj-Carceller et al. [12]	Cross-sectional	T2D (good glycemic control)	Hospital	Not restricted	97	54/43	6.7 vs. 7.3*
Crouch et al. [76]	Retrospective uncontrolled Before and after study	T2D (without insulin treatment)	Primary	Not restricted	71	71/71	7.1 vs. 7.7* (after-before treatment)

PPI proton pump inhibitor

* Statistically significant

groups become so small as to have lack of statistical power. The result was a trend to have lower means of HbA1c for the different antidiabetic therapies combined with a PPI, although as expected, without getting statistical significance except for the sulfonylureas group (in combination with or without metformin and/or thiazolidenedione) that got a reduction in HbA1c of 1.4 %—respect those patients who did not consume a PPI. Limitations of this study include, besides of the study design ones, the heterogeneity of the comparative groups.

After this, Boj-Carceller et al., personal communication—in a smaller study with diabetic in-patients with poor glycemic control (average HbA1c of 9.2 %), where 33.8 % had T1D, found that those who were using a PPI showed lower HbA1c levels, specially if they were T2D not receiving insulin treatment yet.

Hove et al. [13] published the results of a small case–control study conducted to investigate whether treatment with esomeprazole (prescribed for unspecified gastric acid related disorders with a mean duration of treatment of 11 months) improved HbA1c levels in a group of T2D patients receiving insulin as treatment. They found a borderline significant reduction of HbA1c by 0.7 % in patients with T2D treated with the PPI compared with a reduction of 0.2 % in the control group (matched for gender, age, duration of diabetes, treatment, and diabetic complications). Interestingly, in patients with poor glycemic control (HbA1c >9 %) the beneficial effects of esomeprazole were more pronounced. For these patients HbA1c dropped significantly by 1.2 % in the esomeprazole-treated group ($p = 0.004$) compared with only 0.2 % in the control group ($p = 0.287$). Authors conclude since the control group with

elevated HbA1c levels did not experience a significative decline in HbA1c, it is likely that the observation is related to the esomeprazole treatment, but due to the retrospective nature of this study, the results should be interpreted with caution.

Then, Boj-Carceller et al. [12] selected consecutive patients with T2D who had been admitted to hospital in any department, but excluding those with a diagnosis of hyperglycemic decompensation, diabetic onset or pregnancy. They compared HbA1c levels of patients taking a PPI and those not taking. HbA1c was significantly lower in individuals who took PPI: −0.6 % ($p = 0.018$), 95 % CI: −0.12 to −0.83. When they subdivided these two groups based on diabetes treatment, those taking insulin and concurrent PPI had better glycemic control; HbAc1 of −0.8 % points ($p = 0.022$), 95 % CI: −0.12 to −1.48, compared with those taking insulin but not the study drug. For the rest of comparisons, there was a lack of statistical significance, although the trend for lower HbA1c was constant in all groups taking a PPI.

It is interesting to note that patients retrieved for this study had good glycemic control. Previously, they had found similar results in diabetic in-patients with poor glycemic control. This may be an independent effect of the severity of disease.

The last paper has been published by Crouch et al. [76]. They reviewed electronic medical records of patients with T2D for whom PPIs were prescribed. Patients who were on insulin or prolonged corticosteroid therapy were excluded. Authors compared HbA1c during time periods on PPI therapy (7.1 %) versus time periods off PPI therapy (7.7 %). Unfortunately, they do not mention the mean duration of the

Table 2 Clinical trials registered in ClinicalTrials.gov about proton pump inhibitors and diabetes

Sponsor	Study start year	Estimated primary completion date	Objective/s	Diabetes	PPI	Study design	Primary outcome measures	References
Steno Diabetes Center	2008	2009	To test the effect of Nexium® and probiotics on insulin secretion and cardiovascular risk factors on type 2 diabetic patients	T2D	Esomeprazole	Randomized placebo controlled factorial design double blind	Insulin secretion	[79]
City of Hope Medical Center	2010	2012	To explore the extent to which Nexium® increases endogenous gastrin concentrations and to assess whether Nexium® treatment may be useful in the setting of islet cell transplantation for T1D to expand islet cells in vivo after transplant	Healthy volunteers	Esomeprazole	Randomized parallel assignment open label	Endogenous gastrin concentration with three different treatment doses and least amount of side effects	[80]
Sanford Health	2010	2014	To study the combination therapy of oral administration of sitagliptin and lansoprazole versus placebo for the preservation of pancreatic β-cells still present in patients with recent-onset diabetes and possibly regenerating their β-cells, while safely down-regulating the autoimmune response directed against the β-cells	T1D recently diagnosed	Lansoprazole	Randomized parallel assignment double blind	2 h C-peptide AUC	[81]
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	2009	2011	To find out whether a combination treatment of sitagliptin, lansoprazole, and Diamyd will help maintain functioning β-cells and/or cause new β-cells to form to determine how the drug combination affects insulin doses and blood sugar control to determine whether the drug combination affects the immune response involved in T1D	T1D	Lansoprazole	Randomized parallel assignment double blind	Changes in β-cell function (mixed meal, tolerance test, C-peptide, AUC mean)	[82]
Coordinación de Investigación en Salud, Mexico	2012	–	To evaluate the effect of pantoprazole on insulin secretion in drug-naïve patients with T2D	T2D	Pantoprazole	Randomized parallel assignment double blind	Insulin secretion, the hyperglycemic–hyperinsulinemic clamp technique is perform to assess the phases of insulin secretion: first, late and total insulin secretion	[83]

Table 2 continued

Sponsor	Study start year	Estimated primary completion date	Objective/s	Diabetes	PPI	Study design	Primary outcome measures	References
University of Alberta	2008	2011	To study if the administration of medications to increase the secretion of hormones from the intestines can improve glycemic control, reduce insulin use and promote β-cell regeneration/expansion in subjects with T1D following islet transplantation who are back using small doses of insulin because of early graft dysfunction	T1D	Pantoprazole	Interventional single group assignment open label	The primary endpoint will be insulin independence after 6 months of therapy	[84]

PPI treatment (and they do not use appropriate tests for paired data in the statistical analysis.)

When considering confounding factors, the group of Hove et al. mentioned the possibility that general improved well-being caused by relief of gastro-intestinal symptoms could be beyond the results because their patients had been treated with esomeprazole due to unspecified gastric acid related disorders. From our experience many patients are receiving regular PPI treatment for poorly defined reasons or for conditions where PPIs have not been shown to be useful. Current evidence also suggests PPIs are often over used, only half of patients admitted to medical wards in a university hospital had an appropriate indication [77], so probably this third variable is not affecting significantly the results of transversal studies. Moreover, the effect could be underestimated because this drug has become so routine that people sometimes forget to declare its use during anamnesis.

All these studies are retrospective, as expected in the early stage of a research; it is the classical architecture: from general, exploratory studies, toward highly focused studies. Cross-sectional studies are cost-effective ones and case–control studies represent a step in the ability to prove causation but with more probability of bias. The uncontrolled before and after study design is relatively simple to conduct and superior to observational studies [78], but the study of Crouch and coworkers had a retrospective nature and that is not an authentic uncontrolled before and after study.

In conclusion, the level of evidence for the state of the art in this topic is not really high, nevertheless the consistence of the results—positive and with a similar magnitude in spite of the different context—points in a good direction.

Ongoing trials focus on the potential for proton pump inhibitors in the diabetes treatment

The available studies seem to support the hypothesis that PPIs are associated with better glycemic control in T2D with a global glucose-lowering effectiveness around 0.6–0.7 % points of HbA1c, though this idea has to be tested in randomized clinical trials to be the PPI accepted as a new class of anti-diabetic agent.

Currently, different groups are carrying out interventional studies [79–84] focus mainly on T1D and the potential role for PPIs to promote β-cell regeneration/expansion, in contrast with the retrospective studies that mostly heed T2D, although it is also being explored the effect on insulin secretion in patients with T2D treated with a particular PPI (Table 2).

Summary

It has been reviewed the sparse available literature to date developed to assess the new hypothesis that PPIs could be associated with better glycemic control in diabetes, mainly T2D.

All the studies found are retrospective, with their well-known intrinsic limitations, so causality cannot have been proved, but it was the logical beginning to explore a new field of research. Nevertheless, Bradford Hill "viewpoints" [85] for inferring causation are quite respected, specially: strength of association, consistency (similar results in terms of decrease of HbA1c (%) between different studies), plausibility (the mechanism would be through the secondary hypergastrinemia induced by PPIs), coherence (between epidemiological and laboratory findings), and analogy (*H. pylori* infection elevates serum gastrin and it has been told to lower fasting plasma glucose concentrations [86]).

The gastrin incretin effect does exist since during an ordinary protein-rich meal this hormone stimulates the secretion of insulin. Besides, PPIs may share most of the glucoregulatory effects of incretin-based therapies: potential for improvement of β-cell mass/function, slowing gastric emptying, no weight gain, and even adverse events such as no hypoglycemia or susceptibility to infections. Moreover, the glucose-lowering power seems to be inside the range of dipeptidyl peptidase-4 inhibitors (HbA1c reduction ~0.5–1 %) [87].

Nowadays, interventional trials are being performed to prove PPIs ability to promote β-cell regeneration/expansion in subjects with T1D and to study insulin secretion in T2D, so it is expected to get data of their impact on glucose metabolism from the strongest evidence in a near future.

Conflict of interest   There are no conflicts of interest.

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