Effect of proton pump inhibitors on glycemic control in patients with diabetes

Kohzo Takebayashi, Toshihiko Inukai

Kohzo Takebayashi, Toshihiko Inukai, Department of Internal Medicine, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Saitama 343-8555, Japan

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Correspondence to: Kohzo Takebayashi, MD, Department of Internal Medicine, Dokkyo Medical University Koshigaya Hospital, 2-1-50 Minamikoshigaya, Koshigaya, Saitama 343-8555, Japan. takeb@gmail.plala.or.jp
Telephone: +81-48-9651111
Fax: +81-48-9651127

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Abstract

Gastrin is a linear peptide hormone which is secreted mostly in the stomach pyloric antrum G cells. Although the main role of this hormone is the promotion of the secretion of gastric acid from the stomach parietal cells, gastrin can also behave as a growth factor and stimulate gastric cell proliferation. It is also reported that gastrin promotes β cell neogenesis in the pancreatic ductal complex, modest pancreatic β cell replication, and improvement of glucose tolerance in animal models, in which the remodeling of pancreatic tissues is promoted. These findings suggest the possibility that gastrin has the potential to promote an increase of β cell mass in pancreas, and therefore that gastrin may improve glucose tolerance. Proton pump inhibitors (PPIs) are wildly used clinically for the therapy of gastro-esophageal reflex disease, gastritis due to excess stomach acid, and gastric ulcers. PPIs indirectly elevate serum gastrin levels via a negative feedback effect. Recent evidence has revealed the beneficial effect of PPIs on glycemic control especially in patients with type 2 diabetes mellitus (T2DM), probably via the elevation of the levels of serum gastrin, although the detailed mechanism remains unclear. In addition, the beneficial effects of a combination therapy of gastrin or a PPI with a glucagon-like peptide-1 receptor agonist on glycemic control in animal models have been demonstrated. Although PPIs may be possible candidates for a new approach in the therapy of diabetes, a prospective, long-term, randomized, double-blind, placebo-controlled study is needed to establish the effect of PPIs on glycemic control in a large number of patients with T2DM.

Key words: Gastrin; Proton pump inhibitors; Glycemic control; Type 2 diabetes

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Core tip: Recently, it is reported that gastrin may improve glucose tolerance mainly by the promotion of pancreatic β cell neogenesis. Proton pump inhibitors (PPIs) are wildly used clinically for the treatment such as gastric ulcers, and it is known that PPIs indirectly elevate serum gastrin levels. Recent evidence has showed the beneficial effect of PPIs on glycemic control especially in patients with type 2 diabetes, probably...
via the elevation of serum gastrin levels. Therefore, PPIs may have the potential to be candidates for a new approach in the treatment of diabetes.

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INTRODUCTION

Gastrin is a linear peptide hormone which is secreted mostly in the stomach pyloric antrum G cells, in which high biologically active gastrin (gastrin-17 and gastrin-34) is formed[1-2]. The secretion of gastrin is stimulated by various factors, such as considerable distension of the stomach[3], vagal stimulation[3,4], the presence of food (especially protein, peptides, and amino acids) in the stomach[4-6], and high pH levels in the stomach cavity[5,7]. Gastrin is released into the bloodstream. The main role of this hormone is the stimulation of secretion of gastric acid from the stomach parietal cells. The gastrin receptor, cholecystokinin B (CCK-B) receptor, binds to gastrin and to cholecystokinin with a similar high affinity[8]. Gastrin can directly promote the secretion of gastric acid by binding to CCK-B receptor on parietal cells[9,10]. However, the expression of this receptor is also found on enterochromaffin-like cells, and the binding of CCK-B receptor to gastrin on these cells promotes the secretion of the histamine resulting in subsequent promotion of the release of gastric acids by parietal cells, which may be the central mechanism of gastrin-stimulated acid secretion[6,9-12]. Importantly, gastrin is also able to behave as a growth factor and stimulate gastric cell proliferation[6,13]. It is reported that gastrin promotes β cell neogenesis in pancreatic ductal complex[14], modest pancreatic β cell replication[15], and improvement of glucose tolerance[15] in animal models in which the remodeling of pancreatic tissues is promoted. These findings suggest the possibility that gastrin has a potential promoting effect for the increase in the pancreatic β cell mass. Therefore, gastrin improves glucose tolerance, and these effects appear to occur especially during adult pancreatic tissue remodeling but not in the normal tissue state.

Proton pump inhibitors (PPIs) are wildly used clinically for the therapy of gastro-oesophageal reflex disease, gastritis due to excess stomach acid, and gastric ulcers[16]. PPIs can be orally administrated as an inactive form, which enters the bloodstream from the intestine, reaches the gastric parietal cells, and is activated by crossing the cell membrane into the intracellular compartment. After converting to the active form in the unique parietal cell environment, PPIs irreversibly block the proton pump and can strongly reduce the secretion of gastric acid promoted by either gastrin, acetylcholine, or histamine. It is well known that PPIs indirectly elevate serum gastrin levels via a negative feedback effect[17-22]. Interestingly, in type 2 diabetes mellitus (T2DM) animal models, it has been reported that PPIs improved glycemic control, probably via possible effects on augmenting both serum levels of gastrin and β cell mass[23]. Although some clinical studies showed negative results on glycemic control by PPIs in patients with T2DM[24,25], most studies have demonstrated a significant improvement of glycemic control by PPI administration to these patients[26-32]. Therefore, these agents appear to have the possibility of being a new approach for the therapy of diabetes.

BASIC STUDIES ON THE EFFECT OF GASTRIN ON THE INCREASE IN β CELL MASS

Gastrin and the CCK-B receptor are transiently expressed in fetal tissues of pancreas under period of islet neogenesis[33-35], but no expression is observed in both adult pancreatic β cells[36,37] and the exocrine pancreas[38-40]. It has been reported that in a rat model in which the splenic portion of the pancreas is ligated (an animal model for remodeling of pancreas tissue), transdifferentiation of acinar to ductal cells is promoted, and a ductal complex consisting of a mixture of transdifferentiated acinar and ductal cells is formed[41-44]. A similar ductal complex appeared to emerge in 95% of the pancreatectomized rats (an animal model for diabetes in which pancreatic remodeling is promoted)[35]. Although the CCK-B receptor is not expressed in adult β cells even if the pancreatic tissue is undergoing remodeling, the ductal complex shows characteristics of fetal pancreatic ductal cells in addition to those in adult, including the CCK-B receptor expression[34]. So, it appears that gastrin is able to enhance the process of β cell neogenesis, that was already induced during the remodeling state, via the CCK-B receptor followed by budding from the ductal complex[34,41]. In general, gastrin does not affect β cell replication probably because of a lack of the CCK-B receptor on β cells[14], but there is a report suggesting that, in 95% of the pancreatectomized rats, gastrin treatment not only increased β cells neogenesis from ductal cells but also caused both a modest increase in replication and a decrease in apoptosis in β cells with the resultant improvement of glucose tolerance. The detailed mechanism for these activities remains unclear[15]. The replication of β cells is also reported in gastrinoma patients[45] although only β cell islets located near the gastrinomas exhibited β cell turnover despite the fact that serum levels of gastrin were elevated to the degrees to induce clinically apparent gastrointestinal symptoms. Thus, it is possible that other hormones were also involved. On the other hand, the synergistic effect of other hormones, such as transforming growth factor-α[46], epidermal

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growth factor\(^{[47]}\), and glucagon-like peptide-1 (GLP-1)\(^{[48]}\), with gastrin has also been demonstrated. For example, GLP-1 induces both β cell replication with mitogens and neogenesis of β cell from ductal cells\(^{[49]}\). In combination with GLP-1, gastrin appears to enhance β cell neogenesis even when it is added in animal models, such as either \(db/db\) mice (a model of T2DM)\(^{[50]}\) or non-obese diabetic (NOD) mice (a model of type 1 diabetes mellitus (T1DM))\(^{[48]}\), although, in these models, pancreatic remodeling is not necessarily occurring. In addition, an effect on regulating the autoimmune response against pancreatic β cells by combination therapy was also reported in the NOD mice model\(^{[48]}\). Taken together, these effects of gastrin suggest that this hormone may possess a potential protective effect for the progression of diabetes, especially in combination with other hormones, such as GLP-1.

**THE EFFECT OF PPIs ON GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES: RESULTS OF CLINICAL STUDIES**

Despite the possible effects of gastrin on both increasing β cell mass and improving glycemic control, gastrin treatment has not been used with the patients with T2DM mainly because of the difficulty with oral administration and the suggested side effects on the stomach. On the other hand, there are many publications describing the effects of PPIs on glycemic control in patients with T2DM.

Mefford et al\(^{[26]}\) reported that a significant difference was obtained in HbA1c in patients with T2DM taking PPIs (7.0% of HbA1c, \(n = 65\)) vs those not taking PPIs (7.6% of HbA1c, \(n = 282, P = 0.002\)). Similarly, Boj-Carceller et al\(^{[27]}\) reported that HbA1c was significantly different in T2DM patients who received PPIs (6.7% ± 1.0%, \(n = 54\)) compared with those who did not receive PPIs (7.3% ± 1.4%, \(n = 43, P = 0.018\)). When these patients were assigned to two groups by the treatment of diabetes, those taking insulin and concurrent PPIs had better glycemic control, compared with those taking insulin but not PPI (0.8% reduction, \(P = 0.022\)). In a very recent study, Barchetta et al\(^{[28]}\) showed that the significantly different HbA1c and FPG levels were found in the T2DM patients with PPIs for longer than 2 years (\(n = 245\)) compared with those who did not take PPIs (\(n = 303\)) (7.1% ± 1.07% with PPIs vs 7.4% ± 1.4% without PPIs for HbA1c, \(P = 0.011\); 127 ± 36.9 mg/dL with PPIs vs 147.6 ± 49.6 mg/dL without PPIs for FPG, \(P < 0.001\), respectively).

The increase of the differences was observed in patients treated with insulin and in those treated with combination of PPIs and GLP-1 based therapy\(^{[28]}\). The results of these cross-sectional studies suggest the significant association between treatment with PPIs and the improved glycemic control in patients with T2DM.

On the other hand, in a study using a retrospective analysis, patients were assigned to 2 groups: 21 patients who had taken esomeprazole (a PPI) for 11.3± 3 mo and 21 control subjects\(^{[29]}\). Although there was a tendency for a decline in HbA1c in the patients treated with this PPI, it was not statistically significant (8.6% to 7.9%, \(P = 0.054\)), while in a subgroup with HbA1c > 9%, the reduction was statistically significant (9.7% to 8.5%, \(n = 11, P = 0.004\)). No change in HbA1c was found in the entire control group and in a subgroup with HbA1c > 9.0% in control group (9.2% to 9.0%, \(P = 0.455\); 10.3% to 10.0%, \(P = 0.287\), respectively).

Furthermore, Crouch et al\(^{[30]}\) investigated 71 individuals with T2DM who were not taking insulin. The mean HbA1c was 7.11% during periods taking either prescription or over-the-counter PPIs, vs 7.7% during periods not taking PPIs (a significant difference, \(P = 0.001\)). Although there was no significant difference in mean HbA1c in a metformin monotherapy (6.81 treated with PPIs vs 7.10% treated without PPIs, \(P = 0.25\)), mean HbA1c was significantly lower in a concomitant therapy including metformin and/or sulfonylurea and/or glitazone (7.26 treated with PPIs vs 7.80 treated without PPIs, \(n = 27, P = 0.002\)). However, in another recent retrospective study of T2DM patients with relatively low levels of HbA1c, treatment with PPIs for ≥ 2 mo (mean duration: 180 d, \(n = 43\)) did not significantly change HbA1c levels (6.86% ± 1.10% to 6.77% ± 1.07%). Metformin monotherapy did not change HbA1c compared with a combination therapy including metformin and a therapy in antiidiabetic agents not including metformin\(^{[24]}\). Furthermore, 3 recent prospective randomized, double-blind, placebo-controlled studies using PPIs in small number of T2DM patients showed conflicting results with its effect on glycemic control. Singh et al\(^{[31]}\) investigated the effect of a 12-wk pantoprazole (a PPI) therapy regimen on glycemic control in patients with T2DM\(^{[31]}\). Thirty one eligible patients were randomly assigned to take either pantoprazole (\(n = 16\)) or placebo (\(n = 15\)). Pantoprazole (40 mg twice daily) significantly increased both plasma levels of gastrin (54.4 ± 14.9 to 75.6 ± 15.1 pg/mL, \(P < 0.001\)) and those of insulin (10.5 ± 4.0 to 13.9 ± 4.5 μU/mL, \(P < 0.001\)) and improved the function of β cell as calculated by the homeostasis model assessment-β (HOMA-β). HbA1c significantly decreased with pantoprazole therapy (7.60% ± 1.17% to 6.80% ± 1.16%, \(P < 0.001\)). The decrease of HbA1c was positively associated with a significant elevation in both gastrin and insulin levels. González-Oritz et al\(^{[32]}\) investigated the effect of pantoprazole (40 mg once daily for 45 d) on secretion of insulin in 14 drug-naïve patients with T2DM. Significant increases in both the late insulin phase (215 ± 127 to 308 ± 151 pmol/L, \(P = 0.028\)) and total insulin secretion (174 ± 94 to 265 ± 135 pmol/L, \(P = 0.028\)), and significant decreases in HbA1c levels (7.5% to 6.6%, \(P = 0.018\)) were found with pantoprazole administration (\(n = \)
7), while there was no significant changes in these parameters in patients treated with placebo (n = 7). On the other hand, Hove et al. investigated the effect of esomeprazole on glycemic control in 41 T2DM patients using either dietary control or treatment with oral anti-diabetic agents. These patients were randomly assigned to take either add-on esomeprazole (40 mg daily, n = 20) or placebo (n = 21) during 12 wk. In the esomeprazole group, the area under the curve (AUC) for insulin did not change, while the AUC for the placebo group significantly decreased. Esomeprazole treatment caused a nine-fold elevation in the AUC for gastrin. Contrary to the expectation, HbA1c increased from 7.0% ± 0.6% to 7.3% ± 0.8% (P < 0.05) in the esomeprazole group and from 7.0% ± 0.6% to 7.4% ± 0.8% (P < 0.05) in the placebo group with no significant difference in change between both treatments (unadjusted, P = 0.297). These clinical findings from all of these studies are summarized in Table 1. Based on the published data, the degree of the reduction of HbA1c by PPIs therapy in the studies with positive results appears to be approximately 0.6%-0.9%. This is somewhat milder or similar compared with those by recent available anti-diabetic drugs such as dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose co-transporter 2 inhibitors. This suggests that the effect of PPI for glycemic control is probably moderate and that therefore PPI may have the potential for clinical benefit on glycemic control in patients with T2DM.

THE USE OF PPIs FOR THE TREATMENT OF TYPE 2 DIABETES: INTERPRETATION OF THE RESULTS AND POSSIBLE MECHANISMS OF GLYCEMIC CONTROL

As shown in the previous section, it appears that PPIs generally have a beneficial effect on glycemic control for T2DM patients with some studies showing no effect. The results of the different studies do not appear to be dependent on the type of PPI used. Based on the results of most clinical studies in which glycemic control was improved, it appears that the actual basal levels of HbA1c may be important for the PPIs to show the apparent glucose-lowering effect because PPIs significantly decreased HbA1c level only when the basal HbA1c level was high in 1 retrospective study. In addition, the patients in most of the studies with negative results had a tendency to be under good glycemic control (approximate 7.0% of HbA1c), compared with those studies that showed positive results. In addition, treatment with PPIs and HbA1c levels were independent from possible confounders in a multivariate regression analysis in 1 study, suggesting the importance of baseline HbA1c levels for the glucose lowering effect of PPIs. Next, if the possible effect of PPIs on glycemic control is based on the mechanism of increase of β cell mass, treatment with PPIs for a longer period may be more effective in providing the full effect on glycemic control compared with that observed in most of the previous studies. However, in fact, the mechanism of the clinical effect of PPIs on glycemic control largely remains unclear. Because gastrin does not affect β cell neogenesis from the adult pancreatic ductal cells under a non-remodeling state as previously described, it is not apparent whether the elevation of circulating gastrin levels induced by PPIs can really promote the increase of the mass of β cell in patients with T2DM, in whom pancreatic remodeling is not necessarily occurring. Nonetheless, elevated serum gastrin levels could affect the β cell mass in animal models of T2DM although the mechanism is not fully apparent. PPI mono therapy improved glycemic control with the increase in both plasma insulin and β cells mass in Psammomys obesus, an animal model of T2DM. In this study, a significant effect was obtained only when the PPI was used at a very high dose (lansoprazole 10-15 mg/kg); gastrin was elevated nine-fold at this dose. Since vonoprazan (a new generation PPI: potassium-competitive acid blocker) is more effective for inhibition of secretion of gastric acid and increases serum levels of gastrin (approximate six- to seven-fold with 10-40 mg of vonoprazan) compared with that of the existing PPIs, it would be interesting to investigate in a future study whether this agent is also more effective on glycemic control. However, it is important to note that such elevation of serum gastrin levels by PPIs is not always needed to exhibit the clinically apparent glucose-lowering effect in T2DM patients because, in the study by Singh et al., in which positive results were obtained, the increase of gastrin by a PPI (pantoprazole) was only approximately 1.5-fold, which was accompanied with an increase of insulin. These findings suggest the possibility that mechanisms other than the increase of β cell mass are also involved. One possible mechanism involves a gastrin-stimulated increase in insulin secretion by pancreatic β cells. It has been reported that because the secretion of the endogenous gastrin for the oral glucose tolerance test (OGTT) in healthy subjects is very small, it is unlikely that gastrin strongly promotes insulin secretion under this condition. However, an ordinary protein-rich meal (but not glucose-rich) largely increases both circulating gastrin and insulin levels. Therefore, gastrin appears to significantly stimulate secretion of insulin during and after a meal, this may partially explain the effect of PPIs on glycemic control. Another mechanism may involve the interaction of gastrin with other gastric hormones, such as ghrelin, which is reported to have an important role in energy homeostasis and appetite regulation. There is a report showing that ghrelin was down-regulated in primary gastric cells during gastrin-stimulation, and that ghrelin and gastrin levels had a significant negative correlation in humans. For example, a long-term 3-fold increase of
Table 1 Studies showing glucose-lowering effect of proton pump inhibitors in patients with type 2 diabetes

| Study | Outcome measures | Key findings | Safety information |
|-------|------------------|--------------|--------------------|
| Mefford et al[26] | HbA1c levels in patients with type 2 diabetes taking PPIs (n = 65) vs those not taking PPIs (n = 282) was evaluated in cross-sectional design. | There was a significant difference in HbA1c in patients taking PPIs (7.0% vs 7.6%, P = 0.002) | None reported. |
| Boj-Carceller et al[27] | HbA1c levels in patients with type 2 diabetes taking PPIs (n = 54) vs those not taking PPIs (n = 43) was evaluated in cross-sectional design. | HbA1c was significantly lower in type 2 diabetic patients who take PPIs compared with those not taking PPIs (6.7% ± 1.0% vs 7.3% ± 1.4%, P = 0.018) | None reported. |
| Barchetta et al[28] | HbA1c and FPG levels in patients with type 2 diabetes taking PPIs for longer than 2 yr (n = 245) vs those not taking PPIs (n = 303) was evaluated in cross-sectional design. | None reported. | None reported. |
| Hove et al[29] | HbA1c levels were retrospectively evaluated in patients with type 2 diabetes. Patients were assigned to 2 groups: 21 patients who had taken esomeprazole (a PPI) for 11.3 ± 3 mo and 21 control subjects. | There was a tendency for a decline in HbA1c in the patients treated with this PPI (8.6% vs 7.9%, P = 0.054). In a subgroup with HbA1c > 9% (n = 11), the reduction was statistically significant (9.7% vs 8.5%, P = 0.004). No change in HbA1c was observed in the control group (9.2% vs 9.9%, P = 0.455). | None reported. |
| Han et al[30] | HbA1c was retrospectively evaluated in type 2 diabetic patients treated with PPIs for ≥ 2 mo (mean duration: 180 d, n = 43). | None reported. | None reported. |
| Crouch et al[31] | 71 individuals with type 2 diabetes who were not taking insulin was retrospectively investigated for the change of HbA1c. | HbA1c was 7.1% during periods with either prescription or over-the-counter PPIs, vs 7.7% during periods without PPIs (a significant difference; P = 0.001). | None reported. |
| Singh et al[32] | The effect of pantoprazole (40 mg twice daily) therapy regimen on HbA1c, FPG, serum insulin, serum gastrin levels was prospectively measured in patients with type 2 diabetes in randomized double-blind, placebo-controlled study design. Thirty one eligible patients were randomly assigned to receive either pantoprazole (n = 16) or placebo (n = 15). | HbA1c and FPG significantly decreased with pantoprazole therapy (7.60% ± 0.6% to 7.3% ± 0.1%, P < 0.001 for HbA1c and 126.3 ± 49.6 mg/dL, P < 0.001) levels than those who did not take PPIs. | None reported. |
| González-Oritz et al[33] | The effect of pantoprazole (40 mg once daily for 45 d) on insulin secretion in 14 drug naïve patients with type 2 diabetes was prospectively investigated in a randomized, double-blind, placebo-controlled study design. Thirty one eligible patients were randomly assigned to receive either pantoprazole (n = 16) or placebo (n = 15). | HbA1c increased from 7.0% ± 0.5% to 7.4% ± 0.5% (P = 0.079) and significant decreases in HbA1c levels (7.5% ± 0.6% vs 6.9% ± 0.5%, P = 0.001) was observed. | None reported. |
| Hove et al[34] | The effect of esomeprazole on glycemic control in 41 type 2 diabetic patients using either dietary control or therapy by anti-diabetic agents was prospectively examined in a randomized open-label study. After 3 mo of treatment, there were no significant differences in glycemic control parameters in patients treated with placebo (n = 20) or placebo (n = 21) for 12 wk. Insulin secretion, HbA1c levels and cardiovascular risk factors were evaluated. | The AUC for the placebo group significantly decreased (P = 0.002). HbA1c increased from 7.0% ± 0.6% to 7.3% ± 0.8% (P < 0.05) in the esomeprazole-treated group and from 7.0% ± 0.6% to 7.4% ± 0.8% (P < 0.05) in the placebo group (no significant difference in change between both treatments; unadjusted, P = 0.297). The differences in cardiovascular risk factors were not significant between the two groups. | None reported. |
| Takebayashi et al[35] | HbA1c levels were retrospectively evaluated in type 2 diabetic patients taking PPIs for longer than 2 yr (n = 245) vs those not taking PPIs (n = 303) was evaluated in cross-sectional design. | None reported. | None reported. |

PPIs: Proton pump inhibitors.
gastrin in autoimmune gastritis significantly repressed ghrelin secretion\(^{54}\). These findings suggest the possibility that the increase of gastrin levels is associated with less appetite and improvement of glycemic control via the decreased ghrelin levels although there is as yet no clinical evidence. Furthermore, it is known that the CCK-B receptor exists in the brain, especially in the hypothalamic area\(^{45,55}\). Intracerebroventricular injection of gastrin decreases food intake, while inactivation of CCK-B receptor in mice changes the regulation of food-intake and body weight, and results in obesity\(^{56}\).

Despite the limitation of gastrin diffusion into the brain due to the blood brain barrier (BBB)\(^ {57}\), there are reports suggesting that either peptide or peptide fragments might penetrate into the brain because of the lack of a BBB in the circumventricular organs\(^ {58}\), and that intravenous gastrin administration activated neurons in several portions of brain\(^ {59}\). In addition, it is reported that gastrin in circulation is able to stimulate the area postrema neurons that express the CCK-B receptor and project to the nucleus of the solitary tract (NTS)\(^ {60}\). Mouse brain stem NTS-propiomelanocortin neurons are associated with feeding-induced satiety\(^ {61}\). Therefore, we speculate that it might be possible that increased serum gastrin that is regulated by PPIs directly inhibits appetite via the central nervous system, although it may be possible that gastrin also acts indirectly brain stem via the vagal nerve\(^ {60}\). In addition, a recent study revealed that gastrin stimulates GLP-1 secretion in L cells in the intestine\(^ {62}\). This can explain the possible effect of PPIs on glycemic control at least in part. Finally, it may also be important to consider whether PPIs potentially have a beneficial effect on glycemic control via unknown mechanisms independent of gastrin. Taken together, the mechanisms of the possible PPI effects on glycemic control largely remain unclear, and multiple mechanisms appear to be involved. These possible mechanisms are described in Figure 1.

When treating patients, it is important to consider the potentially deleterious effects of PPIs on glycemic control, which may be more serious than the possible beneficial effect and which may modify the results. It is known that diabetes occasionally occurs with gastroesophageal reflux disease (GERD)\(^ {63,64}\). Because PPIs largely improve GERD clinical symptoms, it may be possible that the appetite of the patients with GERD is improved even if the elevation of gastrin levels by PPIs influences circulating ghrelin levels as previously described. These patients can thus potentially have worse glycemic control. In addition, it is reported that PPIs can induce dysbiosis\(^ {65}\), which is connected with metabolic syndrome. Therefore, we speculate that PPIs can worsen glycemic control in this manner as well.

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Figure 1 The possible mechanisms of proton pump inhibitors on the improvement of glycemic control. PPIs indirectly elevate serum gastrin levels. Gastrin promotes an increase in \(\beta\) cell mass by neogenesis of the \(\beta\) cells from the pancreatic ductal complex probably promoted by binding the gastrin with CCK-B receptor during pancreatic remodeling. In addition, a modest increase in the replication of pancreatic \(\beta\) cells during pancreatic remodeling is also reported although the mechanisms are not apparent because of the lack of a CCK-B receptor on \(\beta\) cells. Gastrin can enhance the effect of GLP-1 on \(\beta\) cell neogenesis from ductal cells. A synergistic effect may occur even under non-remodeling conditions in the pancreas. These mechanisms appear to contribute to the improvement of glycemic control in both type 1 and type 2 diabetes. Furthermore, a combination of GLP-1 and gastrin may protect from the onset or progression of type 1 diabetes by an immunoregulatory effect. Other possible gastrin-mediated mechanisms independent of the \(\beta\) cell mass increase may include stimulation of insulin secretion, interaction with other hormones such as ghrelin, direct or indirect (via vagal nerve) effects in the central nervous systems, and promotion of GLP-1 secretion by L cells in the intestine. Finally, it may be possible that PPIs affect glycemic control by unknown mechanisms independent of the elevation of serum gastrin levels. PPIs: Proton pump inhibitors; CCK-B: Cholecystokinin-B; GLP-1: Glucagon like-peptide-1.
THE EFFECT OF COMBINATIONAL THERAPY OF PPIs (OR GASTRIN) WITH DPP-4 INHIBITORS (OR A GLP-1 RECEPTOR AGONIST) ON GLYCEMIC CONTROL IN TYPE 1 AND TYPE 2 DIABETES IN BOTH ANIMAL AND CLINICAL STUDIES

Recent evidence suggests the greater potential beneficial effect of a combination therapy of various hormones over that of a mono hormone therapy. As described in the previous section, gastrin enhances the effect of GLP-1 on β cell neogenesis, and this combination therapy more effectively improved hyperglycemia than mono therapy by each hormone in NOD mice. This result is also supported in the same animal model by combination therapy with DPP-4 inhibitors, which block degradation of GLP-1 by DPP-4 resulting in the elevation of serum active GLP-1 levels, and PPIs. Furthermore, Patel et al. showed that combination therapy with exendin-4 (a GLP-1 receptor agonist) and omeprazole (a PPI) had better glycemic control compared with mono therapy with these drugs in db/db mice. Recently, Hao et al. examined the effects of short periods of lansoprazole, sitagliptin (a DPP-4 inhibitor), and these concomitant therapy on glycemic control in mice with diet-induced obesity (DIO) and in healthy human subjects. In the DIO mice, lansoprazole therapy significantly improved glucose levels and increased both circulating insulin and C peptide levels than treatment in vehicles. Furthermore, concomitant treatment with lansoprazole and sitagliptin decreased glucose levels with higher levels in C-peptide and insulin compared to that with sitagliptin-treated mice. In a human study, the concomitant use (sitagliptin 100 mg daily and lansoprazole 30 mg daily) for 6 d resulted in significant decrease of glucose levels and increase of insulin levels in an OGTT vs the control, lansoprazole-, and sitagliptin-treated groups. Taken together, the results of these studies suggest the possibility that combination therapy with a GLP-1 receptor agonist (or DPP-4 inhibitors) and gastrin (or a PPI) may provide a more beneficial effect for glycemic control than each mono therapy. In addition, in db/db mice, a GLP-1-gastrin dual receptor agonist has showed a more continued regulatory effect of glucose with a significant increase in β-cell mass in pancreatic tissue than that of monotherapy in liraglutide (a GLP-1 receptor agonist). However, the results of recent randomized, prospective studies evaluating the combination therapy with DPP-4 inhibitors and PPIs in patients with T1DM and T2DM were basically negative. Griffin et al. reported the results of a randomized, placebo-controlled, multicenter, phase 2 trial (REPAIR-T1D) on the effect of concomitant use with sitagliptin and lansoprazole in patients with recent-onset T1DM. Patients aged 11-36 years, diagnosed with T1DM within the past 6 mo, were recruited and were randomized (2:1) to take oral sitagliptin with lansoprazole or placebo for 12 mo. At 12 mo, the 2 h C peptide AUC was similar between the combination (n = 40) and placebo (n = 18) groups. HbA1c levels were mainly constant throughout the study period for both groups (no significant difference). HbA1c adjusted by insulin-dose was also similar (no significant difference) for both groups. Although these overall results were negative, this study is still ongoing with reassessments at both 18 and 24 mo. In T2DM, we investigated the effect of alogliptin (a DPP-4 inhibitor) and lansoprazole (n = 46) combination therapy compared with alogliptin therapy without a PPI (n = 43) on glycemic control in a randomized open-label study (Table 1). At 3 mo after the initiation of the therapy, the changes in HbA1c, FPG, HOMA-β, HOMA-insulin resistance (IR) and serum gastrin were evaluated. A significant decrease in both HbA1c (7.6% ± 0.6% to 6.8% ± 0.7%, P < 0.001 in the combination therapy group, and 7.7% ± 0.5% to 6.7% ± 0.5%, P < 0.001 in the alogliptin therapy group) and FPG (152.0 ± 35.6 to 127.3 ± 27.4 mg/dL, P < 0.001 in the combination therapy group, and 153.6 ± 34.4 to 128.5 ± 26.6 mg/dL, P = 0.001 in the alogliptin therapy group), and a significant increase in HOMA-β were noted in both groups. However, significant differences were not obtained in the changes in HbA1c, FPG, and HOMA-β by therapy between the combination and the alogliptin mono therapy group (P = 0.2945, P = 1901, P = 0.3042, respectively). The levels of serum gastrin in the concomitant group was significantly elevated compared with those in the alogliptin mono therapy group (P = 0.0004). With the combination therapy, the serum gastrin levels increased approximately two-fold. Apart from the issue of the period of the administration, one of the possible reasons for these negative results may be due to the use of DPP-4 inhibitors rather than a GLP-1 receptor agonist with the PPI. The elevation of GLP-1 levels by DPP-4 inhibitors is relatively small compared with that observed with the GLP-1 receptor agonist. Therefore, despite the reports with the positive results on glycemic control using a combination of a PPI and DPP-4 inhibitors, the effect may be small when compared to that observed with the combination of a PPI and a GLP-1 receptor agonist. The clinical data on the combination therapy of a PPI and a GLP-1 receptor agonist in patients with T1DM and T2DM are not available yet, but this therapy appears to be an attractive one, and future studies are warranted to confirm the effect of this combination therapy.

CONCLUSION

Although PPI therapy is attractive as a new approach for the therapy of diabetes (especially T2DM), the clinical effect on glycemic control of this drug is not yet fully established. The mechanisms of the clinical effect of PPIs on glycemic control are also not fully elucidated. A prospective, long term, randomized, double-blind,
placebo-controlled study on PPIs in a larger number of the T2DM patients is warranted to confirm the effect of PPIs on glycemic control, especially in patients with relatively poor glycemic control. The combination therapy of a PPI with a GLP-1 receptor agonist (rather than DPP-4 inhibitors) may improve glycemic control in both T1DM and T2DM. A clinical study with a large number of patients is needed to establish the potential efficacy. At present, the clinicians’ concerns are whether the patients can have better glycemic control when PPIs are used for GERD or gastric ulcers in patients with T2DM, because the use of PPIs is not yet allowed for T2DM treatment in every country. If the treatment is for a long-term period, it is also important to consider the possible harmful effects of PPIs, including bone fracture\(^\text{[73]}\) and small intestine bacterial overgrowth\(^\text{[74]}\).

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