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EDITORIAL

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

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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

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 be 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-esophageal 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[34,38-40]. 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), transdifferentitation of acinar to ductal cells is promoted, and a ductal complex consisting of a mixture transdifferented 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)[15]. 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[14,41]. 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 other hand, the synergistic effect of other hormones, such as transforming growth factor-α[46], epidermal

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 withT2DM.

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 received 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 antidiabetic 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 naive 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*[25] 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[25]. 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 to date, the degrees 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[51] or sodium-glucose co-transporter 2 inhibitors[52]. 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[26-32], it appears that the actual basal levels of HbA1c may be important for the PPIs to show the apparent glucose-lowing effect because PPIs significantly decreased HbA1c level only when the basal HbA1c level was high in 1 retrospective study[29]. 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)[24,25], compared with those studies that showed positive results[26-32]. In addition, treatment with PPIs and HbA1c levels were independent from possible confounders in a multivariate regression analysis in 1 study[28], 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[14,15], 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[23]. 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[53], 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-lowing effect in T2DM patients because, in the study by Singh *et al*[31], in which positive results were obtained, the increase of gastrin by a PPI (pantoprazole) was only approximately 1.5-fold[31], 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[2]. 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

Mefford *et al*[26]	Outcome measures: 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 Key findings: There was a significant difference in HbA1c in patients taking PPIs *vs* those not taking PPIs (7.0% *vs* 7.6%, P = 0.002) Safety information: No information is described
Boj-Carceller *et al*[27]	Outcome measures: 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 Key findings: 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) Safety information: No information is described
Barchetta *et al*[28]	Outcome measures: 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 Key findings: Patients with PPIs had significantly lower HbA1c (7.1% ± 1.07% *vs* 7.4% ± 1.4%, P = 0.011) and FPG (127 ± 36.9 mg/dL *vs* 147.6 ± 49.6 mg/dL, P < 0.001) levels than those who did not take PPIs Safety information: No information is described
Hove *et al*[29]	Outcome measures: 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 Key findings: There was a tendency for a decline in HbA1c in the patients treated with this PPI (8.6% to 7.9%, P = 0.054). In a subgroup with HbA1c > 9% (n = 11), the reduction was statistically significant (9.7% to 8.5%, P = 0.004). No change in HbA1c was observed in the control group (9.2% to 9.9%, P = 0.455) Safety information: No information is described
Han *et al*[24]	Outcome measures: HbA1c was retrospectively evaluated in type 2 diabetic patients treated with PPIs for ⩾ 2 mo (mean duration: 180 d, n = 43) Key findings: There was no significant change in HbA1c levels (6.86% ± 1.10% to 6.77% ± 1.07%; P = 0.406) Safety information: No information is described
Crouch *et al*[30]	Outcome measures: 71 individuals with type 2 diabetes who were not taking insulin was retrospectively investigated for the change of HbA1c Key findings: The mean HbA1c was 7.11% during periods with either prescription or over-the-counter PPIs, *vs* 7.7% during periods without PPIs (a significant difference; P = 0.001) Safety information: No information is described
Singh *et al*[31]	Outcome measures: The effect of a 12-wk 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) Key findings: HbA1c and FPG significantly decreased with pantoprazole therapy (7.60% ± 1.17% to 6.80% ± 1.16%, P < 0.001 for HbA1c and 126.3 ± 10.3 to 109.2 ± 13.0 mg/dL, P = 0.017 for FPG), and the differences were significant between the two groups (P = 0.004 for HbA1c, P = 0.019 for FPG). Pantoprazole significantly increased both plasma gastrin (P < 0.001) and insulin levels (P < 0.001) Safety information: Nine patients reported adverse events as nausea, vomiting, headache and myalgia, which were similar and mild in the both groups. None of the patients had hypoglycemia
González-Oritz *et al*[32]	Outcome measures: The effect of pantoprazole (40 mg once daily for 45 d) on insulin secretion in 14 drug naive patients with type 2 diabetes was prospectively investigated in a randomized, double-blind, placebo-controlled study design. Insulin secretion evaluated by hyperglycemic and hyperinsulinemic clamp technique, HbA1c, FPG and serum lipids were measured Key findings: Significant increases in total insulin secretion (P = 0.028), and significant decreases in HbA1c levels (7.5% to 6.6%; P = 0.018) but not FPG levels (P = 0.236) were found with pantoprazole therapy (n = 7), while there was no significant changes in these parameters in patients treated with placebo (n = 7). There were no significant changes in serum lipids in both groups Safety information: Two patients had mild headache (one in each group)
Hove *et al*[25]	Outcome measures: 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 double-blind placebo-controlled 2 × 2 factorial study. These patients were randomly assigned to receive either add-on esomeprazole (40 mg daily, n = 20) or placebo (n = 21) for 12 wk. Insulin secretion, HbA1c levels and cardiovascular risk factors were evaluated Key findings: In the esomeprazole-treated group, the AUC (area under the curve) for insulin did not change (P = 0.838), while 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 Safety information: Flatulence in 2 patients and diarrhea in 1 patient was reported in lansoprazole group, and flatulence in 2 patients and intermittent diarrhea in 1 patient was reported in placebo group
Takebayashi *et al*[72]	Outcome measures: The effect of alogliptin and lansoprazole (n = 46) combination therapy compared with alogliptin therapy without lansoprazole (n = 43) on glycemic control was investigated in a randomized open-label study. After 3 mo of treatment, the changes in HbA1c, FPG, serum gastrin were evaluated Key findings: A significant decrease in both HbA1c and FPG (respective 7.6% ± 0.6% to 6.8% ± 0.7%, P < 0.0001, 52.0 ± 35.6 to 127.3 ± 27.4 mg/dL, P < 0.0001 in the combination therapy group, and respective 7.7% ± 0.5% to 6.7% ± 0.5%, P < 0.0001, 153.6 ± 34.4 to 128.5 ± 26.6 mg/dL, P = 0.0001 in the alogliptin therapy group) was obtained. There were no significant differences in changes in HbA1c, FPG (P = 0.2945, P = 0.1901, respectively) and significant elevation in change in gastrin (approximate twofold, P = 0.0004) before and after therapy between the combination and the alogliptin mono therapy group Safety information: In alogliptin group, 1 patient discontinued the drug due to epi-gastric pain. In the combination group, 1 patient withdrew due to a mild cerebral infarction, and 1 patient noticed occasional hypoglycemic symptoms

PPIs: Proton pump inhibitors.

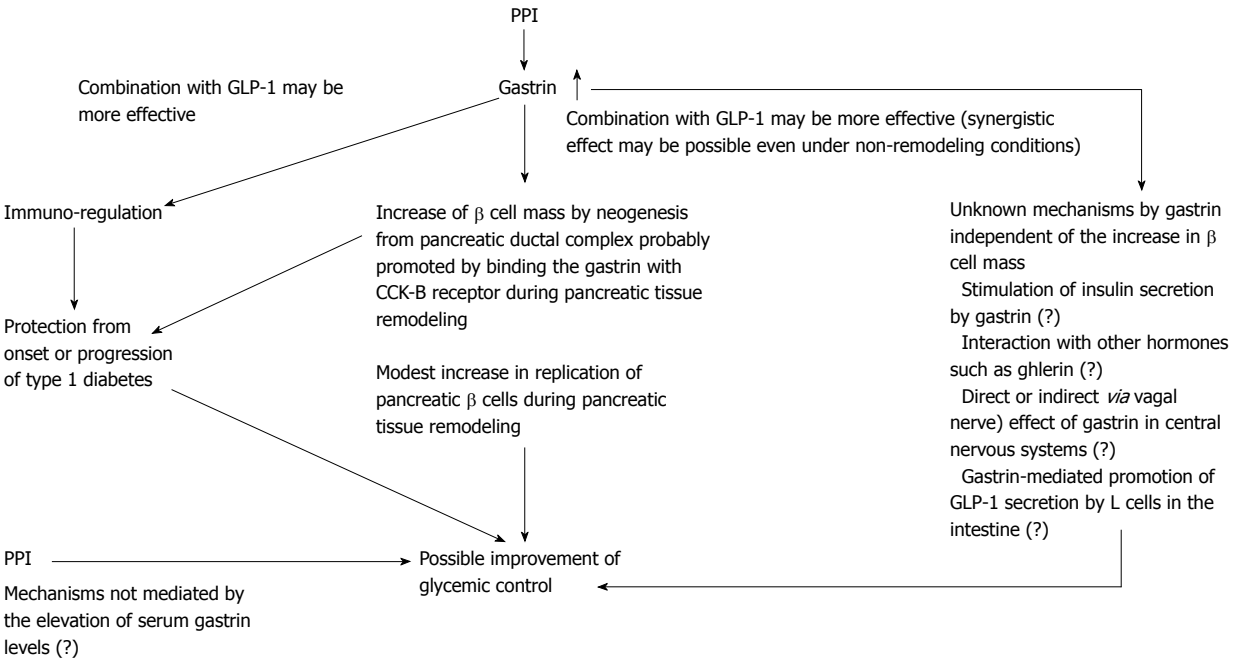

Figure 1 The possible mechanisms of proton pump inhibitors on the improvement of glycemic control. PPIs indirectly elevate serum gastrin levels. Gastrin promotes an increase in β cell mass by neogenesis of the β cells from the pancreatic ductal complex probably promoted by binding the gastrin with CCK-B receptor during pancreatic remodeling. In addition, a modest increase in the replication of pancreatic β cells during pancreatic remodeling is also reported although the mechanisms are not apparent because of the lack of a CCK-B receptor on β cells. Gastrin can enhance the effect of GLP-1 on β 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 β 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.

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 ghlerin 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[8,55]. 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 cirvumventricular 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-proopiomelamocortin 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 mechanism 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.

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[66]. 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[48]. 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[67]. Furthermore, Patel *et al*[68], 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*[69] 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)[70]. 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*[71] 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[72] (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[67,69], 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[73] and small intestine bacterial overgrowth[74].

REFERENCES

1 **Gregory RA**, Tracy HJ. Isolation of two "big gastrins" from Zollinger-Ellison tumour tissue. *Lancet* 1972; **2**: 797-799 [PMID: 4116235]

2 **Rehfeld JF**. Incretin physiology beyond glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide: cholecystokinin and gastrin peptides. *Acta Physiol* (Oxf) 2011; **201**: 405-411 [PMID: 21392266 DOI: 10.1111/j.1748-1716.2010.02235.x]

3 **Schubert ML**, Makhlouf GM. Gastrin secretion induced by distention is mediated by gastric cholinergic and vasoactive intestinal peptide neurons in rats. *Gastroenterology* 1993; **104**: 834-839 [PMID: 8095036]

4 **Schubert ML**, Makhlouf GM. Neural, hormonal, and paracrine regulation of gastrin and acid secretion. *Yale J Biol Med* 1992; **65**: 553-560; discussion 621-623 [PMID: 1364124]

5 **Chueca E**, Lanas A, Piazuelo E. Role of gastrin-peptides in Barrett's and colorectal carcinogenesis. *World J Gastroenterol* 2012; **18**: 6560-6570 [PMID: 23236230 DOI: 10.3748/wjg.v18.i45.6560]

6 **Burkitt MD**, Varro A, Pritchard DM. Importance of gastrin in the pathogenesis and treatment of gastric tumors. *World J Gastroenterol* 2009; **15**: 1-16 [PMID: 19115463]

7 **Brand SJ**, Stone D. Reciprocal regulation of antral gastrin and somatostatin gene expression by omeprazole-induced achlorhydria. *J Clin Invest* 1988; **82**: 1059-1066 [PMID: 2901431]

8 **Dufresne M**, Seva C, Fourmy D. Cholecystokinin and gastrin receptors. *Physiol Rev* 2006; **86**: 805-847 [PMID: 16816139]

9 **Soll AH**, Amirian DA, Thomas LP, Reedy TJ, Elashoff JD. Gastrin receptors on isolated canine parietal cells. *J Clin Invest* 1984; **73**: 1434-1447 [PMID: 6325503]

10 **Bitziou E**, Patel BA. Simultaneous detection of gastric acid and histamine release to unravel the regulation of acid secretion from the guinea pig stomach. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G396-G403 [PMID: 22595991 DOI: 10.1152/ajpgi.00548.2011]

11 **Waldum HL**, Hauso Ø, Fossmark R. The regulation of gastric acid secretion - clinical perspectives. *Acta Physiol* (Oxf) 2014; **210**: 239-256 [PMID: 24279703 DOI: 10.1111/apha.12208]

12 **Schmitz F**, Göke MN, Otte JM, Schrader H, Reimann B, Kruse ML, Siegel EG, Peters J, Herzig KH, Fölsch UR, Schmidt WE. Cellular expression of CCK-A and CCK-B/gastrin receptors in human gastric mucosa. *Regul Pept* 2001; **102**: 101-110 [PMID: 11730982]

13 **Hansen OH**, Pedersen T, Larsen JK, Rehfeld JF. Effect of gastrin on gastric mucosal cell proliferation in man. *Gut* 1976; **17**: 536-541 [PMID: 964686]

14 **Rooman I**, Lardon J, Bouwens L. Gastrin stimulates beta-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. *Diabetes* 2002; **51**: 686-690 [PMID: 11872667]

15 **Téllez N**, Joanny G, Escoriza J, Vilaseca M, Montanya E. Gastrin treatment stimulates β-cell regeneration and improves glucose tolerance in 95% pancreatectomized rats. *Endocrinology* 2011; **152**: 2580-2588 [PMID: 21558313 DOI: 10.1210/en.2011-0066]

16 **Zhang JX**, Ji MY, Song J, Lei HB, Qiu S, Wang J, Ai MH, Wang J, Lv XG, Yang ZR, Dong WG. Proton pump inhibitor for non-erosive reflux disease: a meta-analysis. *World J Gastroenterol* 2013; **19**: 8408-8419 [PMID: 24363534 DOI: 10.3748/wjg.v19.i45.8408]

17 **Sheen E**, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 2011; **56**: 931-950 [PMID: 21365243 DOI: 10.1007/s10620-010-1560-3]

18 **Ligumsky M**, Lysy J, Siguencia G, Friedlander Y. Effect of long-term, continuous versus alternate-day omeprazole therapy on serum gastrin in patients treated for reflux esophagitis. *J Clin Gastroenterol* 2001; **33**: 32-35 [PMID: 11418787]

19 **Hu YM**, Mei Q, Xu XH, Hu XP, Hu NZ, Xu JM. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans. *World J Gastroenterol* 2006; **12**: 4750-4753 [PMID: 16937451]

20 **Cadiot G**, Vissuzaine C, Pospai D, Ruszniewski P, Potet F, Mignon M. [Effect of prolonged treatment with proton pump inhibitors on serum gastrin levels and the fundus mucosa. Preliminary results]. *Gastroenterol Clin Biol* 1995; **19**: 811-817 [PMID: 8566561]

21 **Koop H**, Klein M, Arnold R. Serum gastrin levels during long-term omeprazole treatment. *Aliment Pharmacol Ther* 1990; **4**: 131-138 [PMID: 2104080]

22 **Sanders SW**, Tolman KG, Greski PA, Jennings DE, Hoyos PA, Page JG. The effects of lansoprazole, a new H+,K(+)-ATPase inhibitor, on gastric pH and serum gastrin. *Aliment Pharmacol Ther* 1992; **6**: 359-372 [PMID: 1600052]

23 **Bödvarsdóttir TB**, Hove KD, Gotfredsen CF, Pridal L, Vaag A, Karlsen AE, Petersen JS. Treatment with a proton pump inhibitor improves glycaemic control in Psammomys obesus, a model of type 2 diabetes. *Diabetologia* 2010; **53**: 2220-2223 [PMID: 20585936 DOI: 10.1007/s00125-010-1825-6]

24 **Han N**, Oh M, Park SM, Kim YJ, Lee EJ, Kim TK, Kim TN, Kwon MJ, Kim MK, Lee SH, Rhee BD, Park JH. The effect of proton pump inhibitors on glycated hemoglobin levels in patients with type 2 diabetes mellitus. *Can J Diabetes* 2015; **39**: 24-28 [PMID: 25305802 DOI: 10.1016/j.jcjd.2013.10.008]

25 **Hove KD**, Brøns C, Færch K, Lund SS, Petersen JS, Karlsen AE, Rossing P, Rehfeld JF, Vaag A. Effects of 12 weeks' treatment with a proton pump inhibitor on insulin secretion, glucose metabolism and markers of cardiovascular risk in patients with type 2 diabetes: a randomised double-blind prospective placebo-controlled study. *Diabetologia* 2013; **56**: 22-30 [PMID: 23011351 DOI: 10.1007/s00125-012-2714-y]

26 **Mefford IN**, Wade EU. Proton pump inhibitors as a treatment method for type II diabetes. *Med Hypotheses* 2009; **73**: 29-32 [PMID: 19304401]

27 **Boj-Carceller D**, Bocos-Terraz P, Moreno-Vernis M, Sanz-Paris A, Trincado-Aznar P, Albero-Gamboa R. Are proton pump inhibitors a new antidiabetic drug? A cross sectional study. *World J Diabetes* 2011; **2**: 217-220 [PMID: 22174957 DOI: 10.4239/wjd.v2.i12.217]

28 **Barchetta I**, Guglielmi C, Bertoccini L, Calella D, Manfrini S, Secchi C, Pozzilli P, Cavallo MG. Therapy with proton pump inhibitors in patients with type 2 diabetes is independently associated with improved glycometabolic control. *Acta Diabetol* 2015; Epub ahead of print [PMID: 25716766]

29 **Hove KD**, Færch K, Bödvarsdóttir TB, Karlsen AE, Petersen JS, Vaag A. Treatment with a proton pump inhibitor improves glycaemic control in type 2 diabetic patients - a retrospective analysis. *Diabetes Res Clin Pract* 2010; **90**: e72-e74 [PMID: 20888658 DOI: 10.1016/j.diabres.2010.09.007]

30 **Crouch MA**, Mefford IN, Wade EU. Proton pump inhibitor therapy associated with lower glycosylated hemoglobin levels in type 2 diabetes. *J Am Board Fam Med* 2012; **25**: 50-54 [PMID: 22218624 DOI: 10.3122/jabfm.2012.01.100161]

31 **Singh PK**, Hota D, Dutta P, Sachdeva N, Chakrabarti A, Srinivasan

A, Singh I, Bhansali A. Pantoprazole improves glycemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2012; **97**: E2105-E2108 [PMID: 22904177 DOI: 10.1210/jc.2012-1720]

32 **González-Ortiz M**, Martínez-Abundis E, Mercado-Sesma AR, Álvarez-Carrillo R. Effect of pantoprazole on insulin secretion in drug-naïve patients with type 2 diabetes. *Diabetes Res Clin Pract* 2015; **108**: e11-e13 [PMID: 25704601 DOI: 10.1016/j.diabres.2015.01.039]

33 **Larsson LI**, Rehfeld JF, Sundler F, Håkanson R. Pancreatic gastrin in foetal and neonatal rats. *Nature* 1976; **262**: 609-610 [PMID: 958427]

34 **Rooman I**, Lardon J, Flamez D, Schuit F, Bouwens L. Mitogenic effect of gastrin and expression of gastrin receptors in duct-like cells of rat pancreas. *Gastroenterology* 2001; **121**: 940-949 [PMID: 11606507]

35 **Brand SJ**, Fuller PJ. Differential gastrin gene expression in rat gastrointestinal tract and pancreas during neonatal development. *J Biol Chem* 1988; **263**: 5341-5347 [PMID: 3356689]

36 **Saillan-Barreau C**, Dufresne M, Clerc P, Sanchez D, Corominola H, Moriscot C, Guy-Crotte O, Escrieut C, Vaysse N, Gomis R, Tarasova N, Fourmy D. Evidence for a functional role of the cholecystokinin-B/gastrin receptor in the human fetal and adult pancreas. *Diabetes* 1999; **48**: 2015-2021 [PMID: 10512367]

37 **Morisset J**, Julien S, Lainé J. Localization of cholecystokinin receptor subtypes in the endocine pancreas. *J Histochem Cytochem* 2003; **51**: 1501-1513 [PMID: 14566022]

38 **Bouwens L**, Pipeleers DG. Extra-insular beta cells associated with ductules are frequent in adult human pancreas. *Diabetologia* 1998; **41**: 629-633 [PMID: 9662042]

39 **Ramiya VK**, Maraist M, Arfors KE, Schatz DA, Peck AB, Cornelius JG. Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells. *Nat Med* 2000; **6**: 278-282 [PMID: 10700229]

40 **Yatoh S**, Dodge R, Akashi T, Omer A, Sharma A, Weir GC, Bonner-Weir S. Differentiation of affinity-purified human pancreatic duct cells to beta-cells. *Diabetes* 2007; **56**: 1802-1809 [PMID: 17473224]

41 **Wang RN**, Klöppel G, Bouwens L. Duct- to islet-cell differentiation and islet growth in the pancreas of duct-ligated adult rats. *Diabetologia* 1995; **38**: 1405-1411 [PMID: 8786013]

42 **Bouwens L**. Transdifferentiation versus stem cell hypothesis for the regeneration of islet beta-cells in the pancreas. *Microsc Res Tech* 1998; **43**: 332-336 [PMID: 9849974]

43 **Iovanna JL**. Redifferentiation and apoptosis of pancreatic cells during acute pancreatitis. *Int J Pancreatol* 1996; **20**: 77-84 [PMID: 8968862]

44 **Bockman DE**, Merlino G. Cytological changes in the pancreas of transgenic mice overexpressing transforming growth factor alpha. *Gastroenterology* 1992; **103**: 1883-1892 [PMID: 1451981]

45 **Meier JJ**, Butler AE, Galasso R, Rizza RA, Butler PC. Increased islet beta cell replication adjacent to intrapancreatic gastrinomas in humans. *Diabetologia* 2006; **49**: 2689-2696 [PMID: 17016695]

46 **Wang TC**, Bonner-Weir S, Oates PS, Chulak M, Simon B, Merlino GT, Schmidt EV, Brand SJ. Pancreatic gastrin stimulates islet differentiation of transforming growth factor alpha-induced ductular precursor cells. *J Clin Invest* 1993; **92**: 1349-1356 [PMID: 8376589]

47 **Suarez-Pinzon WL**, Lakey JR, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin induces neogenesis of human islet {beta}-cells from pancreatic duct cells and an increase in functional {beta}-cell mass. *J Clin Endocrinol Metab* 2005; **90**: 3401-3409 [PMID: 15769977]

48 **Suarez-Pinzon WL**, Power RF, Yan Y, Wasserfall C, Atkinson M, Rabinovitch A. Combination therapy with glucagon-like peptide-1 and gastrin restores normoglycemia in diabetic NOD mice. *Diabetes* 2008; **57**: 3281-3288 [PMID: 18835930 DOI: 10.2337/db08-0688]

49 **Lavine JA**, Attie AD. Gastrointestinal hormones and the regulation of β-cell mass. *Ann N Y Acad Sci* 2010; **1212**: 41-58 [PMID: 21039588 DOI: 10.1111/j.1749-6632.2010.05802.x]

50 **Tamaki M**, Fujitani Y, Uchida T, Hirose T, Kawamori R, Watada H. Combination treatment of db/db mice with exendin-4 and gastrin preserves β-cell mass by stimulating β-cell growth and differentiation. *J Diabetes Investig* 2010; **1**: 172-183 [PMID: 24843429 DOI: 10.1111/j.2040-1124.2010.00044.x]

51 **Nauck MA**, Vilsbøll T, Gallwitz B, Garber A, Madsbad S. Incretin-based therapies: viewpoints on the way to consensus. *Diabetes Care* 2009; **32** Suppl 2: S223-S231 [PMID: 19875556 DOI: 10.2337/dc09-S315]

52 **Whalen K**, Miller S, Onge ES. The Role of Sodium-Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes. *Clin Ther* 2015; **37**: 1150-1166 [PMID: 25891804 DOI: 10.1016/j.clinthera.2015.03.004]

53 **Jenkins H**, Sakurai Y, Nishimura A, Okamoto H, Hibberd M, Jenkins R, Yoneyama T, Ashida K, Ogama Y, Warrington S. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. *Aliment Pharmacol Ther* 2015; **41**: 636-648 [PMID: 25707624 DOI: 10.1111/apt.13121]

54 **Rau TT**, Sonst A, Rogler A, Burnat G, Neumann H, Oeckl K, Neuhuber W, Dimmler A, Faller G, Brzozowski T, Hartmann A, Konturek PC. Gastrin mediated down regulation of ghrelin and its pathophysiological role in atrophic gastritis. *J Physiol Pharmacol* 2013; **64**: 719-725 [PMID: 24388886]

55 **Mercer LD**, Le VQ, Nunan J, Jones NM, Beart PM. Direct visualization of cholecystokinin subtype2 receptors in rat central nervous system using anti-peptide antibodies. *Neurosci Lett* 2000; **293**: 167-170 [PMID: 11036187]

56 **Clerc P**, Coll Constans MG, Lulka H, Broussaud S, Guigné C, Leung-Theung-Long S, Perrin C, Knauf C, Carpéné C, Pénicaud L, Seva C, Burcelin R, Valet P, Fourmy D, Dufresne M. Involvement of cholecystokinin 2 receptor in food intake regulation: hyperphagia and increased fat deposition in cholecystokinin 2 receptor-deficient mice. *Endocrinology* 2007; **148**: 1039-1049 [PMID: 17122076]

57 **Greenstein RJ**, Clain DJ, Straus E, Yalow RS. Distribution, molecular forms, and bioactivity of immunoreactive gastrin in a patient with metastatic gastrinoma. *Am J Gastroenterol* 1987; **82**: 886-889 [PMID: 3631036]

58 **Banks WA**, Audus KL, Davis TP. Permeability of the blood-brain barrier to peptides: an approach to the development of therapeutically useful analogs. *Peptides* 1992; **13**: 1289-1294 [PMID: 1494505]

59 **Yakabi K**, Iwabuchi H, Nakamura T, Endo K, Fukunaga Y, Kumaki I, Takayama K. Neuronal expression of Fos protein in the brain after intravenous injection of gastrin in rats. *Neurosci Lett* 2002; **317**: 57-60 [PMID: 11755239]

60 **Danzer M**, Jocic M, Samberger C, Painsipp E, Bock E, Pabst MA, Crailsheim K, Schicho R, Lippe IT, Holzer P. Stomach-brain communication by vagal afferents in response to luminal acid backdiffusion, gastrin, and gastric acid secretion. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**: G403-G411 [PMID: 14592947]

61 **Fan W**, Ellacott KL, Halatchev IG, Takahashi K, Yu P, Cone RD. Cholecystokinin-mediated suppression of feeding involves the brainstem melanocortin system. *Nat Neurosci* 2004; **7**: 335-336 [PMID: 15034587]

62 **Cao Y**, Cao X, Liu XM. Expression of cholecystokinin2-receptor in rat and human L cells and the stimulation of glucagon-like peptide-1 secretion by gastrin treatment. *Acta Histochem* 2015; **117**: 205-210 [PMID: 25601282 DOI: 10.1016/j.acthis.2014.12.007]

63 **Feldman M**, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983; **98**: 378-384 [PMID: 6402969]

64 **Maser RE**, Pfeifer MA, Dorman JS, Kuller LH, Becker DJ, Orchard TJ. Diabetic autonomic neuropathy and cardiovascular risk. Pittsburgh Epidemiology of Diabetes Complications Study III. *Arch Intern Med* 1990; **150**: 1218-1222 [PMID: 2353855]

65 **Wallace JL**, Syer S, Denou E, de Palma G, Vong L, McKnight W, Jury J, Bolla M, Bercik P, Collins SM, Verdu E, Ongini E. Proton pump inhibitors exacerbate NSAID-induced small intestinal injury

by inducing dysbiosis. *Gastroenterology* 2011; **141**: 1314-1322, 1314-1322, [PMID: 21745447 DOI: 10.1053/j.gastro.2011.06.075]

66 **Sadry SA**, Drucker DJ. Emerging combinatorial hormone therapies for the treatment of obesity and T2DM. *Nat Rev Endocrinol* 2013; **9**: 425-433 [PMID: 23478327 DOI: 10.1038/nrendo.2013.47]

67 **Suarez-Pinzon WL**, Cembrowski GS, Rabinovitch A. Combination therapy with a dipeptidyl peptidase-4 inhibitor and a proton pump inhibitor restores normoglycaemia in non-obese diabetic mice. *Diabetologia* 2009; **52**: 1680-1682 [PMID: 19455306 DOI: 10.1007/s00125-009-1390-z]

68 **Patel V**, Joharapurkar A, Gandhi T, Patel K, Dhanesha N, Kshirsagar S, Dhote V, Detroja J, Bahekar R, Jain M. Omeprazole improves the anti-obesity and antidiabetic effects of exendin-4 in db/db mice (-4 db/db)*. *J Diabetes* 2013; **5**: 163-171 [PMID: 22830490 DOI: 10.1111/j.1753-0407.2012.00227.x]

69 **Hao S**, Sun J, Tian X, Sun X, Zhang Z, Gao Y. Lansoprazole enhances the antidiabetic effect of sitagliptin in mice with diet-induced obesity and healthy human subjects. *J Pharm Pharmacol* 2014; **66**: 1133-1139 [PMID: 24628303 DOI: 10.1111/jphp.12237]

70 **Fosgerau K**, Jessen L, Lind Tolborg J, Østerlund T, Schæffer Larsen K, Rolsted K, Brorson M, Jelsing J, Skovlund Ryge Neerup T. The novel GLP-1-gastrin dual agonist, ZP3022, increases β-cell mass and prevents diabetes in db/db mice. *Diabetes Obes Metab* 2013; **15**: 62-71 [PMID: 22862961 DOI: 10.1111/j.1463-1326.2012.01676.x]

71 **Griffin KJ**, Thompson PA, Gottschalk M, Kyllo JH, Rabinovitch A. Combination therapy with sitagliptin and lansoprazole in patients with recent-onset type 1 diabetes (REPAIR-T1D): 12-month results of a multicentre, randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol* 2014; **2**: 710-718 [PMID: 24997559 DOI: 10.1016/S2213-8587(14)70115-9]

72 **Takebayashi K**, Sakurai S, Suzuki T, Hori K, Terasawa T, Naruse R, Hara K, Suetsugu M, Tsuchiya T, Aoki H, Hamasaki T, Shuutou H, Inukai T. Effect of combination therapy with alogliptin and lansoprazole on glycemic control in patients with type 2 diabetes. *Endocr J* 2014; **61**: 1031-1039 [PMID: 25185672]

73 **Leontiadis GI**, Moayyedi P. Proton pump inhibitors and risk of bone fractures. *Curr Treat Options Gastroenterol* 2014; **12**: 414-423 [PMID: 25209137 DOI: 10.1007/s11938-014-0030-y]

74 **Lo WK**, Chan WW. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. *Clin Gastroenterol Hepatol* 2013; **11**: 483-490 [PMID: 23270866 DOI: 10.1016/j.cgh.2012.12.011]

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