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Research Article

EFFECT OF PROTON PUMP INHIBITORS ON TYPE II DIABETES MELLITUS

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Abstract

Diabetes mellitus [DM] is a chronic metabolic disorder with its associated complications. Despite the plethora of available antidiabetic drugs to treat DM search continues to discover newer drugs. Proton pump inhibitors [PPIs] are the drugs which have been tested by researchers in animal models and in clinical set up to treat DM. They appeared to be promising drugs to reduce hyperglycemia. They can be used as supportive drugs along with the primary antidiabetic drugs. PPIs enhance rebound gastrin release, increase beta cell mass and insulin release. They are not hypoglycemic drugs. They reduce blood sugar by increase in gastrin and GLP-1 levels, decrease in ghrelin levels, reduced appetite, delayed gastric emptying and enhanced satiety through action on CNS.PPIs are the inhibitors of organic cation tansporters (OCTs) for which metformin is the substrate and hence the plasma levels of metformin are increased. The potential and safety of PPIs in treatment of DM should be evaluated by long term clinical trials.

Keywords: Antidiabetic, Gastrin, Metformin, Proton Pump Inhibitors

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Introduction

Diabetes mellitus [DM] is a fast growing non infectious disease which affects the population of both developing and developed countries. It is estimated that by 2025, about 380 million people will be affected by type 2 DM.[1] Type 2 DM is more common which is mainly treated by oral antidiabetic drugs.[2] Type 2 DM is characterized by progressive pancreatic beta cell failure and peripheral insulin resistance in muscles and fat. It also comprises accelerated lipolysis, incretin resistance or deficiency, increased renal glucose absorption and hyperglucagonemia and brain insulin resistance. In Type 1 diabetes mellitus, hyperglycemia is due to absolute or relative deficiency of insulin release from pancreatic beta cells.[3] Hence along with other targets for treatment of diabetes mellitus, beta cell regeneration is of utmost importance. Proton pump inhibitors

[PPIs] are the class of drugs which have been tried to achieve the target of beta cell regeneration and increase in beta cell mass.

PPIs are the drugs used to treat acid peptic disease, gastroesophageal reflux disorders, NSAIDS induced gastric mucosal injury, H pylori infection and Zollinger Ellison syndrome.[4] Whenever PPIs are given for long term, along with the reduced acid secretion from stomach they enhance gastrin release as a rebound, feedback phenomenon. Increased acid secretion in response to protein meal is triggered by gastrin release which also secretes pepsin along with HCl in the gastric lumen.[5]

Gastrin is a peptide hormone secreted mainly by antral G cells in the form of biologically active gastrin 17 and gastrin 34.[6,7] Factors which stimulate gastrin secretion are vagal stimulation, [8,9] rise in intragastric pH,[10,11] distention of stomach,[8] and the presence of food mainly protein in nature.[9,10,12] Small quantity of gastrin is synthesized by certain luminal stimuli and also by the presence of dietary protein and amino acids.[12,13] Gastrin stimulates gastric acid secretion from gastric parietal cells. Gastrin and cholecystokinin bind to gastrin and cholecystokinin B [CCK-B] receptors and promote gastric acid secretion.[14-16]

Gastrin is proved to be islet cell growth factor similar to glucagon like polypeptide I [GLP-1] and has trophic effect on beta cell mass.[17-19] Gastrin act as a growth factor and stimulates gastric cell proliferation.[12,20] It also promotes beta cell neogenesis in pancreatic ductal complex[17] and enhances pancreatic beta cell replication considerably. This helps in the control of raised blood sugar level.[21]

Gastrin receptor is a major receptor for gastrin and is expressed abundantly in the entero chromaffin cells of stomach.[22] Gastrin can be called as early incretin hormone as it gets released by oral glucose administration and stimulates the glucose related insulin secretion.[23] PPIs lower blood sugar by enhancing rebound gastrin secretion.[17, 24-26] Based on negative feedback between PPIs and gastrin. PPIs have been tested by researchers to correlate their effect with the control of hyperglycemia in T2 DM.[27-29]

The known factors which stimulate beta cells neogenesis from the pancreatic duct cells in vivo and vitro are epidermal growth factor (EGF), keratinocyte growth factor and transforming growth factor alpha (TGF alfa),[30-33] GLP-1, [34] and gastrin. [17] When gastrin was combined with EGF, accelerated beta cell mass was observed in streptozotocin induced diabetic rats[35] and alloxan induced diabetic mice[36] which also controlled the hyperglycemia. Adult human islet beta cells from pancreatic duct cells when treated with combination of gastrin and EGF, together they increased functional beta cell mass. Both play different roles in the proliferation and differentiation of beta cells. Gastrin induced the expression of transcription factor PDX-1 in the duct cells and helped in differentiation of pancreatic beta cells.[19]

When gastrin was combined with GLP-1, increased beta cell mass was found in the diabetic immunodeficient mice, in whom human beta cells were implanted.[37] Gastrin is proved to be islet cell growth factor like GLP- I and has trophic effect on beta cell mass.[17-19] In animal studies, when gastrin was combined with GLP 1, accelerated beta cell growth and insulin secretion was observed.[38] GLP-1 protects beta cells by reducing apoptosis and by enhancing neogenesis and proliferation. They stimulate ductal cells to transform in to islet cells and also stimulate beta cell regeneration within the islets.[39]

When dipeptidyl peptidase 4 [DPP 4] inhibitors were combined with PPIs, rate of restoration of normoglycemia was almost

double than by that of DPP4 inhibitors used alone in diabetic mice. [40]

PPIs delay the gastric emptying for solids and the possible underlying mechanism for their delayed emptying could relate to the inhibition of peptic hydrolysis due to inhibited acid dependant peptic activity. Gastric emptying of liquids depends on volume and energy density of intra gastric contents. PPIs modify volume and energy density by reducing gastric acid secretion.[41] Like GLP-1, PPIs are found to slow gastric emptying and decrease post prandial hyperglycemia and fluctuations in blood sugar levels.[41,42]

Factors such as gastrointestinal hormones like glucose mimetic insulinotropic peptide (GIP), GLP-1, gastrin and cholecystokinin govern the beta cell turnover.[17,39] Suppressed or decreased gastric acidity acts as a trigger for gastrin release from antral G cells.[43] Gastrin is known to regulate beta cell function. [17, 25, 26, 44] Like GLP1, Gastrin also promote beta cell neogenesis, proliferation, differentiation and increase the mass[17, 36] and eventually reduce blood sugar by improved insulin release.

PPIs are found to improve parameters of beta cell function such as HOMA-B, BSL, HbA1c, fasting insulin, fasting pro insulin and C peptide levels in the normal and T2DM patients. Pantoprazole was found to improve beta cell function and control hyperglycemia in DM. Pantoprazole therapy for 12 weeks improved beta cell function by 16.2% in diabetic group and also there was rise in levels of pro insulin, insulin and C peptide and decrease in HBA1c levels.[45] Various other studies had similar observations.[25,26,44] PPIs therapy increased C peptide which is a known marker of endogenous insulin release.

PPIs could lower blood sugar by enhancing rebound gastrin secretion.[17,25,26,44] PPIs increase gastrin levels by negative feedback mechanism and stimulate beta cell neogenesis , proliferation and enhance insulin release.[46-52] Administration of omeprazole 40 mg daily in healthy men increased the antral gastrin content.[53] In animal models of type 2 DM, PPIs improved glycemic control as a result of increased gastrin levels and beta cell mass.[54] Clinical studies also demonstrated that PPIs significantly improved glycemic control in type 2 DM patients.[27,28,55,29,44,26,56] But some studies did not show improvement in glycemic control.[57,58] PPIs decreased HbA1c levels significantly in type 2 DM patients who had initial high HbA1c and blood sugar levels.[29] As against no significant change in these parameters was observed in those diabetic patients who had reasonably good control of HbA1c and blood sugar levels during the time of study.[57,58]

It is possible that gastrin enhances insulin secretion by directly stimulating pancreatic beta cells other than increasing beta cell mass whose increase is mainly observed during pancreatic remodeling. Protein rich meal without being glucose rich, increases both circulating gastrin and insulin levels which may be without increasing beta cell mass. This also explains the effect of PPIs on glycemic control which is mediated through gastrin, directly stimulating beta cells and increasing insulin release.[7]

Interaction between ghrelin and gastrin is known. Ghrelin plays an important role in appetite regulation and energy homeostasis. Ghrelin has negative correlation with gastrin as observed in human being. Increased gastrin levels suppress ghrelin release, reduces appetite which helps to improve glycemic control.[59]

Possible effect of gastrin on central nervous system needs consideration. Food intake was found to be decreased after intra cebroventricular injection of gastrin.[60] Diffusion of gastrin in the brain through blood

brain barrier [BBB] has got limitations.[61] But it can be possible due to the lack of BBB in circum ventricular organs. The peptide or peptide fragments enter in the brain.[62] Gastrin administered intravenously was found to activate neurons in the several parts of the brain.[63] It was observed that gastrin stimulated neurons of area postrema which have CCK-B receptors and project to the nucleus tractus solitaris [NTS].[64] In mouse NTS-proopiomelanocortin neurons in the brain stem govern satiety.[65] Hence it is possible that PPIs induced increased gastrin levels inhibit appetite through their action on central nervous system, possibly gastrin acting via vagal nerve on the brain stem.[64]

Recently it was found that gastrin stimulated L cells in the intestine and enhanced GLP-1 secretions. This also contribute for glucose lowering effect of gastrin and PPIs.GLP-1 enhances insulin release, reduces glucagon secretion, reduces gastric emptying and enhances satiety.[66]

Metformn is the time tested drug for last 60yrs in the treatment of DM. Transport of metformin in to the cell is governed by organic cation transporters [OCT] 1, 2 and 3 which are expressed specifically in organs like liver, muscles and kidney. Omeprazole, rabeprazole, pantoprazole, and lansoprazole are the potent OCT inhibitors. These PPIs inhibited metformin uptake in the concentration dependent manner by OCTs. PPIs are not the substrates for OCTs. Metformin does not undergo hepatic metabolism. .Hence drug interaction by inhibition of OCTs is important. All these PPIs inhibited metformin uptake transport by inhibiting all 3 OCT proteins.[67]

PPIs are inhibitors of OCTs. Metformin forms a substrate for OCTs.PPI can affect plasma levels of metformin. Studies done with omeprazole and pantaprazole to observe their effect on metformin pharmacokinetics revealed that these PPIs increased the plasma concentration of metformin. Metformin given alone had it's lesser plasma concentration level than when combined with PPIs. Thus PPIs increase plasma metformin levels.[68]

Lansoprazole increased mean maximum plasma concentration of metformin and area under plasma concentration time curve. It also prolonged metformin elimination half from 3.9 to 4.5 hours and also decreased its renal clearance by 13%.[69]

Metformin when was co-administered with rabeprazole, it's plasma concentration was increased by 18.6% and area under curve by 14.5%.Like other PPIs rabeprazole can strongly inhibit the transporting ability of OCTs. It was observed that rabeprazole can strongly inhibit MATE 1 mediated metformin transport in vitro. MATE 1 and OCT 2 are expressed on apical and basal layer of renal tubules abundantly and are responsible for renal excretion of metformin. The change in the pharmacokinetics of metformin can be explained on the basis of its decreased excretion by rabeprazole.[70]

Hence caution needs to be observed while co administering metformin with PPIs as this might reduce blood sugar more. It is known that metformin may produce gastritis which needs the co administration of PPIs to control this. One possibility needs to be considered while prescribing PPIs in cases of DM with gastro oesophageal reflux disorders [GERD] which has a common association in DM.[71,72] PPIs by relieving clinical symptoms of GERD can improve appetite despite the increased gastrin and decreased ghrelin levels and hence can derange glucose control in patients of DM. It is also reported that PPIs can induce dysbiosis, which is connected with metabolic syndrome.[73]

PPIs through gastrin mechanism share the effects of incretin based therapies like glucoregulation, improvement in beta cell

mass and function, slowing of gastric emptying, increase in satiety without weight gain. By inhibiting ghrelin release as a result of increased gastrin levels and through action on central nervous system PPIs help in reducing appetite. They donot produce hypoglycemia. Their glucose lowering effect is somewhat less than that by DPP 4 inhibitors and HbA1c reduction is in the range of 0.5-l%.[74]

PPIs are considered to be safe and effective but like other drugs they also are not devoid of adverse drug reactions [ADRs].These drugs given for long term can invite ADRs like hypo/achlorhydria, nutritional deficiencies of Vit B 12, calcium,magnesium and iron, acute interstitial nephritis, dementia, osteoporosis and fractures, enteric infections like clostridium difficile, pneumonias in ICU settings and increased incidence of myocardial ischemia. So monitoring of ADRs is needed while using these drugs for long term.[75]

Thus PPIs can be considered as potential supportive therapy for DM mainly type2.Long term safety of these drugs needs to be confirmed by conducting clinical trials for prolonged duration. This will definitely encourage the use of PPIs in DM.

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