Pantoprazole Improves Glycemic Control in Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: Proton pump inhibitors, by elevating plasma gastrin, can influence glucose-insulin homeostasis. Because there are no controlled clinical trials, the present study was planned to evaluate the effect of pantoprazole, a proton pump inhibitor, on glucose-insulin homeostasis in patients with type 2 diabetes (T2DM).

Research Design and Methods: In this 12-wk, randomized, double-blind, placebo-controlled study, patients with T2DM were allocated to either the pantoprazole or placebo treatment in an equal ratio. Alterations in glycosylated hemoglobin (HbA1c), fasting plasma glucose, insulin, and gastrin were measured at baseline and at 12 wk.

Results: Thirty-one eligible patients were randomized to receive either the pantoprazole (n = 16) or placebo (n = 15). Twelve weeks of pantoprazole therapy significantly increased plasma gastrin and insulin levels and improved \( \beta \)-cell function (\( P < 0.05 \) for all parameters), along with a significant decrease in HbA1c (7.6 ± 1.17 to 6.8 ± 1.16; \( P < 0.001 \)). The decrease in HbA1c correlated with an increase in gastrin and insulin (\( r = 0.54, P = 0.010 \); and \( r = 0.67, P = 0.01 \), respectively).

Conclusions: Pantoprazole therapy increases plasma gastrin and insulin levels, thereby improving the glycemic control in T2DM. The effect of pantoprazole on glucose-insulin homeostasis requires further study. (J Clin Endocrinol Metab 97: E2105–E2108, 2012)

Type 2 diabetes (T2DM) is a complex heterogeneous group of metabolic conditions characterized by increased levels of blood glucose due to two defects: insulin resistance and insulin deficiency (1). There is a plethora of drugs targeting these two defects. Recently, however, the focus has been on strengthening the enteroinsular axis and incretins. The landmark studies, the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT), which are testimony to “glucose hypothesis,” have convincingly demonstrated that normalizing glycosylated hemoglobin (HbA1c) levels can reduce the incidence and progression of microvascular and possibly macrovascular complications (2).

The existence of an enteroinsular axis involving gastrin, insulin, and islet \( \beta \)-cells in humans has long been recognized. Cowey et al. (3) in 2005 showed the development of central obesity and insulin resistance in gastrin gene knockout mice, thus suggesting the relationship between gastrin and glucose-insulin homeostasis. A group of patients with pernicious anemia (atrophic gastritis) associated with hypergastrinemia, showed an exaggerated insulin response to glucose challenge, whereas those with hypogastrinemia showed a reduced insulin response when compared with normal controls (4). In patients with marked hypogastrinemia due to resection of the antrum, duodenum, and proximal jejunum, a marked reduction in

Abbreviations: FPG, Fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA, homeostasis model of assessment; PPI, proton pump inhibitor; T2DM, type 2 diabetes.
insulin response to glucose challenge was observed (5). Gastrin-producing tumors (gastrinomas) in Zollinger-Ellison syndrome are associated with islet cell hyperplasia. This was further substantiated by Meier et al. (6) in 2006, who showed increased β-cell replication adjacent to human pancreatic gastrinomas, suggesting a possible correlation between gastrin and β-cells.

Proton pump inhibitors (PPIs) such as pantoprazole, omeprazole, lansoprazole, etc., which are used extensively for the treatment of peptic ulcer and related symptoms, indirectly elevate gastrin levels. Studies have shown a dose- and duration-dependent relationship between PPIs and gastrin levels (7–10). Among the available PPIs, pantoprazole exhibits a relatively higher degree of safety, possibly because of its complete hepatic metabolism and minimal potential for drug-drug interactions.

So far, few observational studies have evaluated the effect of PPIs on HbA1c only and not on other parameters of glucose-insulin homeostasis. Therefore, this study was planned to evaluate the effect of pantoprazole in a randomized, placebo-controlled manner on glucose-insulin homeostasis in patients with T2DM.

**Patients and Methods**

The research plan was duly approved by the Institute Ethics Committee before study commencement. Written informed consent was obtained from every patient before any study-specific procedure. The study was conducted according to the Declaration of Helsinki and ICH-GCP (International Conference on Harmonization-Good Clinical Practice) guidelines and was registered with the Clinical Trial Registry of India (www.ctri.nic.in/ClinicalTrials/pmaindet2.php?trialid=2834; no. CTRI/2011/001899).

Adult insulin-naive patients of either sex, having T2DM of less than 5-yr duration and HbA1c less than 8.5%, were recruited. All of the patients were maintained on stable oral antidiabetic therapy with metformin and/or sulfonylurea for at least 1 month before enrollment in the study.

Key exclusion criteria were: past and current users of insulin, pioglitazone, or incretin-based therapies; and evidence of liver disease (more than three times the upper limit of aspartate aminotransferase and alanine aminotransferase), renal disease (plasma creatinine more than 1.5 mg/dl), or any complication of diabetes. Additionally, pregnant or lactating women and patients already on any PPI therapy were excluded from the study.

The present study is a randomized, double-blind, placebo-controlled trial evaluating the effect of add-on pantoprazole in patients with T2DM. A computer-generated randomization list was used for allocation to either pantoprazole or matching placebo in the ratio of 1:1.

T2DM patients satisfying the selection criteria were enrolled and assigned to one of the study groups. Pantoprazole 40 mg twice daily orally or matching placebo was added to the existing therapy. All patients were advised to follow dietary restriction and lifestyle modification as recommended. Blood samples were collected in EDTA Vacutainers. Fasting plasma glucose, HbA1c, fasting plasma gastrin, and insulin levels were estimated at baseline and 12 wk. Intention-to-treat analysis was followed. Compliance was assessed by patient interview and pill counts; those taking more than 80% of the drugs were considered compliant.

Plasma glucose was measured by the glucose oxidase method. HbA1c was estimated by ion-exchange HPLC (Bio-Rad D-10; Bio-Rad, Hercules, CA) and insulin by electrochemiluminescence (COBAS 6000 analyzer; Roche, Basel, Switzerland) using ready kits provided by Roche. The analytical sensitivity of the test was 0.20 μU/ml, and within-run precision expressed as the percentage coefficient of variation was 1.9%. Gastrin was estimated by enzyme immunoassay method using a commercially available kit (RayBiotech, Inc., Norcross, GA) according to the manufacturer’s instructions. The minimum detectable concentration of gastrin was 9.92 pg/ml, and the detection range was 0.1 to 1000 pg/ml. Intra- and interassay coefficients of variation were below 10% and below 15%, respectively, and showed no cross-reactivity with any of the cytokines tested: ghrelin, nesfatin, angiotensin II, NPY, and APC. β-Cell function [homeostasis model of assessment (HOMA)-β] was calculated as: 20*(fasting plasma insulin)/(fasting plasma glucose – 3.5) (11).

Safety data were obtained by patient interviews, physical examination, and laboratory data on hematology and plasma biochemistry on all study visits.

**Statistical analysis**

Considering an α-error of 5% and SD of 0.8 in the measurement of HbA1c concentration with the expected difference of 0.7 between the two groups, 28 patients were required for providing 80% power to the study. Data were expressed as mean with SD, numbers, and percentage. Baseline parameters and laboratory safety parameters were compared using appropriate parametric and nonparametric tests. A P value of less than 0.05 was considered as significant.

**Results**

Forty-nine patients were screened between February 2011 and May 2011, and 31 eligible patients were included in the study. Sixteen patients were randomized to receive pantoprazole, whereas 15 patients were allotted to the placebo group. One patient in the pantoprazole group did not report after the first visit, whereas the rest completed the study.

The mean age of the population was 55.6 ± 9.8 yr in the placebo and 57.4 ± 6.8 yr in the pantoprazole group. All the other baseline characteristics including gender, duration of diabetes, weight, height, body mass index, blood pressure, and smoking and alcohol intake did not differ in the two groups. The majority of the patients were on combination therapy comprised of metformin and sulfonylurea, whereas a few were on metformin alone; their distribution was similar in both the groups.

Table 1 depicts HbA1c, fasting plasma glucose (FPG), gastrin, and insulin levels in the placebo and pantoprazole groups, which were comparable at baseline. After 12 wk of pantoprazole therapy, there was a significant increase in
the fasting plasma gastrin ($P < 0.001$) and insulin ($P < 0.001$), whereas there was no significant change in the placebo group (Fig. 1). When these parameters were compared with the placebo group at 12 wk, significant change was observed for gastrin ($P = 0.001$) but not for insulin ($P = 0.07$).

After 12 wk of therapy, there was a significant reduction of 0.8% in HbA1c levels in the pantoprazole group compared with its baseline ($P < 0.001$), whereas no statistical difference was observed in the placebo group. This difference was also significant between the two groups at 12 wk ($P = 0.004$). Similarly, there was a significant reduction in fasting plasma glucose level at 12 wk when compared with baseline ($P = 0.017$) and in comparison to placebo as well ($P = 0.019$). A significant correlation between the decrease in HbA1c and increase in fasting plasma gastrin ($r = 0.54; P = 0.010$) and insulin ($r = 0.67; P = 0.01$) was found using Pearson’s correlation.

Pantoprazole therapy improved the $\beta$-cell function (HOMA-$\beta$) by 30.1% ($P = 0.016$), and the difference was also significant when compared with the placebo group at 12 wk ($P = 0.025$). However, HOMA for insulin resistance did not show any significant change in either the placebo group or the pantoprazole group (Table 1).

### Adverse events

Nine patients reported adverse events during the study period in the form of nausea, vomiting, headache, and myalgia, which were similar in both the groups and were mild in nature. None of the patients developed hypoglycemia, despite reduction in HbA1c and blood glucose.

### Discussion

The present study is the first randomized, controlled clinical trial evaluating the effect of add-on pantoprazole therapy on glucose-insulin homeostasis in patients with T2DM. Twelve weeks of pantoprazole therapy significantly increased the fasting plasma gastrin and insulin levels and reduced HbA1c.

HbA1c is considered the best parameter for evaluating the glycemic control and assessing the efficacy of antidiabetic medications, and it showed a reduction of 0.8% after pantoprazole therapy in the present study. This reduction is in concordance with the earlier reports where it was 0.5 to 0.7% with PPIs (12–14). However, all these reports were observational in nature and have their inherent limitations such as retrospective design, absence of matching controls, and possibility of observation bias.

The effect of PPIs on HbA1c levels may be due to the incretin-like effect of gastrin because gastrointestinal peptides stimulate $\beta$-cell insulin secretion and/or proliferation, resulting in enhanced glucose-dependent insulin release (14). In pancreatic duct-ligated rat model of diabetes, iv-infused gastrin enhanced $\beta$-cell neogenesis and insulin secretion, resulting in improved blood glucose control (15). Administration of lansoprazole resulted in similar findings in the Psammomys obesus model of T2DM (16), thus establishing the relationship between PPIs, gastrin, and glucose-insulin homeostasis. PPIs also delay gastric emptying, which could result in timely exposure of glucose to ileum, thereby providing conducive ambience for incretin hormones secretion, and thereby resulting into a
decrease in postprandial glucose levels (17, 18). The other possibility may be a direct effect of gastrin on glucose-dependent insulinotropic peptide and glucagon like peptide-1 secretion from the K and L cells of the small intestine, respectively; however, it remains conjectural. The 2- to 3-fold increase in plasma gastrin levels occurs after 24–32 wk of PPI therapy (19). However, 12 wk of pantoprazole therapy in the present study was associated with only a 50% increase in plasma gastrin levels. Therefore, it may be possible that longer treatment with PPI could have further improved the glycemic control because peak gastrin levels could not be achieved in the present study.

The strength of the present study is its prospective and randomized design, with a placebo control. The perceived limitations are the relatively smaller sample size and absence of a non-diabetic control group.

In conclusion, pantoprazole therapy increases fasting plasma gastrin and insulin levels, thereby improving glycemic control. The effect of PPIs on glucose-insulin homeostasis requires further studies in this area.

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P.K.S., I.S., and D.H. conceived the idea and designed the study. A.B. and P.D. contributed substantially to patient recruitment and the supervision and monitoring of the study. P.K.S., D.H., A.S., I.S., N.S., and A.C. collected the data and analyzed and interpreted the results. P.K.S. drafted the final manuscript with substantial input from A.B.

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