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Review Article

Treatment with a proton pump inhibitor improves glycaemic control in type 2 diabetic patients.

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Abstract

Oral hypoglycemic medications sometimes do not control type 2 diabetes well. Proton pump inhibitors as adjunctive therapy might improve diabetes control through increasing serum gastrin & fasting insulin levels. Proton pump inhibitor therapy also associated with lower glycosylated hemoglobin levels in diabetes.

Introduction

Proton pump inhibitors are first introduced in the late 1980 & they are used for the treatment of acid-peptic disorders. PPIs are now most widely prescribed drugs worldwide due to their outstanding efficacy and safety.[1] PPIs available for clinical uses are-omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

All the PPIs are substituted benzimidazoles that resembles H_2 antagonists in structure that have a completely different mechanism of action. PPIs inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion, the proton pump1. In standard doses, PPIs inhibit 90-98% of 24-hour acid secretion.

Clinical uses of PPI[1]:

a) Gastro-esophageal reflux disease.
b) Peptic ulcer disease:
   1) H. pylory-associated ulcers.
   2) NSAID-associated ulcers.
   3) Prevention of re-bleeding from peptic ulcers.
c) Nonulcer dyspepsia.
d) Prevention of stress-related mucosal bleeding.
e) Gastrinoma and other hypersecretory conditions.

Proton pump inhibitors might be useful as adjunctive therapy for type-II diabetes mellitus.[2]

DM:

Type-II diabetes is characterized by insulin resistance and/or deficient pancreatic β-cell mass or production and secretion of insulin.[2]

Common treatments of type 2 diabetes may modify insulin sensitivity, increase insulin secretion, or in some cases either reduce beta-cell dysfunction or slow their degradation.[3]

Effect of PPIs:

A physiological effect of acid suppression with PPIs is a mild/modest hypergastrinemia which occurs with all PPIs.[4] Gastrin is known to be the major regulator of the secretory response to a protein meal, while somatostatin is a potent inhibitor of gastrin and histamine synthesis and release and therefore, of gastric acid secretion.[5]

In rodents, gastrin induces islet β-cell neogenesis[6,7] and in vitro studies, this hormone increases the β-cell mass.[8] A few retrospective studies in adults with diabetes appear to have shown that PPIs are associated with better glycemic control. Mefford et al[9] compared HbA1c levels from type 2 diabetic patients taking PPIs (7%) and type 2 diabetic not taking them (7.6%), obtaining significant differences.

Gastrin has shown to induce β-cell proliferation and neogenesis in various model systems, and also appears to increase the insulin content of individual β-cells.[10] By blocking gastric acid production, proton pump inhibitors (PPIs) remove negative feedback on gastrin production by entero-chromaffin cells. In a rodent model of type 2 diabetes treatment with the PPI lansoprazole increased serum gastrin that was associated with improved glycemic and increased pancreatic insulin content.[11]

Different research evidence:

A research work was done from hospital of spain by Diana Boj et el.[12]

Glycemic control result shown in Table:

	Total	Insulin	Metformin	Sulfonylurea	Others antidiabetic drugs
Withou PPI					
HbA1C (%)	7.3	7.6	7.4	7.2	8.0
SD(%)	1.4	1.5	1.6	1.1	1.2
n	43	19	24	11	4
With PPI					
HbA1C (%)	6.7	6.8	6.7	6.7	7.2
SD(%)	1.0	0.8	1.0	0.7	1.2
n	54	28	2.3	10	13
Absolute difference	-0.6	-0.8	-0.7	-0.5	-0.8
ρ value	0.018	0.022	NS	NS	NS

This study was conducted within total 97 patients admitted to hospital of the year 2010 who had a recent HbA_1c measurement. It compared HbA_1c levels of those taking PPIs and those not. The average HbA_1c level was 7.0% ± 1.2%. Overall PPI consumption was 55.7%. HbA_1c was significantly lower in individuals who took PPIs – 0.6%, people who used PPIs with some type of insulin therapy had a HbA_1c reduction by – 0.8%. For the rest of subgroup analysis based on the antidiabetic drug used, PPI consumption always exhibited lower HbA_1c levels.[12]

Another research was done in USA by I.N.Mefford et al.[13] It was a case report. A 43 year old man with type 2 diabetes, opposed to insulin use and poorly responsive to oral agents over 6 years, was placed on 40-mg twice daily omeprazole. A linear decline in daily fasting blood glucose was observed throughout the first two months treatment. Initial fasting blood glucose, 240mg/dl at the start of treatment, declined to 138mg/dl at the end of 8 weeks. HbA1c was reduced from 11.9% to 8.2%, then sustained at 8.1% after four months. Glucose, insulin, and C-peptide response to a 2-hour glucose tolerance test were consistently improved across this time period.[13]

Fig. -I: Effect of twice daily 40mg omeprazole treatment on serum gastrin and hemoglobin A1c in a type 2 diabetic.

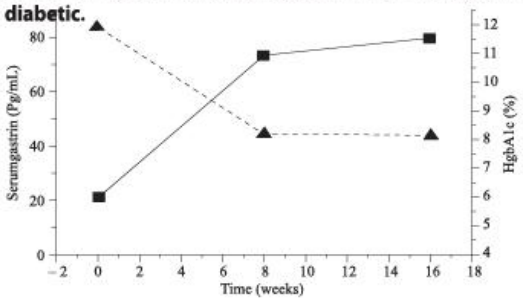
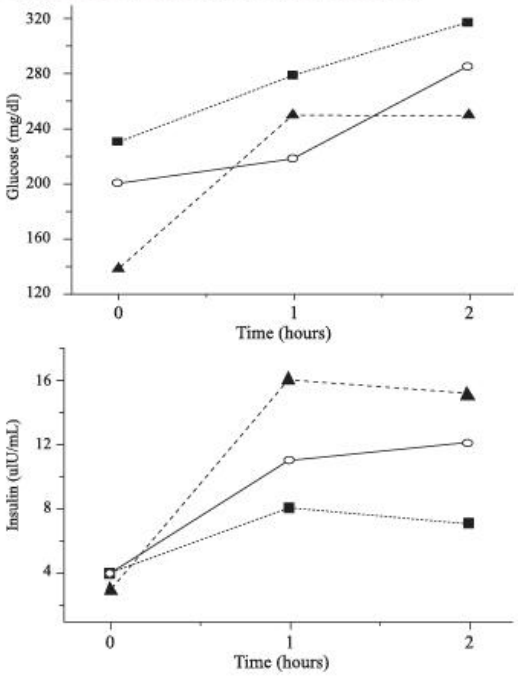


Fig.-II: 2hr glucose tolerance test effects on blood glucose (a), insulin (b) after twice daily 40mg omeprazole treatment in a type 2 diabetic.



Calculated β cell mass increased by 67% by HOMA method. We believe this response is consistent with activation or neogenesis of pancreatic beta cells, possibly through a gastrin-mediated mechanism.

Hove et al[14] conducted a case-control study to investigate whether treatment with esomeprazole improved HbA_1c levels in a group of type 2 diabetic patients. They found a border line significant reduction of HbA_1c by 0.7%.

A study was conducted by Michael A. Crouch, Ivan N. Mefford and Ekpedema U. Wade to investigate whether proton pump inhibitor therapy associated with lower glycosylated hemoglobin level in Type 2 Diabetes.[2] In that study 73 individuals were reviewed with type 2 diabetes (not taking insulin), for whom PPI were prescribed. Values for HbA_1c for periods of time when a PPI had been prescribed were compared with HbA1c levels for periods of time with no record of PPI prescribing or over-the-counter PPI use. The mean HbA1c or patients not taking insulin was 7.11 during periods with recorded prescribing or over-the-counter

use of PPI, compared with 7.70 during periods without recorded PPI therapy (P=0.001). Mean HbA_1c for metformin monotherapy was not significantly different (6.81 with PPI vs. 7.10 without PPI; n=16; p=.25). Mean HbA_1c was significantly different for combination therapy that included metformin and/or sulfonylurea and/or glitazone (7.26 vs. 7.80; n=27; p=.002).

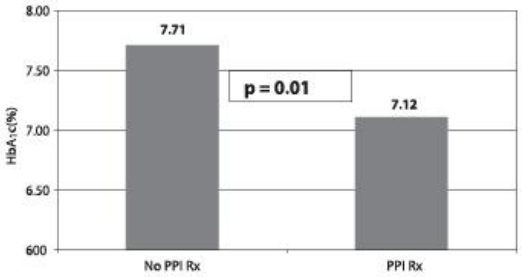


Fig.-III: Mean hemoglobin A_1c with and without an active proton pump inhibitor (PPI) prescription.

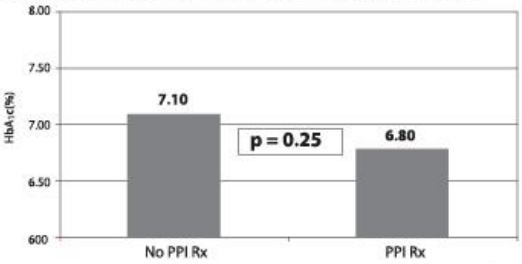


Fig.-IV: Mean hemoglobin A_1c with a prescription for metformin with and without a concomitant proton pump inhibitor (PPI).

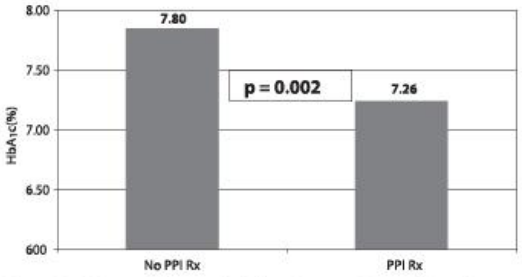


Fig. -V: Mean hemoglobin A_1c with sulfonylurea and/or glitazone and/or metformin with and without a prescription for a concomitant proton pump inhibitor (PPI).

Conclusion

PPIs have a secondary effect on glycemic control. It could be a new antidiabetic drug with a good profile: no hypoglycemic events, good tolerability and safety, and with a limited price.

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