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Proton pump inhibitors may improve glycemic control in patients with Type 2 DM- A prospective cohort study

Dr. Madhan Mohan Rao [1], Dr. S. Parveen[2], S. Deva sree[3], K. Bhargavi[3], Ch. Ascharya[3],A.V. Kavya sree[3], V. Harika[3]

[1](*Associate Professor, Department of General Medicine, Rajiv Gandhi Institute of Medical Sciences, Kadapa Andhra Pradesh-516003, India)*

[2(]*Assistant Professor, Department of pharmacy practice, P. Rami reddy Memorial College of pharmacy, Kadapa Andhra Pradesh-516003, India)*

[3(]*Pharm D Interns, Department of pharmacy practice, P. Rami reddy Memorial College of pharmacy, Kadapa Andhra Pradesh-516003, India)*

Corresponding Author: Dr. S. Parveen

Abstract :
The study objectives were to determine the effect of proton pump inhibitors on glycemic control in patients with Type 2 DM by measuring the parameters like FBS, PPBS and HbA1C. A Prospective Cohort study was conducted in 80 patients at General Medicine Department of RIMS, Kadapa. Then, these patients were divided into two group's i.e., for one group, oral hypoglycemic agents along with proton pump inhibitors were prescribed and for the second group, only oral hypoglycemic agents were given. Both the groups were followed for two months and FBS, PPBS and HbA1C were measured. This procedure repeated with the new study population for the second and third two months, as the study is for about six months. The present study shows the incidence for type 2 DM is 0.017, and the prevalence is 0.06. Out of 80 study population, average base line FBS for patients with PPI (40 patients) was 177.235 and average baseline FBS for patients without PPI (40 patients) was 176. And average FBS in follow up for the patients with and without PPI was 149.425, 156.025 respectively. Out of 80 study population, average base line PPBS for patients with PPI (40 patients) was 254.125and average baseline PPBS for patients without PPI (40 patients) was 265.5. And average PPBS in follow up for the patients with and without PPI was 216.275, 240.25 respectively. Our results suggest a role for PPI as an adjunctive therapy for DM and glucose-insulin homeostasis and better glycemic control.

Key Words: *Proton pump inhibitors, Oral hypoglycemic agents, Type 2 DM, Glycemic control*

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I. Introduction

Diabetes Mellitus is a group of metabolic disorders characterized by hyperglycemia. It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including micro vascular, macro vascular, and neuropathic disorders **[1]**.

Fig 1.0: Symptoms of diabetes

Risk factors for type 2 DM

First degree of family history of DM (i.e. parents or siblings), Obesity, Habitual physical inactivity, Hypertension (Blood pressure ≥ 140/90 mm Hg), High-density lipoproteins (HDL < 35mg/dl or 0.91 mmol/l) and / or Triglyceride level greater than 250mg / dl (2.83mmol/l), History of Gestational diabetes or delivery of baby weighing greater than 4kgs or9 pounds, History of vascular disease, History of polycystic ovary disease **[2]**.

The most common form of diabetes is type-II diabetes. About 90 to 95 percent of people with diabetes have type-II. This form of diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities. About 80 percent of people with type-II diabetes are overweight or obese. When type-II diabetes is diagnosed, the pancreas is usually producing enough insulin, but for unknown reasons the body cannot use the insulin effectively, a condition called insulin resistance. After several years, insulin production decreases. The result is the same as for Type-I diabetes. Present estimates indicate that approximately 170 million people worldwide have diabetes (90% to 95% of diabetes cases are type2 diabetes), and that number is expected to increase approximately 366 million by 2030.Type2 diabetes is highly correlated with overweight/obesity and hypertension **[3].** Diabetes and its complications are major causes of early death in most countries. Cardiovascular disease is one of the leading causes of death for people with diabetes and can account for 50% or more of deaths due to diabetes in some populations **[4**].

Pathogenesis

These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action **[5].**

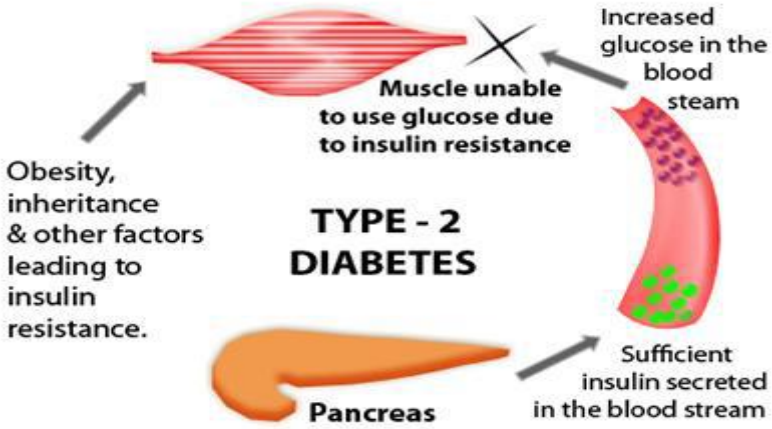

Fig.2.0 Pathogenesis of diabetes

Diabetic complications

Untreated or improperly treated diabetes leads to complications. Diabetes is the only metabolic disorder, which can affect almost every organ of the body. The organ most commonly affected are eyes, kidneys, nerves and blood vessels. Statistics reveal that people with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30-40 times more likely to develop myocardial infarction and twice as likely to suffer a stroke than non- diabetic **[6].**

Mechanism of proton pump inhibitors in glycemic control

Proton pump (H+ K+ ATPase) is a membrane bound enzyme that plays an important role in the final step of gastric acid secretion. The proton pump inhibitors will inhibit the enzyme H+ K+ ATPase, there by inhibiting the acid secretion and strongly reduce the secretion of gastric acid. It is well known that PPIs indirectly elevate serum gastrin levels via a negative feedback effect8.Oral intake of food materials enters into the stomach and stimulates gastric cells and release gastrin hormone into the blood and it binds to gastric receptors and it stimulates release of histamine where it H2 receptors and release H2K+ATPase enzyme gastric juice will secrete per day which will inhibited by PPI therapy indirectly elevates serum gastrin levels via negative feedback mechanism. There elevated gastrin levels will increase β cell mass and therapy insulin

secretion and controls glycemic levels. Interestingly, in type 2 diabetes mellitus, it has been reported that PPIs improved glycemic control, through this negative feedback mechanism by augmenting serum levels of gastrin which increases the β cell mass and thereby helps in better glycemic control. Along with oral hypoglycemic agents, proton pump inhibitors (PPIs) as adjunctive therapy might improve diabetes control through increasing serum gastrin and fasting insulin levels **[7, 8, 9]**

II. Materials and Methods

Study site; General Medicine Department of Rajiv Gandhi Institute of Medical Sciences (RIMS), Kadapa.
Study design; A Prospective Cohort study.
Study duration; 6 Months
Study population; Adults with Type II diabetes mellitus.
Sample size; Patients (approximately 100) with type II DM.
Patient enrollment
Inclusion Criteria

- Patients with type II DM, including newly diagnosed patients are eligible for the study.
- Both men and women of age ≥ 30yrs.
- Patients having FBS > 126mg/dl, PPBS >200mg/dl and HbA1C > 65
- Diabetic Patients with other co morbidities.

Exclusion Criteria

- Patients were excluded if they were unable to comply with the protocol requirements.
- Pregnant women were excluded from the study.
- Type 1 DM patients.
- History of drug or alcohol abuse.
- Patients with haemoglobinopathies and uremia.

Method of study

Subjects with type II DM were recruited into the study based on inclusion and exclusion criteria. Patient related demographic details, past medical/medication history, lab investigations, patient medication chart etc. were collected. After collection of the data, the baseline FBS, PPBS and HbA1c were monitored. Then, these patients were divided into two groups i.e., for one group, oral hypoglycemic agents along with proton pump inhibitors were prescribed and for the second group, only oral hypoglycemic agents were given. Both the groups were followed for two months and FBS, PPBS and HbA1C were measured. This procedure repeated with the new study population for the second and third two months, as the study is for about six months. The results of both the control and treatment groups were compared and the effect of PPI on glycemic control was determined by measuring the parameters like FBS, PPBS and HBA1C for both the groups.

Statistical analysis

The 2-sided t-test was used for the main analyses comparing mean HbA1c, FBS, PPBS levels for patients receiving any hypoglycemic therapy of diabetes medications with versus without concomitant PPI therapy.

III. Results

A prospective cohort study was conducted in South Indian Tertiary Care Teaching Hospital, RIMS, Kadapa for a period of 6 months. A total of 90 patients were recruited in the study. 10 patients were withdrawn from the study as they failed to come for regular follow-ups. The remaining 80 patients were followed up to 6 months of the study duration. A total of 1152 patients were screened in a study period of 6 months. In that we have recruited 80 patients into our study. Out of 80 patients, 20 patients were diagnosed as new cases during the study period. The present study shows the incidence for type 2 DM is **0.017**, and the prevalence is **0.06.**

Patient distribution based on gender

Out of 80 patients, 45(56%) males were found to be more when compared with females 35 (44%).

Distribution of patients based on the age

We categorized the patient to their age groups. Out of 80 patient's majority 28 (32.%) of them were found in between the age group 51- 60 years, followed by 26 (30%) in between the age group 61-70 years, 16(18%) in between the age group 41-50 years, 15 (17%) in between the age group 31-40 years, then finally 3 (3%) in the age group > 70 years.

Distribution of patients based on disease history

Out of 80 patients', majority 34 (42.5%) of them were found to have disease history in between 6-10 years, followed by 28 (35%) in between 0-5 years, 14(21.25%) in between 11-15 years, then finally 4 (5%) in between 16-20 years.

Comorbidities associated with diabetes patients

Table1.0: Patient distribution based on co morbidities

COMORBIDITES	NO. OF PATIENTS	PERCENTAGE
Hypertension	18	22.5%
Respiratory diseases	16	20%
Infections	7	8.75%
Peptic ulcer disease	10	12.5%
Others	5	6.25%

Comparison of baseline and follow up fbs values

Out of 80 study population, average base line FBS for patients with PPI (40 patients) was 177.235 and average baseline FBS for patients without PPI (40 patients) was 176. And average FBS in follow up for the patients with and without PPI was 149.425, 156.025 respectively.

Table 2: Comparison of baseline and follow up FBS values

S. No.	With PPI's		Without PPI's	
	Base line	**Follow up**	**Base line**	**Follow up**
1.	229	173	408	346
2.	280	220	248	226
3.	290	230	220	210
4.	260	220	240	240
5.	335	245	209	200
6.	260	210	265	240
7.	219	184	275	255
8.	280	220	228	210
9.	240	200	240	210
10.	265	200	208	200
11.	208	180	280	240
12.	240	200	280	255
13.	352	290	275	260
14.	332	295	270	255
15.	246	192	289	260
16.	284	200	250	220
17.	250	210	220	200
18.	240	220	200	194
19.	295	230	275	250
20.	240	220	270	220
21.	240	220	280	260
22.	222	216	282	250
23.	255	225	280	240
24.	219	208	408	350
25.	280	220	220	190
26.	243	239	200	190
27.	231	224	240	220
28.	256	249	280	265
29.	252	231	392	350
30.	281	270	352	310
31.	261	236	240	231
32.	170	160	368	320
33.	194	184	280	265
34.	190	190	210	180
35.	240	200	220	196
36.	182	180	280	246
37.	280	220	248	226
38.	290	230	220	210
39.	284	200	250	220
40.	250	210	220	200
Mean	254.125	216.275	265.5	240.25
SD	39.248	28.266	53.802	43.800
P value	< 0.0001		= 0.0240	

Table 3: Mean comparison of PPBS values

	With PPI's	Without PPI's
Base line	254.12	265.5
Follow up	216.27	240.25

Comparison of baseline and follow up HbA1C values

Out of 80 study population, average baseline HbA1C for patients with PPI (40 patients) was 7.225 and average baseline HbA1C for patients without PPI (40 patients) was 7.137. And average HbA1C in follow up for the patients with and without PPI was 6.39, 6.88 respectively.

Table 4: Comparison of baseline and follow up HbA1C values

S. No.	**With PPI's**		**Without PPI's**	
	Base line	**Follow up**	**Base line**	**Follow up**
1.	7.2	6.3	8.4	8.2
2.	7.6	6.6	7.1	6.9
3.	7.6	6.9	6.9	6.8
4.	7.5	6.1	7.4	7.2
5.	6.9	6.2	7.1	6.9
6.	7.3	6.4	6.8	6.7
7.	7.1	6.1	7.8	7.8
8.	6.8	6	6.2	6.2
9.	6.8	6.1	6.8	5.7
10.	6.9	6.2	6.7	6.6
11.	7.1	6.1	7.4	7.1
12.	7.5	6.3	7.5	7.1
13.	7.6	6.8	7.5	7.1
14.	7.9	6.2	6.5	6.4
15.	7.5	6.3	6.9	6.8
16.	6.9	6.3	7	6.8
17.	6.8	6.2	6.8	6.2
18.	6.8	5.9	6.7	6.2
19.	7.5	6.9	6.8	6.7
20.	6.9	6	6.7	6.1
21.	6.8	5.9	7.3	7.1
22.	6.9	6	7.6	7.5
23.	6.9	6.2	7.7	7.4
24.	7.1	6.9	7.6	7.5
25.	7.2	6.8	6.9	6.7
26.	7.2	7	7.3	7.1
27.	7.4	6.8	6.7	6.2
28.	7.4	6.3	6.9	6.8
29.	7.2	6.9	7.9	7.5
30.	7.9	7	7.1	6.8
31.	7.9	7.4	6.9	6.5
32.	7.6	6.2	7.2	7.1
33.	7.4	6.2	7.4	7.4
34.	7.5	6.6	7.2	6.9
35.	7.2	6.2	7.1	6.9
36.	7.3	6.4	6.8	6.5
37.	7.2	7	7.3	7.1
38.	6.9	6	6.7	6.1
39.	6.8	5.9	7.3	7.1
40.	6.9	6	7.6	7.5
Mean	7.225	6.39	7.137	6.88
SD	0.33459	0.38948	0.43186	0.51501
P value	<0.0001		<0.0177	

Table 5: Mean comparison of HbA1c values

	With PPI's	Without PPI's
Base line	7.22	7.13
Follow up	6.39	6.88

IV. Discussion

Patients with type 2 diabetes have reduced beta cell function and mass. Therefore, new and better treatments targeting regeneration of functional beta cell mass are needed. Gastrin is a hormone that stimulates secretion of gastric acid as well as growth and maturation of the gastric mucosa. There is a negative feedback loop between gastric acid and gastrin release; therefore gastrin secretion is inhibited if the level of gastric acid is

high. Conversely, if the secretion of gastric acid is inhibited by for instance proton pump inhibitors (PPIs), plasma gastrin levels will increase due to the lack of feedback inhibition. This could potentially affect beta cell mass and function and thereby improve glycemic control. The findings of the study provide support for that PPIs may be a useful adjunctive therapy for type 2 diabetes. The postulated mechanism for this effect is PPI causing elevation of serum gastrin, enhancing pancreatic β cell function, and stimulating insulin secretion **[10].**

In our study we found 45(56%) males are more when compared with females 35 (44%) which is supported by **Karin D. Hove, et.al** study reveals that males are more than female by 2%. Out of 80 patient's majority 28 (32. %) of them were found in between the age group 51- 60 years, which is supported by **Karin D. Hove, et.al** followed by 26 (30%) in between the age group 61-70 years which is supported by **Karin D. Hove, et.al**, 16(18%) in between the age group 41-50 years, 15 (17%) in between the age group 31-40 years, then finally 3 (3%) in the age group > 70 years**[11].**

We found that majority 34 (42.5%) of study population have disease history in between 6-10 years, followed by 28 (35%) in between 0-5 years, 14(21.25%) in between 11-15 years, then finally 4 (5%) in between 16-20 years. Out of these 80 patients, 56 patients were with co morbidities, patients with hypertension were 18(22.5%), patients with respiratory disease were 16(20%), patients with peptic ulcer were 10(12.5%), patients with infections were 7(8.75%), and patients with other co morbidities were 5 (6.25%). This is supported by **Michael A. Crouch, Ivan N. Meffordet.al, (2012**) in their study hypertension (42.1%) was found to be higher among the other co morbidities **[12].**

We have compared FBS of patients with PPI (40 pts) and without PPI (40 pts) at baseline and follow up. We found that there was slight decrease in the FBS values in patients with PPI when compared to without PPI at follow-up. An extremely statistical significant difference was observed between baseline Vs follow-up ($p<0.0001$) with 95% CI in patients with PPI and without PPI ($p<0.0001$) we have compared PPBS of patients with PPI (40 pts) and without PPI (40 pts) at baseline and follow up. We found that there was slight decrease in the PPBS values in patients with PPI when compared to without PPI at follow-up. An extremely statistical significant difference was observed between baseline Vs follow-up ($p<0.0001$) with 95% CI in patients with PPI and inpatients without PPI statistically significant different was observed between baseline and follow up ($p =0.0240$) with 95% CI.

We have compared HbA1C of patients with PPI (40 pts) and without PPI (40 pts) at baseline and follow up. we found that there was slight decrease in the HbA1C values in patients with PPI when compared to without PPI at follow up. An extremely statistical significant difference was observed between baseline Vs follow-up ($p<0.0001$) with 95% CI in patients with PPI and in patients without PPI, statistically significant different was observed between baseline and follow up ($p < 0.0177$) with 95% CI. This was supported **by F. Inci et.al** they found significant statistical association between FPG and HbA1c in those who are under Pantoprazole therapy. The P-value equals to 0.007, 0.0017 respectively. The described association needed for the investigation with clinical trials measuring gastrin, insulin and HbA1c levels for patients with type 2 DM **[13].**

V. Conclusion

PPI treatment was found to be associated with better glycemic control in patients with type 2 Diabetes Mellitus. Our results suggest a role for PPI as an adjunctive therapy for DM and glucose-insulin homeostasis. It may open a new scenario for diabetes therapy even though further clinical study is needed to evaluate this data and to determine the potential for PPIs to become a new class of anti-diabetic agent.

References

[1]. Joseph. T. Dipiro:"Textbook of Pharmacotherapy", published by the Mc Graw Hill Companies, 7th edition, 2008, Pg no. 14, 1206.
[2]. Alvin C. Power: " Harrisons; Principal of Internal Medicine"; published by McGraw-Hill Medical publishing division,17th edition; volume 2;
[3]. Pg no. 2275-2304.
[4]. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes. Indian Journal of Medical Research 2007; 125(3):
[5]. Pg no. 217-230
[6]. Roglic G, Unwin N, Bennett PH, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. Diabetes Care 2005; 28 (9): 2130-2135
[7]. Russell J Greene and Normal D Harris." Pathology and Therapeutics for pharmacists" A basis for clinical pharmacy practice. Third edition; 582-643.
[8]. Ramachandran, C. Snehalatha and Vijay Viswanathan Burden of type 2 diabetes and its complications –The Indian scenario. Current science, 83, PP.1471-1476 Suarez-Pinzon WL, Yan Y, Power R, Brand SJ, Rabinovitch A. Combination therapy with epidermal growth factor and gastrin increases beta-cell mass and reverses hyperglycemia in diabetic NOD mice. Diabetes 2005; 54: 2596-2601
[9]. 8.. 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 ClinEndocrinolMetab2005; 90: 3401-3409 9. Diana Boj-Carceller, PilarBocos-Terraz et.al. Are proton pump inhibitors a new antidiabetic drug? A cross sectional study, World journal of diabetes 2011; Volume 2; Issue 12.

[10]. Kohzo Takebayashi and Toshihiko inukai et.al: Effect of proton pump inhibitors on glycemic control in patients with diabetes; World journal of diabetes 2015; 6(10); 1122-1131.
[11]. Karin D. Hove, et.al. Treatment with a proton pump inhibitor improves glycemic control in type 2 diabetic patients - a retrospective analysis Diabetes Research and clinical practice 2010 e 72-74.
[12]. Michael A. Crouch, Ivan N. Meffordet.al; Proton Pump Inhibitor Therapy Associated with Lower Glycosylated Hemoglobin Levels in Type 2 Diabetes Memorial family medicine residency programme 2012; 25(1); 50-54.
[13]. F. Inci, M. Atmaca et al. Pantoprazole may improve beta cell function and diabetes mellitus, Journal of Endocrinological investigations; may 2014; 37950; 449-454.

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