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The effect of proton pump inhibitors on glycemic control in patients with type II diabetes

The effect of proton pump inhibitors on glycemic

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Abstract

Aim: Recent studies have shown that gastrin, like other incretin hormones such as GLP1, stimulates the proliferation of pancreatic β-cells and neogenesis, which seems to be able to double insulin level while taking oral glucose. Proton pump inhibitors decrease acid levels and cause relative hypergastrinemia which can better control hyperglycemic state. The present study intended to determine the effect of proton pump inhibitors (omeprazole) on glycemic control in patients with Type II diabetes visiting the endocrinology clinic of Imam Hossein Hospital in the first half of 2013. Material and Method: The present clinical trial study (before-after) was conducted on 40 patients with qualified type II diabetes during 12 weeks. Tests of FBS, HbA1c, 2hpp BS, insulin level and c-peptide were taken from patients before the study and they used omeprazole 20 mg twice a day for 3 months. The patients were asked to visit the clinic with the aforesaid tests results after three months. Results: Following the exclusion criteria, 8 patients (%20) were excluded from the present study. After 12 weeks of treatment with omeprazole, there was a statistically significant reduction in the mean HBA1c before (8.11±0.96) and after (7.13±0.68) the treatment at %95 confidence level (P-value<0.001). Moreover, after 12 weeks of treatment with omeprazole, there was a reduction in the mean 2HPPBS and FBS before and after the treatment which was statistically insignificant in 2HPPBS and significant in FBS (respectively P-value=0.1 & P-value=0.01). Discussion: It was concluded that the treatment with omeprazole increases insulin level, decreases FBS and HbA1c and subsequently improves hyperglycemic state and can be used with other anti-hyperglycemic medications especially in diabetic patients with digestive problems. However, further research is required in this regard.

Keywords

Diabetes Mellitus; Gastrin; Hb A1c; Proton Pump Inhibitor

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Introduction

Diabetes is a chronic metabolic disorder that is highly prevalent throughout the world. Currently, about 366 million people have diabetes around the world which will be reaching 552 million by 2030 according to predictions. About %95 of these patients have type II diabetes [1]. According to statistics in 2007, diabetes was responsible for over 71,000 deaths as an underlying disease and for over 160,000 deaths as a risk factor in America [2]. Iran is no exception i.e. diabetes has become one of the principal health problems in the country in recent years. According to Iranian Diabetes Association, over 6 million people had diabetes in 2013 while over 4,500,000 Iranians had diabetes in 2012 in Iran. Over %8.7 of the country's population has diabetes. The average cost is $414 per diabetic person. Diabetes mellitus is a chronic disease with complex pathophysiology that is associated with not only insulin deficiency in type I diabetes, insulin resistance and progressive destruction of pancreatic β-cells in type II diabetes but also other pathologies such as increased lipolysis, decreased incretin hormones or incretin hormones resistance, hyperglucagonemia, increased absorption of glucose by the kidneys and brain insulin resistance [3]. Nevertheless, the type I and type II hyperglycemia is caused by the partial or complete failure of pancreatic β-cell mass [4]. Diabetes is associated with chronic vascular complications including microvascular (e.g. retinopathy, neuropathy, nephropathy) and macrovascular (e.g. coronary artery disease, peripheral vascular disease, cerebrovascular disease) complications as well as non-vascular complications such as gastrointestinal involvement, skin problems, genitourinary system disorders, cataract, glaucoma, hearing loss and infection [5]. Due to the increasing growth of this disease, the control of diabetes mellitus and its complications is the only way to deal with this problem. Research has shown that accurate glycemic control, appropriate treatment of diabetes and achieving a normal range of plasma glucose postpone the incidence and development of micro and macrovascular complications of diabetes [6 & 7]. The history of diabetes treatment and glycemic control has shown that each patient always needs more than one treatment and that effective treatment requires several medications that are used in combination to correct pathophysiological defects. The important selection criteria for medications include the effect of medications, lack of side effects, tolerability and cost-effectiveness [4]. Glycosylated hemoglobin (HbA1c) is used as a golden standard for glycemic diagnosis and assessment and as a diabetes complications severity index (8-10). HbA1c is a hemoglobin where the beta chains of hemoglobin A1 is attached to glucose with a non-enzymatic reaction; the HbA1c indicates the mean blood glucose over the last 8 to 12 weeks [11 & 12]. Gastrin is the first released incretin hormone upon the receipt of oral glucose which reinforces the glucose-dependent insulin secretion (GSIS) [13]. Acid secretion is a regular and complex process which is done by at least three types of receptors on parietal cells that are sensitive to histamine, gastrin and acetylcholine [14]. Gastrin is the main endocrine-regulating hormone in response to secretory activities upon the intake of protein food [15,16]. Proton pumps (Payment Protection Insurance: PPI) were introduced as the medicinal treatment of gastric acid-related diseases esp. gastro esophageal reflux in the late 1980s. Other uses of PPIs include the prevention and treatment of ulcers caused by NSAIDs, gastritis, gastric and duodenal ulcers, helicobacter pylori, peptic ulcers and functional dyspepsia [14,17]. Proton pump inhibitors decrease acid levels; therefore, they cause relative hypergastrinemia which can better control hyperglycemic state. Since the first medication used for PPI inhibition was omeprazole, the discussion about the safety of this medication is controversial. Research has revealed that 15 years of omeprazole intake is safe despite some side effects [18] such as hypochlorhydria that increases the risk of infections and malabsorption as well as the risk of clostridium difficile and community-acquired pneumonia in the long-term use, decreased calcium absorption which, in turn, leads to osteoporosis and increased risk of fractures. The secondary hypergastrinemia caused by PPI intake can be considered in terms of carcinoid tumor; however, the long-term intake (11 years) of omeprazole is safe [19]. With regard to the fact that few studies have been done in this area, most which were retrospective or addressed the effect of PPI on HbA1c level while did not investigate the other parameters of glucose-insulin homeostasis (FPG, Insulin Level, C-peptide, HOMA-B Cell, HOMA-IR) as well as the fact that no studies have been done in this area in Iran, the present study intended to investigate the effect of proton pump inhibitors on glycemic control in patients with Type II diabetes visiting the endocrinology clinic of Imam Hossein Hospital, with respect to geographical, racial, cultural, nutritional and lifestyle differences between Iran and other countries.

Material and Method

The present clinical trial study (before-after) was conducted on adult outpatients with type II diabetes visiting the endocrinology clinic of Imam Hossein Hospital in 2013. The patients participated in the study voluntarily in compliance with the principles of medical ethics once informed consent was obtained from all patients and they were fully informed about the process of the research. The inclusion criteria comprised type-II diabetic adults of both sexes whose diabetes had not been newly diagnosed with at least one month passed the intake of maintenance doses of oral anti-diabetic metformin or sulfonylurea or both. Moreover, patients with the previous and current intake of insulin, pioglitazone, incretin treatment, liver failure (liver enzymes level greater than 3 times the normal level), kidney disease (cr>1.5), any diabetes complications, alcohol and drug abuse, hemoglobinopathies as well as pregnant and lactating women and those taking proton pump inhibitors were excluded from the study. Like previous studies, about 40 patients were selected and entered the study once the inclusion criteria were applied. The questionnaire contained background and demographic information including age, sex, weight, height, BMI, educational level and place of residence (urban/rural) that were recorded for all patients. All patients were asked to visit the laboratory in the fasting state for venous blood sampling to measure their fasting blood glucose level, FBS, HbA1C, BUN/cr, CBC Diff, fasting insulin level and C-peptide; then, the patients underwent venous blood sampling once more within two hours later for 2hppBs (2-hour post-prandial blood sugar test). Afterwards, the patients were given

oral omeprazole 20 mg capsules twice a day and they were asked to keep on with their normal dietary and treatment during the study. Patients' compliance was assessed based on number of consumed capsules by visiting them or calling them and those whose consumed more than %80 of the capsules were considered to have compliance and their lab tests results were examined. Omeprazole was administered to patients for 3 months; they were asked to undergo FBS, HbA1c, 2hppBS, fasting insulin level and C-peptide once more after 3 months and visit the clinic with the lab tests results. Furthermore, up to one hours after the blood sampling, the plasma was separated and plasma glucose level was measured through enzymatic glucose oxidase method to prevent glycolysis. Besides, HbA1C was measured through Boronate Affinity Chromatography method using NYCOCARD kit. Fasting insulin level and c-peptide was determined via Immunoreactive assay. The indices of HOMA-β and HOMA-IR were calculated via the following formulas in the software.

$$\text{HOMA-IR} = \frac{\text{Glucose} \times \text{Insulin}}{405}$$

$$\text{HOMA-}\beta = \frac{360 \times \text{Insulin}}{\text{Glucose} - 63}\%$$

The observed raw data were entered into $SPSS_{18}$. Kolmogorov-Smirnov Test was used to evaluate the normal distribution of all data based on which appropriate statistical tests were applied. In the present study, the statistical parametric tests such as paired t-test and independent t-test were used for data analysis. Furthermore, the statistical significance level was intended less than 0.05 (P-value).

Results

About 40 patients with type II diabetes participated in the present study. Eight (%20) patients were excluded from the study following the exclusion criteria, lack of readmission and lab sampling and intake of less than %80 of omeprazole capsules. The mean duration of diabetes in participants was 5 years. Twelve (%37.5) out of the rest 32 patients (follow up) were male while 20 patients (%62.5) were female. The mean age of the participants was 54.34±10.85 years. Out of the 8 excluded patients (loss of follow), 3 were male (%37.5) and 5 were female (%62.5). The mean age of the excluded patients was 52.87±8.32 years. The results of the present study showed that there was not any statistically significant difference between the means of both groups (P-value= 0.724). Furthermore, the follow-up group was compared with the loss-of-follow group in terms of the initial values of other parameters including HbA1C, 2HppBS, FBS, BMI, Insulin and C-peptide [Table 1] indicating no statistically significant difference (P-value>0.05).

The changes in HbA1C and Insulin level of the follow-up group were measured after 12 weeks of treatment with omeprazole. The results of statistical analysis indicated a significant difference between the mean of these variables in both groups. That is, the mean HbA1c significantly decrease after 12 weeks of treatment (P-value= 0.001) while the mean insulin level significantly increased during the treatment period (P-value= 0.001) [Figure 1]. It was also indicated that the mean 2hppBS and FBS decreased after 12 weeks of treatment with omeprazole in comparison to before-treatment period, which was statistically significant only for FBS (P-value<0.05). as presented in [Table 2], there was a significant increase in C-peptide which was statistically significant (P-value>0.05).

Following 12 weeks of treatment with omeprazole, the mean β-cell function index (HOMA- β-cell) increased from 54.41±27.06 before the treatment to 79.24±45.32 after the treatment which was statistically significant (P-value=0.007). Moreover, the results showed a statistically significant difference between the mean indices of insulin resistance (HOMA-IR) before the treatment with omeprazole (5.04±2.42) and after the treatment with omeprazole (6.19±2.52) (P-value= 0.001) as displayed in [Figure 2].

Table 1. Comparison of follow-up and loss-of-follow groups

Variables	Status	N	Mean	Std. Deviation	P value
Age	Follow up	32	54.34	10.85	0.724
	Loss to follow	8	52.87	8.32	
BMI	Follow up	32	29.00	2.74	0.905
	Loss to follow	8	28.87	2.03	
HBA1c. before	Follow up	32	8.11	0.96	0.298
	Loss to follow	8	7.73	0.58	
Insulin. before	Follow up	32	13.09	5.65	0.845
	Loss to follow	8	12.64	6.30	
C-peptide. before	Follow up	32	2.94	0.98	0.548
	Loss to follow	8	2.70	1.02	
FBS. before	Follow up	32	156.03	30.87	0.817
	Loss to follow	8	153.25	26.76	
2hppBs. before	Follow up	32	241.78	64.35	0.715
	Loss to follow	8	232.75	50.34	

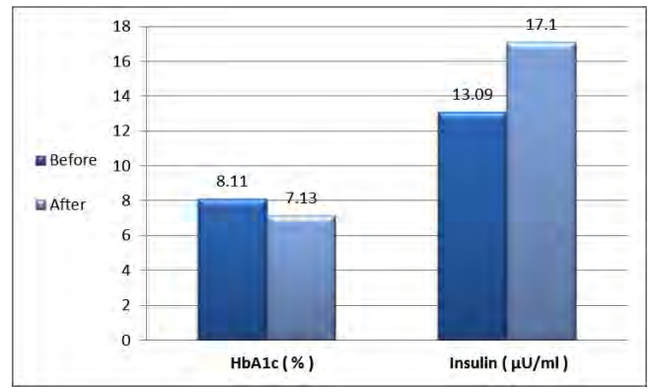

Figure 1. Changes in HbA1c and Insulin level after 12 weeks of treatments with omeprazole in the Follow-up group

Table 2. Comparison of HbA1c, FBS, 2HppBS, insulin and C-peptide before and after Omeprazole

Parameter	Before Omeprazole	After Omeprazole	P –value
HbA1c (%)	8.11±0.96	7.13±0.68	0.001
FBS(mg/dl)	156.03±30.87	146.90±23.88	0.01
2HppBs (mg/dl)	241.78±64.35	226.71±48.45	0.16
Insulin (µU/ml)	13.09±5.65	17.10±7.16	0.001
C-peptide (ng/ml)	2.94±0.98	3.40±1.30	0.003

Discussion

Many studies have investigated the effect of proton pump inhibitors on glycemic control in patients with type II diabetes. The results of the present study were in line with the findings of similar international studies. To name some, Crouch (2012) studied the electrically documented cases of type-II diabetic patients with PPI intake and without PPI intake. In his study, HbA1C level in both groups was %7.7 versus %7.1 respectively. In the present study, this value was %8.1 versus %7.1. However, the duration of PPI intake was not specified in Crouch's study (20). As mentioned earlier, many studies have been done in this area; nevertheless, none of them have measured 2HppBS, C-peptide, Insulin, FBS and indices of HOMA β-cell and HOMA-IR. As measured in the present study, the indices of HOMA β-cell and HOMA-IR qualtify β-cell function index and insulin resistance index which are calculated based on FBS and Fasting insulin via mathematical formulas. Matthews et al. (1985) studied the indices of HOMA β-cell and HOMA-IR indicating that HOMA β-cell was %100 in a young adult aged under 35 years with normal BMI while HOMA-IR index was less than 3 (normal resistance), between 3 and 5 (moderate resistance) and higher than 5 (severe resistance) [21]. In the present study, the indices of HOMA β-cell and HOMA-IR increased after 12 weeks of treatments with omeprazole in comparison to the before-treatment period which was statistically significant (P-value<0.05). In this regard, the results of the present study contradicted the findings of Singh et al.; They showed that HOMA β-cell significantly increase after pantoprazole intake while HOMA-IR remained insignificant [13]. It can be concluded that this difference contributed to racial differences, different sample size and different effects of both omeprazole and pantoprazole medications. Although this claim requires further investigations, what is certain is that insulin resistance index was higher in the diabetic patients of the present study at severe resistance level than the Indian diabetic patients in Singh's study. Nonetheless, omeprazole could meet the expectations of the present researchers to improve β-cell function due to the stimulation of gastrin secretion as an incretin hormone after omeprazole intake and its effect on stimulating β-cells, insulin secretion and β-cells proliferation. The increase of plasma gastrin level by 2 to 3 times occurs after 24 to 32 weeks of PPI intake [16]. However, the 12-week treatment with pantoprazole was associated with %50 increase in plasma gastrin level in Singh's study. This can improve hyperglycemic state with the long-term PPI intake. In this regard, the results of the present study were in line with the findings of Singh.

Bodvarsdottir studied the effect of lansoprazole with different doses on Psammomys Obesus, a kind of rats with type II diabetes, for 17 days. Measuring the morning blood glucose, gastrin and insulin level, he found that gastrin level had a 9-time increase. He also reported the significant decrease of glucose level, increase of insulin level and the %50 increase of beta cells mass. He stated that this can fortify the assumption that there is a close relationship between PPI, Gastrin and glucose-insulin homeostasis [22]. According to Suarez-Pinzon et al. [23] one of the reasons for the effect of omeprazole on the reduction of HbA1c level and improvement of glycemic state is the impact of this medication and other PPIs on delayed gastric emptying after eating a meal which leads to the timely delivery of glucose to the ileum. Appropriate environment secretes incretin hormone and reduces blood sugar level after eating a meal. Improved glycemic state can be due to the direct effect of gastrin on glucose-dependent insulinotropic peptides and GLP1 (Glucagon-Like Peptide 1) secretion from the K and L cells of small intestine; however, this has not been proved yet.

Conclusion

The strengths of the present study are that it is a prospective and randomized controlled trail (RCT) study while it is less strong than other RCT studies due to before-after trials and the absence of a placebo group. In finale, it was concluded that the treatment with omeprazole increases insulin level, decreases FBS and HbA1c and subsequently improves hyperglycemic state and can be used with other anti-hyperglycemic medications especially in diabetic patients with digestive problems. However, further research is required in this regard.

Competing interests

The authors declare that they have no competing interests.

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