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Original Article

The effect of proton pump inhibitors on glycaemic control in diabetic patients

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الملخص

أهداف البحث: أجريت هذه الدراسة لتقييم تأثير مثبطات مضخة البروتون على التحكم في نسبة السكر في الدم بين مرضى السكري الذين يتناولون الأدوية المضادة لمرض السكري.

طرق البحث: أجريت هذه الدراسة السريرية العشوائية التداخلية في معهد العلوم الطبية الأساسية، بمركز جناح للدراسات العليا الطبية بكراتشي. تم إدراج ثمانين مريضا يعانون من مرض السكري من النوع الثاني من كلا الجنسين وتقسيمهم بالتساوي إلى مجموعتين العدد=٤٠، والعمر ٣٠-٦٠ عاما من غير أي أمراض مصاحبة معروفة. تم صرف الميتفورمين والجليمبيرايد للمجموعة أ، بينما أعطي الميتفورمين والجليمبيرايد إضافة إلى أومبيرازول للمجموعة ب. تم تقييم فعالية جميع الأدوية بناء على سكر الدم الصائم وجلوكوز الهيموجلوبين التراكمي. كما تمت مراجعة الكرياتينين في الدم وإختبارات وظائف الكبد لتقييم الملف الآمن في الزيارة الأولى وبعد ١٢ أسبوعا.

النتائج: بعد علاج أومبيرازول لمدة ١٢ أسبوعا، لاحظنا تحسنا كبيرا في التحكم في نسبة السكر في الدم للمجموعة ب عن المجموعة أ، كما ظهرت في سكر الدم الصائم (١٠٨ ± ٢.٣٧ مقابل ١٢٦ ± ٢.٩)، ومستويات جلوكوز الهيموجلوبين التراكمي (٧.٢٩ ± ٠.٠٧ مقابل ٧.٤٧ ± ٠.٠٤) على التوالي.

الاستنتاجات: وجد أن إضافة مثبط مضخة البروتون مع الأدوية المضادة لمرض السكري تكون فعالة في تحقيق تحكم أفضل في نسبة السكر في الدم.

الكلمات المفتاحية: جليمبيرايد؛ الميتفورمين؛ مثبطات مضخة البروتون؛ التحكم في نسبة السكر في الدم

Abstract

Objective: This study aimed to evaluate the effect of proton pump inhibitors on glycaemic control amongst diabetic patients taking anti-diabetic medications.

Methods: This randomised interventional clinical study was conducted in Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi. Eighty patients of either sex (aged 30–60 years) with type 2 diabetes mellitus and without any known comorbidities were equally divided into two groups (i.e., $n = 40$ for each group) and were included in this study. Group A received metformin and glimepiride, while Group B, metformin and glimepiride plus omeprazole. The efficacy of the combination medications was evaluated based on fasting blood sugar (FBS) and glycosylated haemoglobin (HbA1c) levels. Serum creatinine and liver function tests were reviewed to evaluate patients' safety profile at the initial visit and after 12 weeks.

Results: After 12 weeks of omeprazole therapy, we observed a more significant improvement in glycaemic control in group B compared to group A based on the patients' FBS (108 ± 2.37 vs. 126 ± 2.9, P = 0.001) and HbA1c levels (7.29 ± 0.07 vs. 7.47 ± 0.04, P = 0.030).

Conclusion: The addition of a proton pump inhibitor along with anti-diabetic medications was considered effective in achieving better glycaemic control.

Keywords: Glimepiride; Glycaemic control; Metformin; Proton pump inhibitors

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Introduction

Diabetes mellitus is a multifactorial endocrine disorder categorised by metabolic imbalance in the body.[1] The heterogeneity of this imbalance results in multiple pathophysiological disorders that can cause permanent disability and death. Hence, diabetes mellitus requires prompt management. The International Diabetes Federation has reported an increasing global trend of diabetes mellitus, specifically in middle- and low-income countries. According to statistics, approximately 425 million people have diabetes, and it is predicted that a total of 693 million people will be diagnosed with diabetes by 2045.[2] The prevalence of type 2 diabetes mellitus (T2DM) ranges from 87% to 91%.[3–6] However, regardless of such high prevalence, it is believed that almost half of the patients remain undiagnosed.[2]

T2DM is characterised by progressive B-cell dysfunction that reduces insulin release from the pancreas along with insulin resistance that impairs tissue-specific glucose uptake. These factors lead to persistent hyperglycaemia, which results in micro- and macro-vascular complications.[7]

Hyperglycaemia affects multiple organs of the body. Several approaches are being used to manage it effectively including proper intake of a balanced diet, establishment of healthy habits such as performing exercise, and most importantly use of pharmacotherapy.[1] The current standard test for assessing patients' glycaemic levels for the last 3 months is the assessment of glycosylated haemoglobin (HbA1c) levels.[8] To effectively manage and avoid the complications of the disease in diabetic patients, a debate determining a more effective treatment for diabetes, whether an early initiation of combination pharmacotherapy or the traditional use of metformin as monotherapy only, has already been started.[9]

Metformin is widely accepted as a first-line medication used to treat T2DM. If metformin alone is unable to manage blood glucose levels adequately; then, the second agent is usually added in the treatment regimen. Sulfonylurea, a novel anti-diabetic drug group, is still widely recognised as a second-line therapy. Based on the recommendations of the Food and Drug Administration, sulfonylureas such as glimepiride are usually preferred as a monotherapy or as part of a combined regimen along with metformin/insulin.[10]

Interestingly, the use of anti-diabetic drugs such as metformin predisposes to a high prevalence of gastro-oesophageal reflux disease (GERD) amongst diabetic patients.[11] Several mechanisms have been proposed to explicate the association between GERD and diabetes, including the impact of hyperglycaemia on the motility of the gastrointestinal tract and neuronal functioning that can further lead to gastroparesis and oesophageal motility disorder. Proton pump inhibitors (PPIs) are widely prescribed agents for treating GERD, peptic ulcers, and gastritis with a remarkable safety profile.[12] Several retrospective studies on PPIs have documented its promising role in ameliorating glycaemic levels. On the contrary, few clinical studies have reported contradictory results.[13–17]

This study hypothesised that PPIs, as an adjuvant therapy, can improve patients' glycaemic control. Moreover, this study aimed to evaluate the potential role of prescribing PPIs along with anti-diabetic medications in diabetic patients in the management of hyperglycaemia and digestive problems considering the patients' genetic, cultural, and dietary differences since significantly limited literature is available in this context.

Materials and Methods

Setting

This open-label, computer-generated randomised trial was conducted in Basic Medical Sciences, Institute Jinnah Postgraduate Medical Centre, Karachi in collaboration with Memon Diabetic and Diagnostic Centre, Karachi (June 2015 to May 2016).

Sample size

A previous study[18] was used to calculate the sample size using 'OpenEpi version 2', an open-access computer program. A total of 80 patients (40 in each group) were included.[19]

Inclusion and exclusion criteria

All patients provided written informed consent for inclusion in the study. Subsequently, approximately 80 T2DM patients (divided into two groups) aged 30–60 years with HbA1c levels ranging from 7% to 8% were included.[19] The study excluded all type I diabetic patients, patients with comorbidities, and pregnant patients.

Grouping and intervention

Group A comprised diabetic patients without gastric symptoms, and in this group, metformin 500 mg (twice daily) and glimepiride 1 mg (once daily) were administered. Group B comprised diabetic patients with gastric discomfort, and in this group, metformin 500 mg (twice daily), glimepiride 1 mg (once daily), and omeprazole 20 mg (twice daily) were administered. Prior to performing the intervention, patients' demographic data, disease history, and baseline investigations were collected. Glucophage (metformin) by Merck, Amaryl (glimepiride) by Sanofi Aventis, and Risek (omeprazole) by Getz were used in the study.

Method of analysis and blood sample

Patients were evaluated using a predesigned questionnaire. Symptoms of gastric discomfort were determined by assessing any signs of abdominal pain, indigestion, bloating, decreased appetite, and burning with an empty stomach. Blood glucose levels were assessed by obtaining blood

samples on day 0, day 30, day 60, and day 90 (glucose oxidase method). Serum HbA1c levels were assessed by high-performance liquid chromatography (Bio-Rad D10 was used). Serum creatinine and liver function tests were analysed using Chem Well 2910 (Awareness Technology, Inc.) automated analyser and were assessed at day 0 and day 90. All blood samples were examined in the laboratory of Memon Diabetic and Diagnostic Centre, Karachi, using the aforementioned kits/techniques.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20.0. The results were calculated as mean and standard deviation for quantitative variables (fasting blood sugar [FBS], HbA1c,) and percentage/proportion for qualitative variables such as sex, symptoms, and adverse effects. T-test was used for quantitative variables, and P-value < 0.05 was considered significant.

Results

Amongst 80 patients, 5 were dropped out of the study (4 from the control group and 1 from the interventional group). Patients' demographic data including age, sex, height, weight, and body mass index were similar and revealed insignificant differences ($P > 0.05$) between the two groups.

Table 1 presents the FBS, HbA1c, creatinine, serum bilirubin, alkaline phosphatase, and serum glutamic pyruvic transaminase (SGPT) levels in group A (metformin + glimepiride) and group B (metformin + glimepiride + omeprazole), which were similar during baseline. However, the FBS levels in group B were lower than those in group A at day 30 (128 ± 1.42 vs. 135 ± 1.7, $P = 0.004$), day 60 (121 ± 2.38 vs. 130 ± 3.1, $P = 0.016$), and day 90 (108 ± 2.37 vs. 126 ± 2.9, $P = 0.001$). At the end of the therapy, percentage change in the FBS level in group B (22.8%) was significantly lower than that in group A (11.3%). Similarly, at day 90 after omeprazole therapy, a significant difference was observed between groups B and A (7.29 ± 0.07 vs. 7.47 ± 0.04, $P = 0.030$). When percentage changes were interpreted within each group, percentage change in the FBS level in group B (5.2%) was higher than that in group A (2.1%) at day 0.

The patients' safety profiles between the two groups were compared including creatinine, serum bilirubin, alkaline phosphatase, and serum SGPT levels, and insignificant differences were observed in both groups as presented in Table 1.

Symptoms and adverse effects including intense thirst, decreased appetite, nausea/vomiting, abdominal pain, frequent urination, weaknesses, and intense hunger were observed and compared at the end of the study. Percentage changes in symptoms and adverse events were lower in group B than those in group A. However, the percentage change in decreased appetite was slightly higher in group A (12.8%) than that in group B (7.7%), as depicted in Figure 1a and b.

Discussion

Diabetes mellitus is a worldwide health phenomenon and is ranked amongst the top 10 causes of global mortality.

Table 1: Comparison of treatment with and without proton pump inhibitors on haematological and biochemical parameters.

Variables	Group A (metformin + glimepiride) (n = 36) SEM	Group B (metformin + glimepiride + omeprazole) (n = 39) SEM
FBS		
Day 0	142 ± 1.8	140 ± 1.66
Day 30	135 ± 1.7	128 ± 1.42*
Day 60	130 ± 3.1	121 ± 2.38*
Day 90	126 ± 2.9	108 ± 2.37**
HbA1c		
Day 0	7.63 ± 0.04	7.69 ± 0.04
Day 90	7.47 ± 0.04 *	7.29 ± 0.07**
Creatinine		
Day 0	0.75 ± 0.02	0.72 ± 0.01
Day 90	0.75 ± 0.02	0.75 ± 0.02
Bilirubin		
Day 0	0.67 ± 0.01	0.67 ± 0.01
Day 90	0.66 ± 0.01	0.68 ± 0.01
Alk. phosphates		
Day 0	217 ± 4.0	227 ± 3.09
Day 90	216 ± 4.45	226 ± 4.53
SGPT		
Day 0	33.3 ± 1.21	34.1 ± 1.19
Day 90	33.6 ± 1.31	35.7 ± 1.41

*$P \leq 0.05$ is significant.
**$P \leq 0.001$ is highly significant.

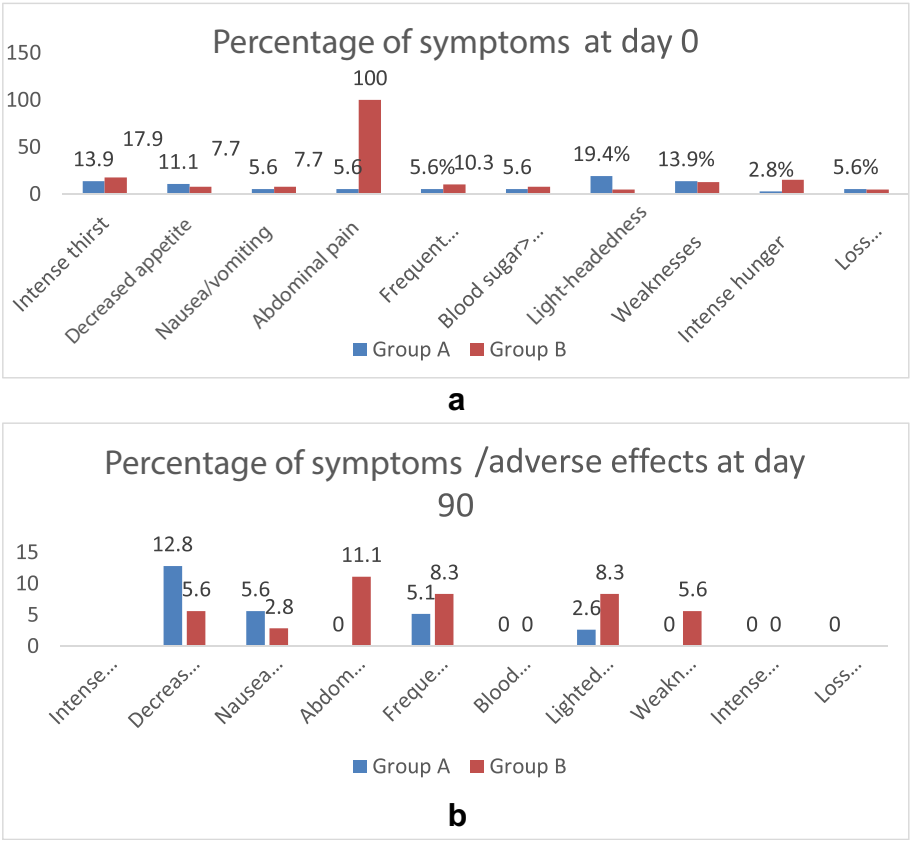

Figure 1: a. Comparison of diabetic symptoms and adverse effects in groups A and B at day 0. b. Comparison of diabetic symptoms and adverse effects in groups A and B at day 90.

Amongst the 425 million individuals diagnosed with this disease, 79% of these reside in low- and middle-income countries.[2]

GORD is a common manifestation amongst type 2 diabetic patients.[11] Recently, it was found that PPIs have beneficial effects on glycaemic control.[20] Therefore, an adjuvant use of PPI with anti-glycaemic agents can significantly treat GORD and T2DM simultaneously.[11,20] Moreover, the UK Prospective Diabetes Survey and US National Health and Nutrition Examination Survey promulgated the early initiation of anti-diabetic combination therapy rather than monotherapy treatment to achieve better control of HbA1c levels.[21,22]

The present study is a prospective interventional study that aimed to evaluate the effects of PPI on glycaemic control in T2DM patients. Amongst the types of PPIs, omeprazole, a commonly prescribed medication in patients presenting with symptoms of GORD, was used in this study.[23] Omeprazole therapy significantly improved blood glucose levels, as evidenced by the improvement in HbA1c levels. These findings are consistent with the findings of prior international studies, which used various combinations of anti-glycaemic agents in conjunction with PPIs and assessed the FBS and HbA1c levels.[24,25] Interestingly the use of PPIs led to a profound effect on FBS within 30 days. In contrast to the studies mentioned above, the findings of the present study are inconsistent to the findings of a few studies, which revealed insignificant improvement in HbA1c levels before and after PPI therapy.[26,27]

The information obtained from the above-cited studies provides significant insights into the possible mechanisms of PPIs as an adjuvant therapy to several anti-diabetic medications.[10] Primarily, it significantly involves the concept of gastrin and incretin structural resemblance. PPIs affect gastric acid secretion, which acts as a physiological regulator of gastrin release. Blocking gastric acid can increase serum gastrin levels. Consequently, the increase in serum gastrin levels, due to its structural similarity to incretin hormone, can potentiate insulin release.[26] Gastrin stimulates beta cell neogenesis, along with a decrease in apoptosis. Furthermore, gastrin negatively regulates ghrelin, thus playing a crucial role in suppressing appetite and enabling a better glycaemic control on increased gastrin release.[28] The use of PPIs also increases the bioavailability of anti-diabetic medications such as metformin and glimepiride. Hence, modifying the current anti-diabetic medication dosage to diabetic patients is suggested.[29,30]

To assess the safety profile of using PPI in diabetic patients, serum bilirubin, alkaline phosphatase, and SGPT levels were analysed, which showed no statistically significant results regarding the safety profile of PPI. Additionally, creatinine levels had no significant effect in this study; however, a controversy exists as regards this considering the presence of few contrasting studies. Hence, a long-term monitoring for creatinine levels should be performed in future studies,[31,32] although one of the previous studies observed constant renal functions, a finding consistent with that of the current study.[26]

A previous study has evaluated the adverse effects associated with metformin and glimepiride combination, and according to this study, mild adverse effects were observed. Hence, metformin and glimepiride combination therapy should be continued.[33] In the current study, when we added omeprazole and evaluated its adverse effects, only mild adverse effects were observed, a result consistent with that of the previous study.[20] On the contrary, the percentage change of decreased appetite was relatively higher in group B than that in group A in this study, which is probably due to the influence of hunger suppression by ghrelin as discussed in a previous study.[28]

Conclusion

The results suggested that omeprazole as a PPI in combination with metformin and glimepiride has a potential role in glycaemic control in T2DM patients. However, further clinical trials with larger sample sizes and longer duration periods are recommended to evaluate the long-term safety and efficacy of PPI in glycaemic control of T2DM patients.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This randomised interventional clinical study was approved by the ethical committee #F.2−81/2014-GENL/6003/JPMC.

Authors contributions

FA, MAR, and TZ conceived and designed this study, conducted research, provided research materials, and collected, organised, analysed, and interpreted the data. SZ and GK wrote the initial and final draft of the article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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