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Original research article

NEW INSIGHTS INTO THE THIAZOLIDINEDIONES AS AN ADD-ON THERAPY TO METFORMIN AND GLIMEPIRIDE IN PATIENTS WITH UNCONTROLLED TYPE 2 DIABETES MELLITUS

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Abstract: *Diabetes mellitus is a complex metabolic disorder that requires multifaceted management, including frequent blood glucose monitoring, polypharmacy, and timely therapeutic adjustments. Thiazolidinediones have been proposed as an effective add-on therapy to existing regimens to improve glycemic control in patients with Type 2 Diabetes Mellitus (T2DM).* ***Objective:*** *To evaluate the effectiveness of Thiazolidinediones as add-on therapy in diabetic patients already taking metformin and glimepiride.* ***Methods:*** *This observational, comparative, and follow-up cohort study was conducted in a tertiary care hospital in Pakistan. A total of 90 patients with poorly controlled T2DM were enrolled and randomly divided into two groups: Group A (n=45) received standard oral therapy with metformin and glimepiride, while Group B (n=45) received metformin, glimepiride, and Thiazolidinediones. The study outcomes included changes in Hemoglobin A1c (HbA1c), fasting blood sugar (FBS), and body mass index (BMI) throughout the study. Statistical analyses were performed using appropriate methods, with significance at $p < 0.05$.* ***Results:*** *The addition of Thiazolidinediones in Group B resulted in superior glycemic control compared to Group A. Group B exhibited a 16.1% reduction in HbA1c versus an 8.2% reduction in Group A ($p < 0.05$). FBS levels decreased by 28.8% in Group B compared to a 14.6% decrease in Group A ($p < 0.05$). Additionally, BMI decreased by 1.5% in Group B, whereas Group A showed a slight increase of 0.06% ($p < 0.05$). Significantly, the addition of Thiazolidinediones did not exacerbate the toxicity of the existing drug regimen.* ***Conclusion:*** *The study demonstrates that Thiazolidinediones, when added to standard therapy with metformin and glimepiride, offer significant improvements in glycemic control without additional toxicity. This combination therapy may be a beneficial strategy for managing poorly controlled Type 2 diabetes mellitus in the Pakistani population.*

Keywords: Empagliflozin, metformin, glimepiride, diabetes mellitus, HbA1c.

Introduction

The American Diabetes Association defines type 2 diabetes as "a cluster of metabolic abnormalities manifested by steadily increasing blood glucose levels due to issues with either insulin release or insulin resistance"(1). In Pakistan, the rate of prediabetes was 11%, with 17% of the population having a definitive diagnosis of Type 2 diabetes mellitus. The prevalence was found to be highest in people aged 51-60 years (26%), illiterate (18%), obese (35%), familial (31%), and female (18%). (2). The primary goal of diabetes management is to reduce symptoms and improve quality of life (3). However, because Type 1 Diabetes Mellitus is entirely dependent on insulin, achieving these goals is difficult. In contrast, both pharmacological and nonpharmacological interventions can easily prevent and control the symptoms of Type 2 diabetes mellitus. Diet and weight control are usually the first steps in treatment. These changes in daily routine may sometimes be ineffective, emphasizing the need to take medications to lower plasma glucose concentrations (4). Many oral antidiabetic medications, both natural and synthetic, control blood sugar levels via different techniques. These categories are used to group the numerous oral diabetic medicines. a Secretariats (e.g., glipizide, glyburide, glimepiride, and gliclazide) (b) Thiazolidinediones (such as metformin) and sensitizers (e.g., rosiglitazone) (c) Inhibitors of alpha-glycosidase (e.g., acarbose and miglitol) (d) Incretin mimics, GLP analogs (exenatide, for example), dipeptidyl peptidase-4 inhibitors (sitagliptin), glucosuria, and gliflozins (e.g., empagliflozin) (5). The glycosuric is a more recent group of diabetes drugs, which includes empagliflozin. The primary transporter, Sodium-Glucose Cotransporter 2, in the proximal renal tubules, is constrained as part of the mechanism of action, causing glucose reabsorption (6). 10 mg is the suggested daily dosage, which can be increased to 25 mg. The American Diabetes Association recommends Thiazolidinediones as a second-line treatment for Type 2 diabetes mellitus following metformin in patients with heart failure and chronic renal impairment (7). When metformin fails to keep blood glucose at its ideal levels, it is taken as a backup medication (8). According to a different trial, adding Thiazolidinediones to metformin and sulfonylurea therapy led to better clinical outcomes than upping the dosage of the first drugs (9). The trial aimed to compare the efficacy and safety of Thiazolidinediones to standard medication in individuals with Type 2 diabetes mellitus who had insufficient blood glucose control. This is the first diabetic treatment study in Pakistan that focuses explicitly on Thiazolidinediones add-on medication, to the best of our knowledge and research.

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Methodology

The current study was an observational, comparative, and follow-up cohort study. It was conducted in tertiary care, a non-teaching private hospital in Karachi, Pakistan. The hospital is accredited to ISO 2010 standards and is situated in Karachi's North neighborhood. The study lasted six months, from January 2020 to June 2020.

In order to participate in this trial, participants had to be both male and female, with an informed written agreement, with uncontrolled Type-2 diabetes mellitus and HBA1c>7%, and be on stable dosages of metformin (1500mg/day) and glimepiride (3mg/day), as well as a control diet and exercise, for 12 weeks—those who had a BMI of at least 20 kg/m2 qualified.

Any malignancy, untreated diabetes, Diabetic neuropathy, insulin injections, myocardial infarction (mi (ACS), migraine, or cardiac arrest within 12 weeks of consent, and coronary artery disease (cad) are prohibited from participating. Individuals with any hepatic or renal condition that has been proven (eGFR>30ml/min/1.73), including hepatitis or chronic kidney disease, as well as a history of recent surgery or treatment. Women who had alcoholism were expecting or nursing children, had intending pregnancies during the trial period, or had previously used weight loss medicines within three months of consent were not allowed to participate.

An online calculator was utilized to determine the sample size (10). Forty-five patients per group should be included in the sample to detect a statistically significant result with a 95% confidence level and a 0.05 margin of error. No medical or surgical procedures were carried out during this investigation. The study's therapeutics are widely used and regularly prescribed for treating people with Type 2 diabetes mellitus. The 16-week trial included 90 participants who met the inclusion above requirements. Two groups, A and B, each with 45 patients, were formed from the patients. Patients in Group A received Metformin (1500mg/day) and Glimepiride (3mg/day) at predetermined daily doses, whereas patients in Group B received Thiazolidinediones(10mg/day). All mandatory baseline demographic parameters were established prior to the start of the study using physical and biochemical tests. All other medication doses for patients with co-morbidities will remain unchanged.

In both study groups (FBS), baseline changes in HbA1c levels, modifications in body mass index (BMI), adjustments in waist circumference (WC), and changes in fasting blood sugar levels were all measured.

The hospital's ethical review committee approved the study (Ethical Approval # ZM/CG-IRNo.07-20). The study followed the International Conference on Harmonization's Harmonized Tripartite Guideline for Good Clinical Practice and the Helsinki Declaration (11).

The data is presented as the mean standard deviation (SD) of 45 groups. The Fisher exact test was used to examine nominal quantitative variables. For parametric variables, a two-tailed unpaired t-test was used to analyze continuous variables. A statistically significant p-value of less than 0.05 was considered. IBM SPSS version 20 software was used for statistical analysis.

Results

As per the study protocol, the Group A patients (n=45) were initiated on Metformin and Glimepiride combination therapy, while Group B patients (n=45) were initiated on combination therapy of empagliflozin, metformin, and glimepiride. No significant statistical difference was observed for the demographic characteristics: age (53.8 years vs. 50.6 years; P<0.05), gender (female patients; 49% vs 56%; P<0.05), and weight (76.8 kg vs. 80.1 kg; P<0.05) of patients among both study groups. The comparison of different demographic characteristics is summarized in Table 1.

The Mean±SD values of different parameters of both treatment groups are summarized in Table 2. For the HbA1c outcome parameter, a 16.1% decrease with a mean difference of -1.4 % was observed for Group B patients compared to an 8.2% decrease with a mean difference of 0.7% for Group A patients. On comparing both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (7.52±0.14 vs 7.3±0.18; P-value=<0.05) at 16-week intervals. For the FBS outcome parameter, a 28.8% decrease with a mean difference of -50.3mg/dl was observed for Group B patients compared to a 14.6% decrease with a mean difference of -30.7mg/dl for Group A patients. On comparing both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (189.6±6.48 vs 162.5±6.13; P-value=<0.05) at 16-week intervals.

Table 1: Demographic characteristics of enrolled patients

Characteristics	Group A (n=45) (Metformin + Glimepiride)	Group B (n=45) (Thiazolidinediones+ Metformin + Glimepiride)	P-value
Age (years)	53.8 ± 8.4	50.6 ± 9.4	0.92
Male patients	28 (51.1%)	24 (44.4%)	0.67
Female patients	22 (48.9%)	25 (55.6%)	-
Smokers (yes)	6 (13.3%)	7 (15.6%)	0.98
Creatinine (mg/dl)	0.88 ± 0.11	0.9 ± 0.14	0.45
Creatinine clearance (ml/min)	98.93 ± 13.8	99.76 ± 15.9	0.79
Family history of T2DM	26 (57.8%)	24 (53.2%)	0.83
Hypertension	25 (55.6%)	28 (62.2%	0.67
Dyslipidemia	29 (64.4%)	25 (55.7%)	0.52
Time of diagnoses of T2DM			
Less Than one year	1 (2.2%)	2 (4.4%)	-
2- 5 years	8 (17.8%)	7 (15.6%)	--
5-10 years	28 (51.1%)	24 (4.4%)	
>10 years	13 (28.9%)	16 (35.6%)	-

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Table 2: Estimation of different outcome parameters at different time intervals

Parameter	Treatment Group A				Treatment Group B			
	Baseline (Mean±SD)	After 16 weeks (Mean±SD)	% Outcome	Mean Difference	Baseline (Mean±SD)	After 16 weeks (Mean±SD)	% Outcome	Mean Difference
HbA1c (%)	8.44±0.16	7.52±0.14	8.2%↓	-0.7±0.032	8.7±0.17	7.3±0.18	16.1%↓	-1.4±0.037
FBS (mg/dl)	219.30±5.85	189.60±6.48	14.6%↓	-30.7±1.301	211.8±5.67	162.5±6.13	28.8%↓	-50.3±1.245
BMI (Kg/m^2)	31.56±0.71	31.58 ± 0.64	0.06%↑	+0.024±0.142	31.45±0.50	30.98±0.34	1.5%↓	-0.470±0.090
Waist (cm)	92.24±1.04	92.46 ± 1.04	0.2%↑	+0.224±0.219	91.96±1.21	90.56±1.36	1.6%↓	-1.40±0.271

Group B patients experienced a 1.5% decrease in the BMI index outcome parameter with a mean difference of -0.470kg/m2. Group A patients experienced a 0.06% increase with a mean difference of +0.024kg/m2. When the two treatment groups were compared, a statistically significant decrease was observed for Group B patients compared to Group A patients (31.58±0.64 vs 30.98±0.34; P-value=0.05) at 16-week intervals.

For the waist circumference parameter, Group B patients experienced a 1.6% decrease with a mean difference of -1.40cm, while Group A patients experienced a 0.2% increase with a mean difference of +0.224cm. On comparing both treatment groups, a statistically significant decrease was observed for Group B patients as compared to Group A patients (92.46±1.04 vs 90.56±1.36; P-value=<0.05) at 16-week intervals.

Discussion

Diabetes Mellitus is a complex metabolic disease that frequently necessitates polypharmacy and timely management decisions. When standard therapies such as metformin with or without sulphonyl urea fail to achieve adequate glycemic levels, patients with type 2 diabetes mellitus frequently require a second additional antidiabetic drug (1). The current study sought to evaluate empagliflozin's effectiveness in treating Pakistani patients as a supplemental medication. The current study discovered that adding Thiazolidinediones to the typical combination therapy, which includes metformin and a sulphonylurea (glimepiride), led to better outcomes than treatment group A in terms of a substantial decline in HbA1c, FBS, BMI, and WC (patients initiated on dual therapy of metformin & glimepiride). The demographic and baseline features of the individuals in the current investigation are similar for both groups (table 1). As a result, it is impossible for start point changes to play a role in determining the study's findings. Management of diabetes complications requires adequate glucose control. Patients with Type 2 Diabetes Mellitus who have a high HbA1c concentration have had good glycemic control over the past two to three months. In addition to the average HbA1c level, variations in these levels and HbA1c at different disease phases might give doctors important information when examining the connections between diabetic problems and high HBA1c levels (12). According to the results of the current study, adding Thiazolidinediones to the commonly prescribed regimen of metformin and glimepiride significantly decreased HbA1c levels from baseline, with Group B patients experiencing a 16.1% decrease with a mean difference of -1.4% and Group A patients experiencing an 8.2% decrease with a mean difference of 0.7%. Although, under normal conditions, HbA1c is still the strongest indicator of glycemic control. Nonetheless, FBS and RBS are frequently used alternative measures to screen for and monitor effective blood glucose control in persons with diabetes due to limited resources, particularly in poor, remote locations and under conditions when their usage is prohibited (13). The current study discovered that Group B's FBS was considerably lower than Group A's after adding Thiazolidinediones to the diet. The comparison of initial and final readings between treatment groups showed that patients in Group B saw a 28.8% drop with a mean difference of -50.3 mg/dl. In contrast, patients in Group A experienced a 14.6% decrease with a mean difference of -30.7 mg/dl. Add biguanides, a thiazolidinedione, alpha-glucosidase, DPP-4 inhibitors, and GLP analogs to pioglitazone with or without metformin (14) and linagliptin (15, 16). Our results supported the current recommendation for Thiazolidinediones as an adjunctive therapy, which states that it should be used "in case metformin fails as a single agent or in combination with insulin causing hypoglycemia" (17-19). The average waist size and average BMI were statistically significantly lower in Group B patients receiving therapy compared to Group A patients, according to comparisons of physical indicators in this study. According to the examination of the initial and end treatment group results, therapy reduced waist circumference and BMI overall by 1.6% and 1.5% in patients in Group B compared to 0.2% and 0.06% increases in patients in Group A, respectively. Due to insulin resistance, people with diabetes who are overweight have an increased risk of cardiovascular events; as a result, management is challenging. Patients taking diabetic drugs that result in significant weight gain find it more difficult to achieve ideal body weight control and insulin resistance (20). Drug safety is a crucial issue that influences the prescriber's choice and efficacy. As a result, the current investigation identified various toxicological indications. Regarding adverse medication reactions such as diabetes, bacterial infection, genitourinary infection, nausea, and vomiting, it was discovered that both groups were comparable. Thiazolidinediones use has also been associated with an increase in genital infections (21). On the other hand, our results did not indicate such a result in the therapy group. This result can also be attributable to the world's hygiene practices. Nonetheless, more research is necessary for clarification. The anti-diabetic medication that produces hypoglycemia in Type 2 Diabetes Mellitus patients presents a safety risk concern and may interfere with patient compliance and treatment adherence (22). In neither of the therapy groups, the current investigation identified a substantial incidence of severe hypoglycemia. Little limitations were found in the current study because it was relatively short, had few parameters, and few patients. Empagliflozin's effects and results for the long-term treatment of patients with type 2 diabetes with

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cardiovascular and kidney dysfunction were not examined. The advantages and disadvantages of this add-on therapy could be more clearly explained in a multi-center, twofold, randomized controlled research with more participants.

Conclusion

Finally, the current study supports the use of Thiazolidinediones in Type 2 diabetes mellitus patients as an add-on medication, leading to appreciable reductions in HbA1c and blood glucose levels and favorable effects on BMI and body waist. Also, incorporating it into the current regimen did not lead to an increase in side effects. It follows that empagliflozin, in addition to conventional diabetes treatment, may have positive benefits on the management of Type 2 Diabetes Mellitus in the Pakistani population.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned. (IRB: ZM/CG-IRNo.07-20)
Consent for publication
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Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

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