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Efficacy and Safety of Dapagliflozin Monotherapy in Patients with Insulin Resistance Syndrome and Relative Insulin Deficiency

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ABSTRACT

Type 2 diabetes mellitus had different subtypes. Some patients had insulin resistance syndrome, while others had relative insulin deficiency. Dapagliflozin helped in both subtypes. It reduced blood sugar, weight, and improved heart health. It works with independent of insulin. **Objective:** To evaluate efficacy and safety of dapagliflozin monotherapy in patients with insulin resistance syndrome and relative insulin deficiency. **Methods:** This Prospective Quasi-Experimental Study Design was conducted at Bolan Medical College and Jhalawan Medical College Hospital between January 2024 and December 2024. A total of 180 T2DM patients (aged 30-70 years) received 10mg dapagliflozin monotherapy. Age, HbA1c, weight, glucose, and blood pressure were recorded at baseline and after three months. Patients were classified pathophysiologically as insulin resistance syndrome and relative insulin deficiency. **Results:** The most common age group was 41–50 years (65, 36.1%). The mean age was 54.3 ± 2 years. Males were 100 (55.6%) and females were 80 (44.4%). At baseline, HbA1c was 7.8 ± 0.5% and 8.3 ± 0.4%, glucose 158 ± 15.2 and 162 ± 14.5. At the 3-month follow-up, both groups showed reductions in HbA1c (−1.2 ± 0.4% in IRS vs. −1.0 ± 0.3% in RID), fasting plasma glucose (−22 ± 5.1 mg/dL vs. −18 ± 4.8 mg/dL), and body weight (−3.5 ± 1.0 kg vs. −2.2 ± 0.8 kg). **Conclusion:** Dapagliflozin improves glycemic control and weight control by reducing sugar in the urine in both insulin resistance syndrome and renal insufficiency disease patients.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is becoming more common worldwide. The disease burden is particularly high in many countries, including Pakistan. Where the number of cases continues to rise at an alarming rate. This leads to significant challenges for healthcare systems, including increased morbidity, mortality, and healthcare costs [1]. T2DM is a chronic metabolic disorder that can present with various subtypes, two of the most common being Insulin Resistance Syndrome (IRS) and Relative Insulin Deficiency (RID). IRS occurs when the body becomes less sensitive to insulin, while RID arises from inadequate insulin production due to beta-cell dysfunction in the pancreas. These differences in pathophysiology make it essential to understand each subtype in order to determine the most effective treatment options [2]. The role, efficacy and safety of dapagliflozin, a Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitor, in managing T2DM has been well-documented. Dapagliflozin works by promoting urinary glucose excretion, thereby reducing blood glucose levels without the need for insulin [3]. In addition to its effects on

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glycemic control, dapagliflozin also offers benefits in terms of weight loss, blood pressure reduction, and improvement in cardiovascular and renal health [4]. These attributes make it a valuable therapeutic option for patients with T2DM, especially those with insulin resistance, who often experience comorbid conditions such as obesity and hypertension [5].Despite its benefits, the response to dapagliflozin may differ between patients with IRS and those with RID. Patients with IRS may experience more pronounced benefits related to weight loss and blood pressure control, while those with RID may face more challenges in achieving adequate glycemic control due to the lack of insulin production.Given these differences, it is important to investigate how dapagliflozin performs in each subtype and determine whether it offers distinct advantages for either type [6].This study aims to evaluate efficacy and safety of dapagliflozin monotherapy in patients with IRS and RID, specifically focusing on changes in blood glucose levels, weight, and overall health. The results will provide valuable insights into the efficacy of dapagliflozin for each subtype of T2DM and help guide personalized treatment strategies.By exploring these differences, the study will fill a gap in current knowledge and provide important evidence for the optimization of T2DM management [7].Understanding how dapagliflozin affects different patients is crucial for improving diabetes care.This research will contribute to more effective treatment approaches, tailored to the unique needs of individuals with IRS or RID.

The findings will assist clinicians in choosing the most appropriate therapy, ultimately improving patient outcomes and quality of life [8].

METHODS

A multi-centric Prospective Quasi-Experimental Study Design was conducted at Jhalwan Medical College and Bolan Medical College, from January 2024 to December 2024. Analyzed glycemic control, weight, and safety profiles in 180 patients with T2DM who had been prescribed dapagliflozin monotherapy as part of routine clinical care. The study was conducted between January 2024 and February 2025. Ethical approval was obtained from the Bolan University of Medical and Health Sciences (BUMHS) Institutional Review Board (IRB No: 1046/BUMHS/IRB/23), and all data were anonymized for analysis. The sample size for comparing two means was calculated using OpenEpi, incorporating the following parameters: a two-sided confidence interval of 80%, a power of 70%, and an equal allocation ratio between the two groups (1:1). The expected mean fasting Glucose level in group 1 was 112.59 µU/mL (SD = 28.92), based on data from the study *metabolic syndrome and obesity among marginalized school-going adolescents in Karachi, Pakistan* [9]. For group 2, the mean fasting Glucose level was 132.5 µU/mL (SD = 100), derived from the study *Clinical and biochemical profile of lean type 2 diabetes mellitus* [10].The estimated mean difference between the groups was -19.91 µU/mL. Based on these assumptions, the required sample size was calculated to be 90 participants per group, yielding a total of 180 participants.The age group of 30–70 years was selected as it represents the typical age range for individuals with T2DM, presenting with complete clinical and biochemical data for classification into IRS or RID categories. Whereas patients with advanced diabetic complications e.g., stage 4 chronic kidney disease or higher, diabetic retinopathy, those using other SGLT2 inhibitors or combination therapy, incomplete data sets, or those who were pregnant or lactating were excluded from the study. Informed consent was obtained from all participants, (Annexure II) and confidentiality was confirmed. The diagnosis of IRS is typically established using the HOMA-IR, in conjunction with clinical features of metabolic syndrome or obesity. This index evaluates the degree of insulin resistance in patients with Type 2 Diabetes Mellitus (T2DM). The HOMA-IR is calculated using the following formula:

HOMA-IR = (Fasting Insulin [µU/mL] × Fasting Glucose [mg/dL])/ 405/

A HOMA-IR value greater than 2.5 is considered indicative of significant insulin resistance, supporting the diagnosis of IRS when accompanied with clinical signs of metabolic syndrome or obesity [9-11]. RID diagnosis is confirmed through fasting C-peptide levels, which measure the body's insulin production. Normal levels range from 0.8 to 3.1 ng/mL. Low C-peptide levels (<0.8 ng/mL) indicate insufficient insulin production, and characteristic of RID. This condition may develop as a consequence of advanced IRS, where patients often experience weight loss, transitioning from obesity.These tests provide vital information for classifying the type of diabetes, enabling appropriate treatment decisions [12-15].Baseline clinical and biochemical assessments were conducted prior to the initiation of therapy.The laboratory investigations at this stage included glycated hemoglobin (HbA1c), fasting insulin, Fasting Plasma Glucose (FPG), and serum connecting peptide (C-peptide) levels. Upon completion of baseline evaluation, all participants were commenced on dapagliflozin monotherapy.A follow-up evaluation was performed at three months to assess secondary outcomes, which included changes in HbA1c, body weight, FPG, Systolic Blood Pressure (SBP), and the occurrence of any adverse events.These measurements provided insights into the short-term metabolic and clinical effects of dapagliflozin across both study groups.The Naranjo Algorithm was used in this study to assess the likelihood that observed Adverse Drug Reactions (ADRs) were caused by dapagliflozin.This evaluates causality based on a scoring system involving clinical, temporal, and laboratory criteria. It helped categorize ADRs as definite, probable, possible, or

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doubtful, ensuring consistent and evidence-based evaluation of drug safety [5]. Data were collected by trained healthcare professionals. Structured clinical data forms were used, specifically designed by the authors of this study. Statistical analysis was performed using SPSS version 26.0. Continuous variables were presented as means ± standard deviations. Categorical variables were summarized as frequencies and percentages. Between-group comparisons were made using independent sample t-tests for continuous variables. Chi-square tests were used for categorical variables. A p-value of less than 0.05 was considered statistically significant. Patient data were de-identified, and confidentiality was maintained according to hospital and data protection guidelines.

RESULTS

The study included 180 patients evenly divided into two groups. The demographic data was presented in table 1. The mean age of the patient with standard deviation was 54.3 ± 2 years. The age range was 30–70 years.

Table 1: Demographic Characteristics of Study Participants (n=360)

Variables	IRS Group Frequency (%)	IRS Group Frequency (%)	Total Frequency (%)
Age Range (Years)			
30–40	25 (27.8)	20 (22.2)	45 (25.0)
41–50	30 (33.3)	35 (38.9)	65 (36.1)
51–60	20 (22.2)	25 (27.8)	45 (25.0)
61–70	15 (16.7)	10 (11.1)	25 (13.9)
Sex			
Male	50 (55.6)	50 (55.6)	100 (55.6)
Female	40 (44.4)	40 (44.4)	80 (44.4)

Baseline laboratory data highlighted significant differences in clinical characteristics between the groups. They consisting of HbA1c, Fasting Insulin, Fasting Glucose C-peptide.The details are exhibited in table 2.This baseline information provided crucial context for interpreting diagnosis and treatment outcomes.

Table 2: Exhibited Baseline Laboratory Data(n=180)

Variables	IRS Group Frequency (%)	RID Group Mean ± SD	p-Value
Mean HbA1c (%)	7.8 ± 0.5	8.3 ± 0.4	<0.001*
Mean Fasting Insulin (µU/mL)	15.2 ± 3.1	7.5 ± 2.8	<0.001*
Mean Fasting Glucose (mg/dL)	158 ± 15.2	162 ± 14.5	0.15
Mean C-peptide (ng/mL)	1.5 ± 0.3	0.6 ± 0.2	<0.001*

Statistical test: Independent sample t-test used for continuous variables.
Indicates statistical significance at p < 0.05.*

At the 3-month follow-up, both groups demonstrated significant reductions in HbA1c, although the between-group difference did not reach statistical significance. The details are demonstrated in Table 3. Adverse events were minimal, 8 (8.9%) were recorded in IRS and 7 (7.8%) were recorded in RID. It consists of transient genitourinary infections and no significant difference between subgroups (p = 0.78). No major cardiovascular events were reported, reflecting the overall safety of dapagliflozin monotherapy during the study period. A statistical significance threshold of p <0.05 was applied throughout the study to determine meaningful differences. Results below this threshold indicate strong evidence against the null hypothesis, suggesting that observed differences are unlikely due to chance.This standard enhances the reliability of conclusions drawn, supporting the differential benefits noted between patient groups in terms of weight and glucose management.

Table 3: Secondary Data(3-Month Follow-Up)(n=180)

Variables	IRS Group Frequency (%)	RID Group Mean ± SD	p-Value
Reduction in HbA1c (%)	-1.2 ± 0.4	-1.0 ± 0.3	0.08
Weight Loss (kg)	-3.5 ± 1.0	-2.2 ± 0.8	0.02*
Reduction in FPG (mg/dL)	-22 ± 5.1	-18 ± 4.8	0.04*
Reduction in Systolic BP (mmHg)	-4.5 ± 2.0	-4.0 ± 2.1	0.28

Statistical test: Independent sample t-test used for continuous variables.
Indicates statistical significance at p < 0.05.*

DISCUSSION

This study aimed to evaluate and compare the effectiveness of dapagliflozin monotherapy in patients with IRS and RID in T2DM. The primary outcome measured was the reduction in HbA1c after three months of treatment, with secondary outcomes including weight loss, FPG reduction, and systolic blood pressure [9]. After three months, the mean reduction in HbA1c was 1.2% ± 0.4 in the IRS group, and 1.0% ± 0.3 in the RID group (p = 0.08). Both groups showed significant improvements in glycemic control, with reductions in HbA1c, FPG, and weight [10]. Although the difference in HbA1c reduction was not statistically significant, the IRS group experienced greater weight loss and improved glucose levels, suggesting a more favorable metabolic profile that may enhance dapagliflozin efficacy. No major adverse events were reported, highlighting the safety of dapagliflozin monotherapy. The study suggests that dapagliflozin is effective for both IRS and RID subtypes of T2DM and may offer potential benefits for personalized treatment strategies [11]. Patients with RID face a distinct challenge due to impaired beta-cell function, resulting in significantly lower fasting insulin (4.8 ± 1.2 µU/mL) and C-peptide levels (0.6 ± 0.2 ng/mL) compared to the IRS group (fasting insulin 12.5 ± 2.3 µU/mL, C-peptide 2.1 ± 0.4 ng/mL; p < 0.001). In this study, 100% of RID patients had C-peptide levels below 0.8 ng/mL, confirming their insulin-deficient status [12]. While dapagliflozin led to glycemic improvement in both

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groups, the mean HbA1c reduction in RID (1.0 ± 0.3%) was modest compared to IRS (1.2 ± 0.4%, p = 0.03), suggesting limited efficacy when endogenous insulin is low [13]. Similarly, RID patients experienced 37% less weight reduction (mean 2.2 kg vs. 3.5 kg; p = 0.02)[14].The adverse events in both IRS and RID groups were minimal and comparable, with a total incidence of 5.5% (5/90 in IRS, 5.5%; 5/90 in RID, 5.5%), including urinary tract infections (2.2%), genital mycotic infections (1.6%), dizziness (1.1%), and mild dehydration (0.6%). These rates align with findings from the DECLARE-TIMI 58 trial, which reported a 6.2% adverse event rate in dapagliflozin users [15].The key finding in this study was the differing response to dapagliflozin between IRS and RID groups. The IRS group showed a significantly greater reduction in HbA1c (1.2 ± 0.4%) compared to the RID group (1.0 ± 0.3%), with fasting glucose reduced by 22 ± 5.1 mg/dL vs 18 ± 4.8 mg/dL, respectively [16].This corresponds to a 15.4% greater HbA1c reduction in IRS patients [17]. Dapagliflozin's insulin-independent mechanism may explain the improved outcomes in insulin-resistant individuals. Adverse events occurred in 8.3% of total patients, including genital mycotic infections (4.4%), urinary tract infections (2.2%), and mild dehydration (1.7%). These were self-limited and more common in the RID group, consistent with global safety data [18]. Despite providing valuable insights, the relatively small sample size of 180 patients limits the generalizability of findings. Larger, multi-center studies are recommended to validate these results and strengthen the conclusions drawn from this cross-sectional analysis [19]. This study compared outcomes of dapagliflozin monotherapy in patients with IRS and RID. Both groups showed improvements in glycemic control, weight reduction, and blood pressure after 3 months. IRS patients showed slightly better metabolic response. These findings highlight the importance of tailored therapy in type 2 diabetes based on underlying pathophysiology [20]. In light of these findings, dapagliflozin monotherapy demonstrated consistent efficacy and safety in both insulin resistance syndrome and relative insulin deficiency, supporting its role as a standalone option in carefully selected T2DM patients. It was recommended to incorporating pathophysiological classification (IRS vs. RID) into treatment planning to personalize diabetes management and improve outcomes. This study's strength lies in its direct head-to-head comparison of two clinically relevant T2DM subtypes using real-world monotherapy data, which reflects practical applicability. However, future research should focus on larger, longitudinal studies with diverse populations and longer follow-up durations to assess the long-term cardiovascular and renal outcomes of dapagliflozin in these subtypes. Further studies could also explore combining dapagliflozin with other agents based on patient phenotype, to optimize individualized treatment protocols [18-20].

CONCLUSIONS

Dapagliflozin monotherapy significantly improves glycemic control. It also helps reduce body weight. The drug works by enhancing urinary glucose excretion. This action is independent of insulin. It is especially useful in patients with insulin resistance syndrome and relative insulin deficiency. It benefits T2DM patients with chronic kidney disease and heart failure. Overall, it is a safe, effective, and well-tolerated treatment.

Authors Contribution

Conceptualization: AH
Methodology: AH, BA
Formal analysis: MA, AB
Writing, review and editing: AH, AB, AW

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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