doi.org/10.36721/PJPS.2024.37.2.REG.357-366.1

Evaluating the efficacy and safety of empagliflozin addition to insulin and oral antidiabetic medication (OAD) regimen in poorly controlled type 2 diabetes and obese patients

Hina Sharif[1]*, Sana Sharif Sheikh[2], Ambreen Salman[3], Zahida Jawed[4], Ishrat Karim[4], Tehseena Sohail[4] and Nadia Mohsin[4]

[1]Research & Publication Department SINA Health, Education & Welfare Trust, Karachi, Pakistan
[2]SINA Health Education & Welfare Trust, Karachi, Pakistan
[3]Medical Quality Assurance, SINA Health, Education & Welfare Trust, Karachi, Pakistan
[4]SINA Health, Education & Welfare Trust, Karachi, Pakistan

Abstract: Insulin resistance complicates diabetes care. Its effectiveness and tolerability as an addition to metformin, DPP4 inhibitor and insulin treatment in type 2 diabetic patients will be examined in this research. Participants with type 2 diabetes from poor socio-economic backgrounds had HbA1c values ≥8.5% when using Insulin+Metformin+DPP-4 inhibitors. They received 10mg Empagliflozin daily for 12 weeks (n=143). The main outcome was change in HbA1c at 12th week from baseline. Secondary outcomes were baseline weight and week 12 FPG. Adjusted mean (SE) HbA1c increases at week 12 were: Mean ± SD 10.38 (6.8-17.0) vs. Mean±SD 9.05±1.77 (5.60-16.0) with empagliflozin 10mg. When added to the regimen, empagliflozin significantly reduced FPG, systolic and diastolic blood pressure. The mean (SE) BMI increases from baseline were 31.28±5.89 (16.0-66.0) and 29.73±5.47 (3.0-46.0) with 10mg empagliflozin. Two individuals experienced urinary tract infections as AEs, but no genital infections. Adding empagliflozin 10mg daily to metformin+DPP4 inhibitor+insulin improved glycemic control, body weight and blood pressure for 12 weeks. The intervention was well-tolerated, highlighting empagliflozin's therapeutic potential.

Keywords: Insulin resistance, type 2 diabetes, overweight, add-on therapy, glycemic control.

INTRODUCTION

Diabetes is an urgent worldwide health issue, especially in Pakistan. The International Diabetes Federation (IDF) Atlas reported by Sun *et al*. (2022), ranks diabetes mellitus as the third most common illness worldwide, affecting 33 million Pakistanis. This rising tendency is especially noticeable in lower-middle-income nations, emphasizing the necessity for competent management.

Insulin resistance complicates diabetes care (Freeman and Pennings 2018). Many reasons cause insulin resistance, including obesity and diabetes dyslipidemia (Fujji *et al*., 2018). This problem requires diverse methods to glycemic control, weight management and lipid profile modification as discussed by Marušić *et al*., (2021).Increased insulin dose in conjunction with metformin and DPP-4 inhibitors has been used to treat insulin resistance, which increases the risk of hypoglycemia period in T2D Gallwitz, (2019). This technique may backfire since anti-diabetic drugs might worsen weight gain and harm the patient. Diverse research across areas have examined combinations of antidiabetic medicines to address this issue, but the increased complexity and expense may affect patient compliance and therapeutic outcome Frampton 2018.

Given these complexities, our study's reasoning highlights empagliflozin's potential advantages in regulating blood sugar and reducing body weight (Grabarczyk and Wissman 2020; Younis, 2020). This dual mode of action may help people with obesity and insulin-resistant type 2 diabetes (T2D).

Scheen (2019) reported that empagliflozin, a potent and selective SGLT2 inhibitor, may treat type 2 diabetes (T2D). In addition to this, due to its efficacy and safety, this antihyperglycemic drug is licensed globally for T2D. Its once-daily oral dose and insulin-independent action lessen hypoglycemia risk, making it versatile. To enhance T2D glycemic control, empagliflozin may be used alone or alongside other antidiabetics. Besides glycemic benefits, empagliflozin lowers weight and blood pressure. Cardioprotective and Reno protective properties demonstrate its value beyond glucose management. Evidence suggests non-glycemic advantages for T2D and CVD patients (Reifsnider *et al*., 2021). Empagliflozin does not enhance amputation or bone fracture risk like canagliflozin. The effectiveness of empagliflozin makes it an important T2D therapy. The drug's cardioprotective characteristics make it ideal for high-risk patients who require additional antidiabetic treatment to accomplish glycemic goals Scheen (2019). Empirical data demonstrates empagliflozin has improved T2D therapy for difficult patients. Many empagliflozin studies have indicated diabetic and cardiovascular health benefits. The

**Corresponding author:* e-mail: Hina.shf19@gmail.com

early EMPRISE findings revealed its advantage over sitagliptin. Empagliflozin reduced heart failure risk in hospitalized patients and type 2 diabetics on routine therapy, independent of cardiovascular history (Khalid, 2021). It also works in type 1 diabetes. It improved weight and glycemic control without hypoglycemia. Ketone monitoring and lower empagliflozin doses lowered ketoacidosis risk (Haidar *et al*., 2021). Empagliflozin benefits go beyond glycemic management. It improves myocardial diastolic stiffness and function independent of diabetes (Ferdinand *et al*., 2019). A November 2020-September 2021 Pakistani comparative study revealed empagliflozin effective for T2D therapy. In 200 patients, serum blood glucose, body weight, waist circumference, SBP and DBP decreased significantly (Aamir *et al*., 2022). Similar investigations have happened worldwide. A 2012 Chinese study found that liraglutide and insulin help poorly treated T2D and abdominal obesity (Huthmacher *et al*., 2020). Another 2012 study found that insulin add-on sitagliptin improved glycemic management with fewer hypoglycemia and weight gain (Gomez-Peralta, 2018). Diabetics fear weight gain, which impairs insulin resistance and glycemic control. Recent studies relate elevated endogenous insulin levels to weight gain and resistance (Mathieu *et al*., 2018 and Moreira *et al*., 2023).

Pakistani research in 2021 demonstrated SGLT2 inhibitors' expanding value. Empagliflozin may manage diabetes and heart failure and may be studied (Aamir *et al*., 2022). Islamabad investigated SGLT2 inhibitor dapagliflozin in 2020. It improved weight reduction, blood pressure and HbA1c (Hussain *et al*., 2021). This study reveals dapagliflozin's diabetes therapy potential (Hussain *et al*., 2021). These trials show that empagliflozin and other SGLT2 inhibitors improve diabetes control, cardiovascular outcomes and associated metrics. The growing body of research suggests better diabetes therapy and control.

The primary aim of this study is to assess the impact of incorporating empagliflozin, an oral sodium-glucose co-transporter 2 (SGLT2) inhibitor, into the existing therapeutic regimen of Insulin+Metformin+DPP4 inhibitor (DPP4I) in poorly controlled type 2 diabetes mellitus (T2DM) patients. The study seeks to evaluate its effect on achieving glycemic goals in this patient population.

Objectives

1. ***Glycemic control improvement:*** the addition of empagliflozin to the current treatment regimen leads to a significant improvement in glycemic control among poorly controlled T2DM patients.
2. ***Insulin dose reduction:*** the potential impact of empagliflozin on insulin sensitivity and requirements, thereby investigating the feasibility of reducing insulin doses while maintaining effective glycemic control.
3. ***Weight reduction:*** the impact of empagliflozin on weight reduction among T2DM patients,

MATERIALS AND METHODS

Site selection

The study was strategically situated across four clinics operated by SINA Health and Education Welfare Trust, a distinguished non-profit organization situated in urban slums within Karachi. Clinics were meticulously chosen through a process of random selection, facilitated by a random number table and employing simple random sampling techniques. This approach ensured unbiased representation in the study's clinic sites. Post-treatment data were meticulously gathered over a time span of three months, offering a comprehensive window into the effects of the intervention.

SINA Health Education & Welfare Trust is a not-for-profit primary healthcare organization with 38 clinics in Karachi slums. The distance from one clinic to another is approximately 7km or a maximum of 20 km or around. All clinics of SINA are divided into 6 clusters with 38 clinics and 3 locations are for mobile clinics. The mean number of patients per day is around 120 ± 30.

Study design

An adaptive research design was judiciously employed to navigate the complexities of this research. Leveraging a secondary dataset, the study engaged data from registered diabetic patients who had been consistently monitored by SINA over the past six months. These existing datasets formed the foundation for analysis, enabling informed decision-making. Based on rigorous analytical evaluations, a standardized treatment protocol was established, with patients prescribed empagliflozin 10mg of three months duration.

Following the completion of this three-month treatment phase, a comprehensive assessment ensued. Clinical laboratory tests were re-conducted and the ensuing results were meticulously collected and juxtaposed with the previously recorded laboratory outcomes. This comparative analysis aimed to discern the effects of empagliflozin intervention on the health parameters under consideration. This research was conducted out on the registered clinical trial in clinictrials.gov with registration number was NCT06145360**,** in compliance with the Helsinki Declaration principles and with the approval of The Research and Development Solutions Institutional Review Board (RADS IRB). Its approval with the reference number RADS IRB-00010843

Sample size

Based the estimates of the International Diabetes Federation, there will be roughly 33,000,000 cases of

diabetes worldwide in 2022, with 26.7% of people in Pakistan afflicted [20]. On the basis of this, following are the calculation of sample size calculation.

Patient sample size = (4pq/d2) *25% NRR (no response rate)

$$= 4*26.7*25.7/5^2$$

$$= 109.7 \sim 110 +25\% = 138$$

Where p = anticipated the prevalence, q= (1-p), d=margin of error), d = 5%, q= p-1=25.7

A total of 143 patients were included in the study as depicted in fig. 1.

Study procedures and study visits: A step-wise description

a) ***Clinic Selection:*** Out of a total of 38 clinics, a rigorous process of simple random sampling was applied to select four clinics affiliated with SINA Health and Education Welfare Trust, ensuring a representative selection.

b) ***Clinic identification:*** The chosen clinics were named as Mehran (M), Jumma Goth (JG), Shireen Jinnah (SJ) and North Clinic (N), facilitating easy reference throughout the study.

c) ***Sample size:*** Each of the selected clinics enrolled a sample size of 35 to 36 patients, as per the inclusion criteria.

d) ***Baseline intervention:*** The study commenced by administering the intervention to patients with a documented history, alongside baseline laboratory investigation tests.

e) ***Sample labeling:*** To ensure accurate tracking and identification, all drawn samples were meticulously labeled with the respective clinic codes (M1, JG1, SJ1, N1). Furthermore, a distinct red colored tape was utilized for differentiation.

f) ***Intervention period:*** Following the completion of necessary preliminary procedures, the intervention phase spanned three months, during which the prescribed treatment regimen was administered.

g) ***Regular monitoring:*** Glucose tests were conducted on a weekly basis to vigilantly monitor glycemic control, while estimated Glomerular Filtration Rate (eGFR) assessments were conducted 45 days into the intervention to evaluate kidney function following empagliflozin's introduction.

h) ***Post-treatment analysis:*** Upon the conclusion of the three-month intervention, post-treatment laboratory investigations were conducted, with the resulting data subjected to comprehensive analysis.

i) ***Doctor availability:*** The recruited doctor remained available during clinic hours to address any queries or concerns raised by the participating patients.

j) ***Established rapport:*** Due to the patients' existing registration at SINA clinics, a robust rapport existed between them and the participating doctors. This pre-existing rapport facilitated effective communication throughout the study.

k) ***Follow-up visits:*** Patients adhered to a schedule of follow-up visits occurring every 7 days. During these visits, patients brought their previous empty medicine blister to ensure accurate tracking of medication adherence.

l) ***EMR system:*** Leveraging a robust Electronic Medical Record (EMR) system, SINA ensured transparency, accessibility and systematic patient follow-up. Qualified healthcare providers staffed the clinics and a dependable referral system to tertiary and specialist care hospitals was in place for any escalated medical needs.

Inclusion criteria

Patients aged 35 years or older, diagnosed with type 2 Diabetes Mellitus and registered at SINA clinics are eligible for inclusion in the study. Specifically, individuals with a documented HbA1c level equal to or exceeding 8.5% over the course of the last six months or more are considered eligible candidates. Furthermore, these patients should currently be undergoing treatment involving a combination of Insulin and either Metformin or Sitagliptin. This stringent criterion serves to select participants who represent the target population for this study, ensuring that the investigation's outcomes are relevant and impactful within the context of poorly controlled Type 2 Diabetes Mellitus management.

Exclusion criteria

Patients with a history of recurrent urinary tract infections or those who are currently pregnant are excluded from participation in the study. Additionally, patients with an estimated Glomerular Filtration Rate (eGFR) exceeding 40 ml/min/1.73m², calculated using the CKD-EPI Creatinine Equation (2021), are ineligible for inclusion. Furthermore, individuals with other concurrent medical conditions and those who are unable to provide informed consent for the study, have also been excluded. This careful selection process ensures that the study is conducted within a well-defined and relevant patient population, fostering accurate and meaningful findings.

Patient and public involvement

No patients or members of the general public were involved in the planning, execution, reporting, or distribution of our study.

Data collection

The clinical records encompass a comprehensive set of data variables, essential for a thorough understanding of the study's impact. These variables include:

Patient demographic profile

- Age (35 or above): Patient's age, ensuring inclusion of the specified age group.
- Socio-economic Background: Insights into the patient's socio-economic status, offering contextual information.

- Residential Area/Living Conditions: Understanding the patient's living environment and conditions.
- Duration of Illness:
- Past History of Diabetes: Duration of the patient's diabetes, providing a historical perspective.
- Clinical Investigations (Baseline and End of Study):
- HbA1c: Measurement of HbA1c levels, an integral marker of glycemic control.
- BMI (Body Mass Index): An assessment of the patient's weight relative to their height, aiding in evaluating body composition.
- eGFR (Estimated Glomerular Filtration Rate): Calculated eGFR value, indicative of kidney function.
- Serum Creatinine: Measurement of serum creatinine levels, further contributing to the evaluation of kidney health.

This comprehensive compilation of data variables ensures a holistic approach to the study, encompassing patient demographics, illness history and essential clinical parameters. These variables collectively provide a nuanced view of the patient population under study, facilitating a rigorous and informed analysis of the intervention's impact.

Endpoints and evaluations

The primary focus of evaluation was the change in HbA1c from baseline at the culmination of a 12-week double-blind therapy, referred to as week 12. In this context, "baseline" signifies the final observation prior to the initiation of any double-blind, randomized treatment. Notably, significant secondary endpoints included alterations in fasting plasma glucose (FPG) levels and weight from the baseline at week 12.

For patients whose baseline HbA1c level was equal to or greater than 8.5%, additional key endpoints encompassed the occurrence of HbA1c levels at or surpassing 8.5% at week 12. Moreover, changes from baseline in systolic and diastolic blood pressure (SBP and DBP) were assessed. This evaluation extended to encompass alterations from baseline in HbA1c, FPG, weight, SBP and DBP over the course of time.

Upon the culmination of the 12-week open-label empagliflozin treatment period, the study explored effectiveness endpoints, namely variations in HbA1c, FPG, weight, SBP and DBP from the pretreatment values.

The safety assessments encompassed vital signs, clinical laboratory data and adverse events, aligned with the criteria set by the US Pharmacopeia. All adverse events (AEs) beginning after the first dose of open-label empagliflozin and up to 7 days after the final dose of study medication were regarded as treatment-emergent AEs. Specific attention was devoted to confirmed hypoglycemia AEs, requiring medical attention and/or associated with plasma glucose levels below 3.9 mmol/L. The study also meticulously evaluated episodes suggestive of urinary tract infections (UTIs), vaginal infections, hypersensitivity reactions, pancreatitis and diabetic ketoacidosis.

STATISTICAL ANALYSIS

The data underwent thorough entry using Microsoft Excel version 2013 and was subsequently transferred to SAS version 9.4 for meticulous analysis. Every collected datum was subjected to a rigorous validation process, ensuring the data's precision and uniformity. Our study focused on investigating six specific factors between the pre-Empagliflozin (EMPAA) and post-EMPAA treatment phases.

To commence, we diligently summarized the outcome variables using descriptive statistics, offering insights through mean values and standard deviations. Additionally, we meticulously examined the risk or independent factors, quantifying their presence through counts and proportions. In our pursuit to gauge the significance of the intervention's effects, we executed paired sample t-tests on the outcome variables, effectively comparing pre and post-treatment values. The outcome was the derivation of mean differences alongside the associated significance levels (p-value < 0.05).

RESULTS

Characteristics of the patient

Table 1(a) presents the outcome variables, thoughtfully summarized with mean values and standard deviations. Notably, across each outcome variable, the pre-treatment mean values for EMPAA surpassed those observed post-EMPAA treatment, indicating a discernible trend in the data. Out of 143 patients, 13 were lost to follow-up during the study duration hence excluded from the study. Whole inclusion process has shown in fig. (1).

In table 1(b), delve into the descriptive statistics of demographic and risk factors. A significant majority of study participants were female, constituting 81%, while males represented 19% of the cohort. An overwhelming 97% of participants were married. In terms of age distribution, the “41-60” year range emerged as the most prominent, encompassing 56% of participants. Pathan ethnic background predominantly featured, accounting for 54% of the participants.

Furthermore, it is noteworthy that a considerable portion of the cohort, specifically 67%, had a diagnosis of hypertension. Additionally, 55% of participants reported a family history of diabetes. The prevalence of daily smokers stood at 49% among the study participants. A noteworthy trend emerged with the lifestyle pattern, as a majority-71%-exhibited a sedentary way of life.

Table 1(a): Descriptive statistics of outcome variables

Variables	Pre-treatment of EMPAA		Post- treatment of EMPAA	
	Mean ± SD	Min - Max	Mean ± SD	Min - Max
Hb1Ac (%)	10.38 + 1.44	6.8 - 17.0	9.05 + 1.77	5.60 - 16.20
BMI	31.28 + 5.89	16.0 - 66.0	29.73 + 5.47	3.90 - 46.0
eGFR (mg/dl)	64.32 + 14.06	35.20 - 105.40	59.31 + 12.79	26.10 - 88.20
FBS (mg/dl)	36.83 + 68.79	235.76 - 69.91	199.34 + 63.47	89.0 - 382.0
S.Cr (mg/dl)	0.99 + 0.20	0.60 - 1.80	0.96 + 0.21	0.50 - 1.80
UMA (mg/l)	61.30 + 34.88	1.00 - 117.00	36.83 + 68.79	0.80 - 91.00

SD: Standard Deviation; Min: Minimum value; Max: Maximum value; Hb1Ac: glycated hemoglobin; S.Cr.: Serum creatinine; eGFR: estimated Glomerular Filtration Rate; BMI: Body Mass Index; FBS: fasting blood sugar; UMA: Urine micro albumin.

Table 1(b): Descriptive statistics of risk factors

	n	%
Sex		
Female	103	81.12
Male	27	18.88
Age		
18-30	3	2.10
31-45	15	19.58
46-60	80	55.94
61-85	32	22.38
Ethnicity		
Afghan	2	1.40
Baloch	3	2.10
Pathan	77	53.85
Punjabi	11	7.69
Sindhi	21	14.69
Urdu Speakers	16	11.89
Hypertension		
Yes	96	67.13
No	34	32.87
Smoking		
Yes	70	48.95
No	60	51.05
Diabetes History		
Yes	79	55.24
No	51	44.76
Marital Status		
Married	126	97.20
Widow	4	2.80
Physical Activity		
Mild	24	23.78
Moderate	8	5.59
Sedentary	98	70.63

Table 2: Mean difference among outcome variables

	MD ± SD	COR	t statistics	95% CI	P-value
$Hb1Ac_{(pre)}$ - $Hb1Ac_{(post)}$	1.3230 ± 1.757	0.419	8.586	1.018-1.628	†
$S.Cr._{(pre)}$ - $S.Cr._{(post)}$	0.3508 ± 0.2048	0.526	1.953	-0.0046 - 0.071	ns
$eGFR_{(pre)}$ - $eGFR_{(post)}$	5.324 ± 9.854	0.741	6.161	3.614 - 7.034	†
$BMI_{(pre)}$ - $BMI_{(post)}$	1.543 ± 4.074	-0.192	4.303	0.833 - 2.253	†
$FBS_{(pre)}$ - $FBS_{(post)}$	35.92 ± 34.251	0.330	5.179	9.128 - 20.397	†
$UMA_{(pre)}$ - $UMA_{(post)}$	24.471 ± 69.959	0.220	3.911	12.086 - 36.856	†

† p-value<0.001; ¥ p-value<0.05; ns: not significant; pre: pre-treatment; post: post-treatment; MD: Mean difference; SD: Standard deviation; COR: Correlation; CI: Confidence interval; SD: Standard Deviation; Min: Minimum value; Max: Maximum value; Hb1Ac: glycated hemoglobin; S.Cr.: Serum creatinine; eGFR: estimated Glomerular Filtration Rate; BMI: Body Mass Index; FBS: fasting blood sugar; UMA: Urine micro albumin.

Table 3: Multivariate statistics between risk factors and outcome variables

Variables	Outcome variables											
	Hb1Ac (%)		S.Cr (mg/dl)		eGFR (mg/dl)		BMI		FBS (mg/dl)		UMA (mg/l)	
	OR	Sig	OR	Sig	OR	Sig	OR	Sig	OR	Sig	OR	Sig
Sex												
Female	-	ns	-	ns		ns	-	ns	-	ns	-	ns
Male												
Age												
18-30									0.242			
31-45	-	ns	-	ns	-	ns	-	ns	0.295	‡	-	ns
46-60									0.586¥			
61-85									Ref			
Ethnicity												
Afghan												
Baloch												
Pathan	-	ns	-	ns	-	ns	-	ns	-	ns	-	ns
Punjabi												
Sindhi												
Urdu Speakers												
Marital Status												
Married	-	ns	-	ns	-	ns	-	ns	-	ns	-	ns
Widow												
Hypertension												
Yes	0.400	¥	-	ns	-	ns	2.082¥	¥	-	ns	0.897¥	¥
No	Ref						Ref				Ref	
Smoking												
Yes	-	ns	1.059	¥	-	ns	1.74¥	¥	-	ns	5.432¥	¥
No			Ref				Ref				Ref	
Diabetes History												
Yes	0.011	‡	0.924	‡	2.646	¥	-	ns	1.801	‡	-	ns
No	Ref		Ref		Ref				Ref			
Physical Activity												
Sedentary	0.886¥	‡	-	ns	-	ns	6.498¥	‡	4.710¥	‡	5.95¥	‡
Moderate	0.836						2.272		0.158		2.59	
Mild	Ref						Ref		Ref		Ref	

‡: P-value< 0.05; ¥:P-value< 0.001; ns: not significant; OR: Odds ratio; Sig: Significance level.
Hb1Ac: glycated hemoglobin; S.Cr.: Serum creatinine; eGFR: estimated Glomerular Filtration Rate; BMI: Body Mass Index; FBS: fasting blood sugar; UMA: Urine micro albumin.

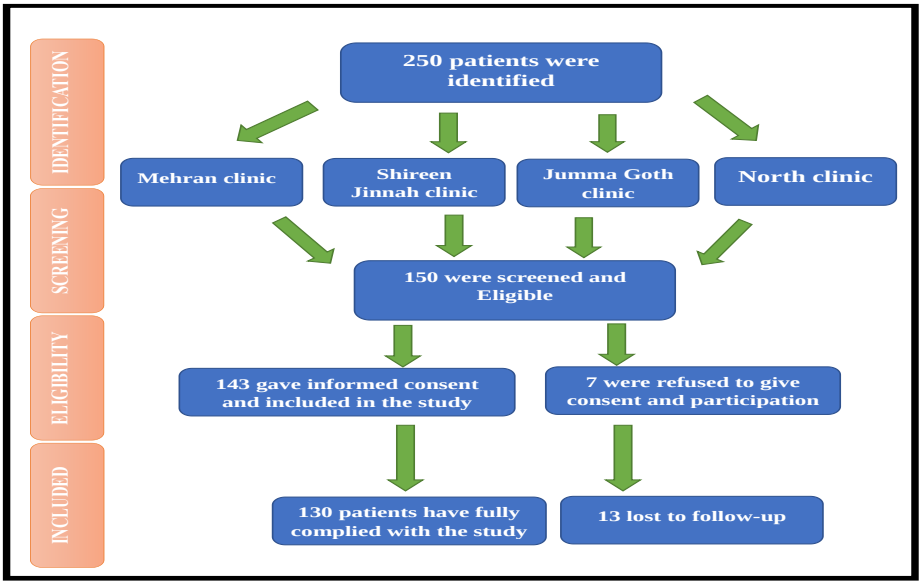

Fig. 1: Inclusion process of the study.

Mean differences among paired outcome variables

Table 2 delves into the nuanced variations in clinical risk factors between the pre-treatment and post-treatment phases of EMPAA medication. Notably, a compelling narrative unfolds as we explore the impact of EMPAA treatment on study participants with diabetes.

Following EMPAA treatment, a pronounced mean difference in HbA1c emerges, underscored by a highly significant p-value. This profound effect is further accentuated by a strong positive correlation, solidifying the notion that the administration of EMPAA correlates with a meaningful reduction in HbA1c levels.

The impact on eGFR, another critical clinical risk factor, is equally noteworthy. The p-value points to a significant mean difference between pre and post EMPAA treatment, accompanied by a robust correlation. This association suggests that the estimated GFR experiences a decrease in tandem with EMPAA treatment.

An intriguing pattern unfolds in the context of BMI. The mean difference between pre and post EMPAA treatment yields a strong negative correlation, coupled with a significant p-value. This interplay indicates that the introduction of EMPAA medication aligns with a noteworthy reduction in BMI levels.

Similarly, the treatment's influence on FBS levels is profound, as evidenced by a substantial mean difference in p-value. This significant change translates to a decrease in FBS levels post-treatment among study participants with diabetes.

The theme continues with UMA levels, where a robust correlation and a significant mean difference in p-value ($p<0.001$) are evident. This compelling association underscores that the UMA levels notably decrease with the administration of EMPAA among diabetes-afflicted participants.

Furthermore, our study identifies an insignificant mean difference in serum creatinine levels between pre and post EMPAA treatment ($p>0.05$). This observation elucidates that EMPAA's impact on serum creatinine levels is not statistically significant within our study participants.

Multivariate analysis

Table 3 shown that the intricate multivariate associations between outcome variables and potential risk factors. This insightful analysis discerns patterns within the data, shedding light on the interplay between these factors and the outcomes of interest.

In the realm of glycemic control, among individuals grappling with diabetes and hypertension, the odds of witnessing a 1% increase in glycated hemoglobin (HbA1c) levels are notably insignificant by $p= 0.40$ compared to those without hypertension. Similarly, for those adopting a sedentary lifestyle amidst diabetes, the odds of a 1% elevation in HbA1c levels are reduced by a factor of 0.886 compared to individuals who engage in mild physical activities. In the context of serum creatinine levels, participants who smoke tobacco while contending with diabetes encounter 1.06 times greater odds of experiencing a 1mg/dl increase in serum creatinine compared to non-smokers.

A profound insight emerges regarding estimated glomerular filtration rate (eGFR). Individuals with a family history of diabetes exhibit 2.47 times higher odds of a 1mg/dl increase in eGFR compared to those lacking such a history. The interplay of diabetes and hypertension magnifies the odds of increasing BMI by a factor of 2.08 compared to individuals without hypertension. Similarly, among participants with diabetes, smokers encounter 1.74 times higher odds of increasing BMI compared to non-smokers. Adopting a sedentary lifestyle escalates the odds of increasing BMI by 6.49 times when contrasted with individuals engaged in mild physical activities.

Shifting our gaze to fasting blood sugar (FBS), individuals aged 46-60 years with diabetes encounter 0.59 times the odds of increasing FBS compared to those aged 61-85 years. The adoption of a sedentary lifestyle amplifies the odds of a 1mg/dl increase in FBS by 4.71 times ($p<0.001$) when juxtaposed against mild physical activities.

Delving into urine microalbumin (UMA) levels, hypertension amplifies the odds of a 1mg/ml increase in UMA by a factor of 0.89 among individuals with diabetes. Smokers experience 5.43 times greater odds of increasing UMA compared to non-smokers. Similarly, adopting a sedentary lifestyle elevates the odds of increasing UMA by 5.95 times ($p<0.001$) when contrasted with mild physical activities.

In (Table 3), the shaded area elegantly encapsulates associations that do not reach statistical significance. Marital status and ethnicity, in particular, bear no statistically significant linkages with the respective outcome variables, as indicated by p-values exceeding 0.05. This comprehensive exploration enhances our comprehension of the intricate web of associations among independent risk factors, demographic variables and outcomes, adding depth and clarity to our study's findings.

DISCUSSION

Empagliflozin stands out as an effective and well-tolerated antihyperglycemic drug, demonstrating its potency as a highly selective sodium glucose cotransporter-2 (SGLT2) inhibitor. Its approval for

treating individuals with type 2 diabetes (T2D) across various regions including the EU, USA and Japan underscores its global recognition and acceptance (Azeem *et al*., 2022).

This study focuses on a population hailing from a low-socioeconomic status. The positive impact of Empagliflozin on lowering HbA1c levels from baseline aligns with findings reported in empirical trials centered around Empagliflozin (Alshahrani *et al*., 2023). A distinctive feature of our study is the assessment of empagliflozin as an add-on treatment with other hyperglycemic agents, including insulin (Kapoor *et al*. 2022). This approach not only contributes to glycemic control but also aids in weight loss, particularly among elderly individuals, while lowering plasma glucose levels, corroborating results observed in a US-based study (Chait A and Den Hartigh, 2020). Similar benefits were underscored in a 2015 Germany study, emphasizing that empagliflozin added to metformin aids in both HbA1c reduction and weight loss in T2D individuals (Matsumura *et al*., 2022). Additional treatments are necessary when metformin monotherapy is no longer able to maintain glycemic control, but many of the medications used as second-line therapies have tolerability problems, such as gastrointestinal side effects, hypoglycemia and weight gain (Mahabaleshwarkar *et al*. 2019). Therefore, when metformin treatment alone fails to maintain glycemic control, there is a need for additional, effective and well-tolerated medications that may be added (Ambery *et al*. 2018)

Empagliflozin's positive impact on blood pressure, as established by US researchers (Hu *et al*., 2018; Ferdinand *et al*., 2019), harmonizes with our findings, further validating its role in managing T2D. A prominent aspect is empagliflozin's ability to induce significant reductions in body weight, bolstered by several studies (Abohelwa *et al*.; Azeez *et al*. 2021; Rendell, 2023; Motkova *et al*. 2019). Our study reinforces this phenomenon, though it's worth noting that a study contradicted this trend, reporting no substantial weight reduction with empagliflozin in diabetes patients (Mottalib *et al*., 2018). According to a National Diabetes Information Clearinghouse (NDIC) 2012, conducted by researchers, it was shown that a significant majority, namely over 80%, of individuals diagnosed with type 2 diabetes exhibit characteristics of being overweight or obese. The presence of overweight or obesity poses a substantial cardiovascular risk, as shown by previous studies (Motkova *et al*., 2019; Mottalib *et al*., 2018). Moreover, it may complicate the treatment and control of type 2 diabetes due to its association with heightened insulin resistance and impaired glucose tolerance (Azeez *et al*. 2021; Rendell *et al*., 2023). Achieving weight management is a significant challenge for those diagnosed with type 2 diabetes and this endeavor may be further exacerbated by the potential adverse effects of medication (Motkova *et al*., 2019; Mottalib *et al*., 2018). One of the sedentary lifestyle also worsen the conditions of diabetes' patients. One of the recent study on people belong to the low socio-economic status have diabetes due to their sedentary life-style (Sharif *et al*., 2023).

In assessing kidney function, our findings only hint at minor differences. However, previous literature consistently suggests empagliflozin's beneficial influence on kidney function in people with diabetes (Wanner *et al*., 2018).

New oral diabetic medications known as SGLT2 inhibitors work independently of -cell function and insulin resistance to lower hyperglycemia by increasing urine glucose excretion and decreasing glucose reabsorption (Thomas and Cherney, 2018). This technique has a minimal risk of hypoglycemia and also helps people lose weight and lower their blood pressure (BP) (Thomas and Cherney, 2018; Wright, 2021). The landscape of studies both supporting and challenging empagliflozin's effects on various aspects of T2D management underscores the complexity of its impact. Our research adds to this discourse by providing insights into the experiences of a specific demographic. By considering a diverse array of studies, we acknowledge that empagliflozin's effects can be influenced by numerous variables, from patient characteristics to treatment regimens. These discussions contribute to a comprehensive understanding of empagliflozin's role in the management of T2D and its multifaceted implications for patients' well-being.

LIMITATIONS

Firstly, it is imperative to underscore the preliminary nature of this research, primarily attributed to the relatively modest sample size employed in the study. The limited number of participants warrants careful consideration when extrapolating the findings to broader populations.

Secondly, it is worth highlighting that the majority of individuals included in our study were elderly individuals dealing with type 2 diabetes and hypertension and interestingly, they exhibited preserved kidney function. This unique demographic characteristic may influence the generalizability of our findings to a more diverse range of patients within the T2D spectrum.

Moreover, the lower baseline values further suggest that our study cohort might have encompassed individuals with a relatively milder disease profile. This aspect should be acknowledged when interpreting the results, as the inclusion of less severely affected participants could potentially limit the scope of applicability to more comprehensive populations.

Challenges also arose due to instances of lost follow-up, a common hurdle in studies with constrained sample sizes. This issue, stemming from the limitations inherent in smaller-scale research, necessitates a cautious approach when interpreting the results and conclusions drawn from this study.

CONCLUSION

The clinical trial findings underscore the promising potential of empagliflozin as a standalone therapy or as part of a combination with other glucose-lowering agents. These investigations reveal tangible improvements in glycemic control among patients who embarked on empagliflozin treatment. Notably, individuals initiating empagliflozin therapy can expect to witness modest yet meaningful reductions in body weight and systolic blood pressure.

A hallmark of empagliflozin is its commendable tolerability profile. This antihyperglycemic agent stands out for its ability to be well-tolerated by patients, leading to minimal adverse effects. Specifically, the likelihood of hypoglycemia remains notably low, except in cases where empagliflozin is co-administered with insulin or insulin secretagogues. These attributes position empagliflozin as a valuable therapeutic option, offering tangible benefits in glycemic control, weight management and blood pressure regulation, all while maintaining a favorable safety and tolerability profile.

ACKNOWLEDGEMENT

The Medical Board of SINA Health and Welfare Educational Trust was instrumental in approving the research, and the authors are grateful. We really appreciate the assistance and cooperation from Horizon Pharmaceuticals (Pvt.) Ltd. Their participation helped complete this study.

REFERENCES

Amir AH, Raja UY, Qureshi FM, Asghar A, Mahar SA, Ahmed I, Ghaffar T, Zafar J, Hasan MI, Riaz A and Raza SA (2022). Safety and efficacy of Empagliflozin in Pakistani Muslim patients with type 2 diabetes (SAFE-PAK); A randomized clinical trial. *BMC Endocr. Disord.*, **22**(1): 295.

Abohelwa M, Kopel J, Shurmur S, Ansari MM, Awasthi Y and Awasthi S (2023). The framingham study on cardiovascular disease risk and stress-defenses: A historical review. *J. Vasc. Dis.*, **2**(1): 122-164.

Alshahrani AA, Al QS, Al QA, Mashhour SM, Alkhtani ZS and Alragea YM (2023). Metabolic and renal outcomes of empagliflozin in patients with type 2 diabetes mellitus attending Armed Forces Hospital in Saudi Arabia. *Saudi Med. J.*, **44**(7): 674-8.

Ambery P, Parker VE, Stumvoll M, Posch MG, Heise T, Plum-Moerschel L, Tsai LF, Robertson D, Jain M, Petrone M and Rondinone C (2018). MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: A randomised, controlled, double-blind, ascending dose and phase 2a study. *The Lancet*, **391**(10140): 2607-2618.

Azeem S, Khan U and Liaquat A (2022). The increasing rate of diabetes in Pakistan: A silent killer. *Ann. Med. Surg. (Lond)*, **79**(2022): 1-2.

Azeez TA, Adeleye J, Enigbokan OA, Adejimi B and Oladapo JS (2021). Metabolic syndrome among Nigerians with type 2 diabetes mellitus: A comparative study of the diagnostic criteria. *J. Cardio-diabetes Metabolic Disorders*, **1**(2): 51-58.

Chait A and Den Hartigh LJ (2020). Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. *Front Cardiovasc. Med*., **7**: 22.

Ferdinand KC, Izzo JL, Lee J, Meng L, George J, Salsali A and Seman L (2019). Antihyperglycemic and blood pressure effects of empagliflozin in black patients with type 2 diabetes mellitus and hypertension. *Am. Heart Assoc.*, **139**(18): 2098-2109.

Frampton JE (2018). Empagliflozin: A review in type 2 diabetes. *Drugs*, **78**: 1037-1048.

Freeman AM and Pennings N (2018). Insulin resistance. StatPearls Publishing, Treasure Island, FL, **13**(1): 278.

Fujii H, Kawada N and Japan Study Group of Nafld (JSG-NAFLD) (2020). The role of insulin resistance and diabetes in nonalcoholic fatty liver disease. *Int. J. Mol. Sci.*, **21**(11): 3863.

Gallwitz B (2019). Clinical use of DPP-4 inhibitors. *Front Endocrinol.*, **10**: 389.

Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, Barranco RJ and Umpierrez GE (2018). Safety and efficacy of DPP4 inhibitor and basal insulin in type 2 diabetes: an updated review and challenging clinical scenarios. *Diabetes Therapy*, **9**: 1775-1789.

Grabarczyk TR and Wissman NK (2020). Weight outcomes with empagliflozin as compared with Liraglutide in veterans with type 2 diabetes mellitus. *Ann. Pharmacother.*, **54**(10): 981-987.

Haidar A, Yale JF, Lovblom LE, Cardinez N, Orszag A, Falappa CM, Gouchie- Provencher N, Tsoukas MA, El Fathi A, Rene J and Eldelekli D (2021). Reducing the need for carbohydrate counting in type 1 diabetes using closed- loop automated insulin delivery (artificial pancreas) and empagliflozin: A randomized, controlled, non- inferiority, crossover pilot trial. *Diabetes Obes. Metab.*, **23**(6): 1272-1281.

Hu M, Cai X, Yang W, Zhang S, Nie L and Ji L (2020). Effect of hemoglobin A1c reduction or weight reduction on blood pressure in glucagon- like peptide- 1 receptor agonist and sodium- glucose

cotransporter- 2 inhibitor treatment in type 2 diabetes mellitus: A meta- analysis. *J. Am. Heart Assoc.*, **9**(7): e015323.

Hussain M, Atif M, Babar M and Akhtar L (2021). Comparison of efficacy and safety profile of empagliflozin versus dapagliflozin as add on therapy in type 2 diabetic patients. *J. Ayub Med. Coll. Abbottabad*, **33**(4): 593.

Huthmacher JA, Meier JJ and Nauck MA (2020). Efficacy and safety of short-and long-acting glucagon-like peptide 1 receptor agonists on a background of basal insulin in type 2 diabetes: A meta-analysis. *Am. Diabetes Assoc.*, **43**(9): 2303-2312.

Kapoor G, Bhutani R, Dutta M, Sharma A, Khan F and Bhatt P (2022). Future technology based HPLC analytical procedures and pharmaceutical description of empagliflozin. *J Pharm Negat Results*, **2022**: 1453-1465.

Khalid T, Naveen N and Gull K (2021). Comparative analysis of sitagliptan vs empagliflozin as an add on therapy to metformin in Pakistani type 2 diabetic patients. *Age*, **45**(12): 5-8.

Mahabaleshwarkar R, Liu TL and Mulder H (2019). Comparative effectiveness of metformin dosage uptitration versus adding another antihyperglycemic medication on glycemic control in type 2 diabetes patients failing initial metformin monotherapy: A retrospective cohort study. *Population Health Management*, **22**(5): 457-463.

Marušić M, Paić M, Knobloch M and Liberati Pršo AM (2021). NAFLD, insulin resistance and diabetes mellitus type 2. *Can. J. Gastroenterol. Hepatol.*, **2021**(34): 1-9.

Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, Lind M, Bain SC, Jabbour S, Arya N and Hansen L (2018). Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care*, **41**(9): 1938-1946.

Matsumura T, Makabe T, Ueda S, Fujimoto Y, Sadahiro K, Tsuruyama S, Ookubo Y, Kondo T and Araki E (2022). Clinical benefit of switching from low-dose to high-dose empagliflozin in patients with type 2 diabetes. *Diabetes Therapy*, **13**(9): 1621-1634.

Moreira R, Martins AD, Ferreira R, Alves MG, Pereira MDL and Oliveira PF (2023). Impact of chromium picolinate on leydig cell steroidogenesis and antioxidant balance using an *in vitro* insulin resistance model. *Antioxidants*, **13**(1): 40.

Motkova SI, Savelyeva LV, Rudina LM, Gurkina MV, Surkova EV, Valeeva FV, Galstyan GR and Shestakova MV (2019). Multidisciplinary lifestyle management approach in patients with type 2 diabetes mellitus in real clinical practice. Results of application "life is easy" programme in Russia. *Diabetes Mellitus*, **22**(2): 115-126.

Mottalib A, Salsberg V, Mohd-Yusof BN, Mohamed W, Carolan P, Pober DM, Mitri J and Hamdy O (2018). Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. *Nutrition J*. **17**(1): 1-10.

National Diabetes Information Clearinghouse (NDIC). Diabetes Overview [Internet], 2012. Bethesda, MD, http://diabetes.niddk.nih.gov/dm/pubs/overview/index.aspx. [Accessed 8 August 2023].

Reifsnider OS, Kansal AR, Gandhi PK, Cragin L, Brand SB, Pfarr E, Fahrbach K and Ustyugova A (2021). Cost-effectiveness of empagliflozin versus canagliflozin, dapagliflozin, or standard of care in patients with type 2 diabetes and established cardiovascular disease. *BMJ Open Diabetes Res. Care*, **9**(1): p.e001313.

Rendell MS (2023). Obesity and diabetes: The final frontier. *Expert Rev. Endocrinol. Metab.*, **18**(1): 81-94.

Scheen AJ (2019). An update on the safety of SGLT2 inhibitors. *Expert Opin. Drug Saf.*, **18**(4): 295-311.

Scott LJ (2014). Empagliflozin: A review of its use in patients with type 2 diabetes mellitus. *Drugs*, **74**(15): 1769-1784.

Sharif S, Sharif H, Rehman J and Fatima Z (2023). Is a sedentary lifestyle a leading causal factor of obesity and distress in type 2 diabetes? A cross-sectional study in low-socioeconomic areas of Karachi, Pakistan. *BMJ Public Health*, **1**(1): 1-9.

Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JC, Mbanya JC and Pavkov ME (2022). IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract. Suppl.*, **183**(1): 109119.

Thomas MC and Cherney DZ (2018). The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia*, **61**(8): 2098-2107.

Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, Woerle HJ, Broedl UC, von Eynatten M and Zinman B (2018). Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease and chronic kidney disease. *Circulation*, **137**(2): 119-129.

Wright EM (2021). SGLT2 inhibitors: physiology and pharmacology. Kidney360. **2**(12): 2027.

Younis M (2020). Combination of topiramate and empagliflozin is considered a good option for treatment of obesity. *In*: Endocrine Abstracts. *Bioscientifica*, **70**: 37-49.