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Research Article

Impact of Clinical Pharmacist Intervention and Dapagliflozin Add-On Therapy on Glycemic Control in Type 2 Diabetes

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Abstract

Background: Type 2 diabetes is a major global health issue. Poor glycemic control, often due to non-adherence, increases complications. Pharmacologic intensification and pharmacist-led interventions help optimize diabetes management. ***Objectives***: To assess clinical pharmacist interventions and dapagliflozin effects on glycemic control, safety, and adherence in type 2 diabetes. ***Methods***: A 3-month, three-arm open-label randomized controlled trial (RCT) conducted in Sulaimani city, Iraq, on adults with T2DM (HbA1c 7–10%, n=138) were randomized to dapagliflozin add-on (G1, n=46), clinical pharmacist intervention (G2, n=46; including medication optimization, adherence support, and counselling), or standard therapy (G3, n=46). Primary outcomes were HbA1c, fasting plasma glucose (FPG) changes, and safety; secondary included lipids, blood pressure, and adherence (Modified Hill-Bone scale). ***Results***: Among 125 completers, the median (IQR) difference in the HbA1c % was -0.7(-1.6 to 0.0) for G1, -0.665 (-1.55 to -0.245) for G2, and +0.05 (-0.3 to 0.597) for G3, which was significantly different between G1 and G3 and G2 and G3. The difference in the FPG was -37 (-83 to 1.0) for G1, -14.5 (-38.75 to 6) for G2, and -1.5 (-11.75 to 30.75) for G3. The difference is significant between G1 and G3, and G2 and G3. Medication adherence improved significantly only in G2 (high adherence: 80% to 95%, p=0.043). Adverse events were low in all groups (hypoglycemia: 4.5–7.3%), while UTIs were 7.3% in G1 only. ***Conclusions***: Clinical pharmacist-led interventions were equally effective as dapagliflozin for glycemic control but superior in enhancing medication adherence.

Keywords: Clinical pharmacist intervention, Dapagliflozin, Glycemic control, Medication adherence, Type 2 diabetes mellitus.

تأثير تدخل الصيدلي السريري والعلاج الإضافي بداباغليفلوزين على التحكم في نسبة السكر في الدم لدى مرض السكري من النوع 2

الخلاصة

الخلفية: مرض السكري من النوع 2 هو قضية صحية عالمية رئيسية. يؤدي ضعف التحكم في نسبة السكر في الدم ، غالبا بسبب عدم الالتزام ، إلى زيادة المضاعفات. يساعد التكثيف الدوائي والتدخلات التي يقودها الصيدلة على تحسين إدارة مرض السكري. **الأهداف**: تقييم تدخلات الصيدلة السريرية وتأثيرات داباغليفلوزين على التحكم في نسبة السكر في الدم وسلامته والالتزام به في مرض السكري من النوع 2. **الطرائق**: تم إجراء تجربة معشاة ذات شواهد مفتوحة التسمية لمدة 3 أشهر أجريت في مدينة السليمانية بالعراق على البالغين المصابين بداء السكري (n=138، HbA1c 7-10٪) عشوائيا إلى الوظيفة الإضافية داباغليفلوزين (G1، العدد = 46)، أو تدخل الصيدلي السريري (G2، العدد = 46؛ بما في ذلك تحسين الدواء، ودعم الالتزام، والاستشارة)، أو العلاج المعياري (G3، العدد = 46). كانت النتائج الأولية هي HbA1c، وتغيرات جلوكوز البلازما الصائم (FPG)، والمأمونية. وشملت الثانوية الدهون وضغط الدم والالتزام (مقياس هيل بون المعدل). **النتائج**: من بين 125 مشاركا، كان متوسط الفرق (IQR) في HbA1c ٪ -0.7 (-1.6 إلى 0.0) ل G1 ، -0.665 (-1.55 إلى -0.245) ل G2 ، و +0.05 (-0.3 إلى 0.597) ل G3، والذي كان مختلفا بشكل كبير بين G1 و G3 و G2 و G3. كان الفرق في FPG -37 (-83 إلى 1.0) ل G1 ، و -14.5 (-38.75 إلى 6) ل G2 ، و -1.5 (-11.75 إلى 30.75) ل G3. الفرق كبير بين G1 و G3 و G2 و G3. تحسن الالتزام بالأدوية بشكل ملحوظ فقط في G2 (الالتزام العالي: 80٪ إلى 95٪ ، p = 0.043). كانت الأحداث الضائرة منخفضة في G1 فقط (نقص السكر في الدم: 4.5-7.3٪؛ عدوى المسالك البولية: 7.3٪). **الاستنتاجات**: كانت التدخلات التي يقودها الصيدلي السريري فعالة بنفس القدر من داباغليفلوزين للتحكم في نسبة السكر في الدم ولكنها متفوقة في تعزيز الالتزام بالأدوية.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM), a progressive metabolic disorder, arises from a critical breakdown in the body's ability to manage glucose. At its core, this condition stems from two main factors: the pancreas's impaired production of insulin, which is a hormone vital for blood sugar control, and a diminished responsiveness to insulin in muscles, fat, and liver tissues, known as insulin resistance. Since insulin secretion and function are critical for maintaining glucose homeostasis, the biological processes governing insulin production, release, and cellular response are highly controlled [1]. Type 2 diabetes mellitus is more common in individuals older than 40 years old, but in recent years it has been seen

more often in younger people and in children also [2]. Globally, T2DM affects approximately 10% of the population (2024 estimates) [3]. In Iraq, including the Kurdistan region, prevalence rates range from 8.5% to 19.7%, reflecting regional and methodological variability [4]. Complications of diabetes, including cardiovascular disease, renal disease, neuropathy, retinopathy, and lower-limb amputation, are a major contributor to raising morbidity and mortality among people with diabetes and contribute substantially to health care costs [5]. In people with diabetes, particularly type 2 diabetes, cardiovascular disease accounts for roughly 70% of deaths and is a major contributor to morbidity [6,7] . Cardiovascular disease complications can include coronary artery disease (CAD), heart failure (HF), cardiomyopathy, and arrhythmias (8). Prevalence of diabetic retinopathy can vary among different studies, and a study showed DR prevalence to be about 25.1% in T2DM patients [9]. The prevalence of diabetic peripheral neuropathy varies and is generally estimated to be between 10% and 50% [10]. Studies indicate that 15-20% of diabetic patients will have a foot ulcer at some point in their lifetime, and a significant percentage of these ulcers can lead to amputations [11]. Suboptimal glycemic control in people living with type 2 diabetes mellitus (T2DM) constitutes a substantial public health challenge and markedly heightens the likelihood of progression of diabetes-related complications [12]. A study showed that despite available treatments, nearly half (45%) of individuals with type 2 diabetes (T2D) do not reach their target blood sugar levels (HbA1c <7%), and a key reason for this is poor adherence to prescribed medications; therefore, medication non-adherence is shown not only to worsen glycemic control but also to raise the risk of diabetes-related complications, hospitalizations, and overall mortality and morbidity. Furthermore, poor adherence increases healthcare costs due to more frequent clinic visits, emergency care, and the long-term management of diabetes-related complications [13]. In type 2 diabetes, the initial approach to treatment includes diet and exercise, along with oral hypoglycemic medications, to help improve blood sugar control and reduce the risk of both microvascular and macrovascular complications [14]. The treatment landscape for type 2 diabetes mellitus has broadened significantly with the development of novel oral hypoglycemic agents (OHAs) [15]. OHAs can include biguanides, sulfonylureas, meglitinides, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones, α-glucosidase inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors [16]. SGLT2 inhibitors provide an alternative therapeutic strategy for glycemic control through their insulin-independent mechanism, which involves inhibiting renal glucose reabsorption and promoting glycosuria, and SGLT2 inhibitors can be prescribed alone or alongside other oral hypoglycemic medications [17]. Numerous disease management approaches have been created and applied across different clinical settings globally, and an important element of maintaining patient adherence to medications and self-management is the good relationship between patients with diabetes mellitus and the healthcare team [18]. Medication nonadherence, whether due to forgetfulness and doubt about the necessity, low literacy making them not understand instructions or misunderstanding instructions, polypharmacy or complex regimen, inability to afford drug products or high cost, lack of availability, or side effects, can lead to suboptimal glycemic control and is associated with higher HbA1c and increased risk of diabetes complications [19]. Clinical pharmacists play a key role in reducing diabetes-related health disparities by offering verbal or video-based patient education, supporting medication adherence, monitoring therapy, and helping patients achieve treatment goals, among other services, and improving medication adherence is a key area where clinical pharmacist intervention has proven highly effective in T2DM [20–22]. Research consistently shows that diabetes care models integrating clinical pharmacists achieve better outcomes, including improved glycemic control (HbA1c and blood glucose), blood pressure management, medication adherence, and a vital role in enhancing quality of life of diabetic patients [23–25]. T2DM patients often have complex medication regimens (for hyperglycemia and for comorbid conditions), making them prone to drug therapy problems such as suboptimal drug choices, dosing problems, adverse drug reactions, drug–drug interactions, and non-adherence. and pharmacists are trained to systematically detect these issues [26–28]. Clinical pharmacists' contributions to diabetes management were recognized by many ethnic minority patients from low-income backgrounds struggling with uncontrolled type 2 diabetes [29]. Therefore, we hypothesized that clinical pharmacist intervention can be as effective as adding dapagliflozin, an SGLT2 inhibitor, as add-on therapy in terms of glycemic control in patients with type 2 diabetes. This is the first RCT comparing pharmacist-led interventions directly with dapagliflozin add-on therapy in T2DM. The aim of the study is to evaluate the impact of clinical pharmacist-led intervention compared to dapagliflozin as add-on therapy regarding glycemic control, disease management, and improving patient adherence to medicines in type 2 diabetic patients.

METHODS

Study design and ethical approval

The study was designed as a three-arm open-label randomized controlled clinical trial performed from December 2024 to April 2025 at the Diabetes and Endocrinology Centre, Directory of Health, Sulaimani City. The study protocol was approved by the Ethics and Research Registration Committee of the College of Pharmacy, University of Sulaimani (Registration No: PH141-24 on 30/11/2024) and the Directorate of Health (DOH)-Ethical Committee in accordance with the principles of the Declaration of Helsinki as revised

in 2000; all patients gave informed consent. The protocol of the study has been registered in the clinicaltrial.gov https://clinicaltrials.gov/study/NCT06719661 registration database with a ClinicalTrials.gov Identifier: NCT06719661.

Intervention and randomization

The eligible patients were referred by a senior clinical endocrinologist to the researcher (pharmacist). The randomization sequence was generated using a simple, deterministic allocation approach where participants were sequentially assigned to groups in the order of enrollment (Group I, Group II, Group III, repeating cyclically). This method ensured equal distribution of participants across the three groups (dapagliflozin, pharmacist-led intervention, standard care) as they were enrolled. Due to resource constraints, allocation concealment was not explicitly implemented (e.g., sealed envelopes or a centralized system). However, the pharmacist responsible for enrollment followed a strict protocol to assign participants strictly based on the pre-defined sequence, minimizing discretionary assignment. Lab personnel were blinded to group allocation during sample analysis. Patients have been under supervision of a clinical pharmacist for three months, and only 125 patients completed the study (Figure 1).

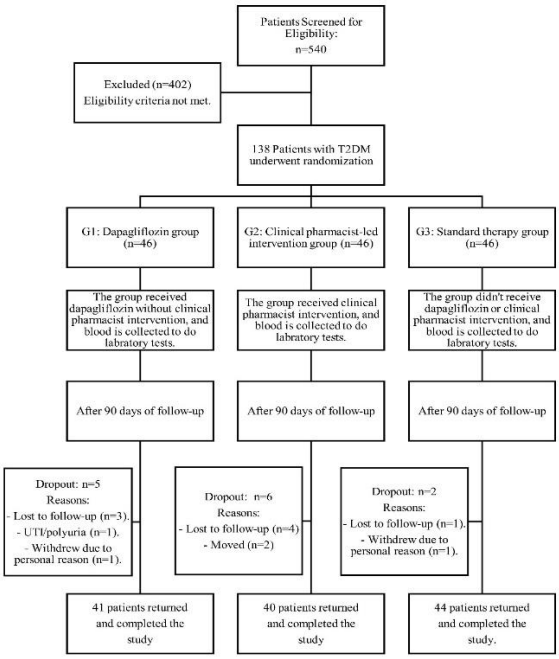

Figure 1: Flowchart illustrating screening, randomization and intervention of participants.

Inclusion and exclusion criteria

The inclusion criteria were patients diagnosed with type 2 diabetes mellitus. age between 18 and 65 years, HbA1c level between 7.0% and 10%, and patients willing to provide informed consent. Exclusion criteria were presence of comorbidities (e.g., cancer, severe renal impairment (eGFR < 30 mL/min/1.73m²), thyroid dysfunction, liver dysfunction), presence of type 1 diabetes mellitus, elderly patients, history of diabetic ketoacidosis, pregnancy or breastfeeding, cognitive impairment or inability to provide informed consent, and patients that need urgent intervention by an endocrinologist.

Sample size estimation

The required sample size was calculated using the two-sample t-test formula for comparing independent means, targeting pairwise comparisons within and between each intervention group and the control group. Parameters were derived from [30], where Z_α is 1.96 for the P value of 0.05, Z_β is 0.842 for the study power of 80%, S^2: is the variance of the main variable in previous studies (as the average of the standard deviation of HbA1c from previous studies is 0.8, so the variance is 0.64), and d is the degree of precision (here we put the difference in the mean HbA1c between two similar groups in previous studies), which is 0.5. The formula used was:

$$n = \frac{(Z_\alpha + Z_\beta)^2 * 2 * S^2}{d^2}$$

$$n = \frac{(1.96 + 0.842)^2 * 2 * 0.8^2}{0.5^2} = 41$$

To account for a 10% dropout rate, the target sample size was adjusted to 46 participants per group (41 + 10%), totaling 138 participants across three groups.

Intervention procedure

The clinical pharmacist completed a questionnaire by direct interview with the patients; the first set was about patient characteristics, and the second one was about compliance to diabetes treatment plan using the Hill-Bone Compliance Scale for high blood pressure medication [31–33], but as a new challenge, this questionnaire is also used to apply to diabetic patient compliance. The original hypertension-focused tool was contextualized to diabetes by revising terminology (e.g., replacing 'blood pressure medications' with 'diabetes medications') and aligning dietary questions with diabetes-specific recommendations (e.g., salt consumption to sugar consumption). The scale retained 14 items across three domains: one for appointment keeping (3 items), one for diet (2 items), and one for medication adherence (9 items). The domains gave scores from 1 for "none of the time" to 5 for "don't know," and then patients were divided into 3 subgroups (good compliance, average compliance, and poor compliance) according to their score on the questionnaire [33], and no Cronbach's alpha analysis was performed to assess internal consistency. While this new modification and adaptation provided practical utility, formal validation for diabetes populations is required to be performed in future studies. The eligible patients (n=138) were randomly allocated into three groups as follows. Dapagliflozin add-on therapy group (G1) (n=46), in which forty-six

patients received a 10 mg dapagliflozin tablet orally once daily. Clinical pharmacist-led intervention group (G2) (n=46), in which forty-six patients received clinical pharmacist-led intervention. Standard therapy group (G3) (n=46), in which forty-six patients received their standard therapy. All the groups received their own previously taken hypoglycemic drugs with the above interventions, and the duration of the treatment was 90 days. In G1, forty-six patients received dapagliflozin 10 mg once daily orally alongside their established oral hypoglycemic agents for 3 months without receiving pharmaceutical care intervention. In G2, forty-six patients received pharmaceutical care intervention alongside their established oral hypoglycemic agents for 3 months without receiving dapagliflozin. Pharmaceutical care interventions include the dosage adjustment method, which is performed according to ADA guidelines. The dose of metformin, sulfonylurea, and/or Dpp-4 inhibitors has been adjusted, whether decreased or increased up to the maximum daily dose, to meet patients' needs (34). Counselling regarding the administration of OADs is given, including their side effects, such as some patients may experience gastrointestinal disturbances, including nausea, vomiting, abdominal pain, cramps, and diarrhea, as well as systemic effects, such as appetite loss, malaise, or weight reduction, to overcome these side effects. Furthermore, patients are educated to take their pills during mealtimes to prevent nausea and to increase their absorption. Medication timing is another important point; patients should take their medication at the right time during the day. For instance, insulin secretagogues should be taken 15-30 min before a meal (34). Specific dietary modification methods and lifestyle modifications are advised according to the Eatwell Guide and ADA diabetes meal planning. Patients are advised to have a low-fat, low-carbohydrate, and higher-fiber diet, including making the meal plate half non-starchy vegetables and the other half divided into protein and carbohydrates. Patients are advised to reduce the consumption of refined sugars and salts, as well as limit alcohol intake. Regarding snacks, patients are advised to take high-protein, low-carbohydrate snacks and mild intake of fruits per day. Patients are advised to decrease their body weight and perform regular exercise, targeting 150 min/week of moderate-intensity aerobic exercise such as walking, swimming, etc. Strategies to increase adherence and to monitor study medication adherence are given, including weekly pillbox containers that have been given to patients. Additionally, telephone-based intervention on a monthly follow-up was performed. The adherence was monitored through an indirect method. The direct method is the measurement of the drug/or metabolite level, which was not applicable in the current study. While the indirect strategy was followed to assess and enhance the medication adherences through the researcher's questionnaire and pill boxes. The participants were free to withdraw from the study whenever they wanted. The researcher may withdraw any participants who develop any adverse reaction or exhibit non-compliance with the study medication or get medical conditions that interfere with the study. Counselling on the management of hypoglycemia is given, in which patients have been warned about symptoms of hypoglycemia. For conscious patients with initial or intermediate hypoglycemic symptoms and a blood glucose level below 70 mg/dl, eating 15-20 g of carbohydrates, such as a cup of fruit juice, is advised to raise the blood glucose, and it should be checked after 15 minutes. If it is still below 70 mg/dl. Repeat it until the blood glucose level reaches 70 mg/dL or higher. Once the blood sugar is back to normal, the patient should eat a meal or snack containing complex carbohydrates such as bread to keep it from dropping again. In G3, forty-six patients received their established oral hypoglycemic agents for 3 months without receiving dapagliflozin or pharmaceutical care intervention. One hundred twenty-five patients completed the study: 41 in G1, 40 in G2, and 44 in G3. A total of thirteen patients did not complete the follow-up visits for various reasons. In G1 five patients discontinued due to loss of follow-up (n=3), urinary tract infection (UTI)/polyuria (n=1), and withdrawing consent due to personal reasons (n=1); in G2 six patients discontinued due to loss of follow-up (n=4) and moving to another area (n=2); while in G3 two patients discontinued due to loss of follow-up (n=1) and withdrawing consent due to personal reasons (n=1).

Processing of samples and analysis

After 12 hours of fasting, blood samples (7.0 ml) were taken from each patient at the beginning and after 90 days by vein puncture; 2.0 ml was added in EDTA-containing tubes and utilized for analysis of HbA1c. The other 5.0 ml was added in a plain tube and left to clot, then centrifuged at 4000 rpm for 15 min to obtain the serum. The serum was used for analysis of fasting glucose, and lipid profile. Blood samples were analyzed using a Cobas C111 analyzer (Roche Diagnostics GmbH, Germany) for HbA1c via enzymatic assay using the immunoturbidimetric method (R1 antibody reagent and SR Polyhapten reagent) with the Glycohemoglobin Kit, and a Cobas C311 automated analyzer (Roche Diagnostics GmbH, Germany) is used for glucose and lipid profile using the following methods and kits, glucose is analyzed via hexokinase method with Glucose Kit and lipid profile is analyzed using homogeneous enzymatic colorimetric assay, Cholesterol Oxidase-Peroxidase Amino antipyrine Phenol (CHOD-PAP) method for total cholesterol (TC), direct measurement method using selective masking agents for high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) and Glycerol Phosphate Oxidase-Peroxidase Amino antipyrine (GPO-PAP) method for triglyceride (TG).

Statistical analysis

The results are presented as numbers, percentages, and medians (interquartile ranges). The data were

analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA) and Excel 10 (Excel Products Inc., Arnold, USA). The normality of the data was assessed using the Shapiro-Wilk test. The continuous data were analyzed using a non-parametric Kruskal-Wallis 1-way ANOVA, all pairs, and the categorized data were analyzed using a chi-squared test and, for small samples, with a chi-square test with Yates' correction. A probability (*p*) value less than 0.05 is significant.

RESULTS

One hundred twenty-five patients completed the study: 41 patients in the dapagliflozin group, 40 in the clinical pharmacist-led intervention group, and 44 in the standard therapy group. A total of thirteen patients did not complete the follow-up visits for various reasons. Table 1 illustrates the baseline characteristics of the participants enrolled in the study for each group.

Table 1: The characteristics of the participants enrolled in the study

Characters	Group I (n=41)	Group II (n=40)	Group III (n=44)	*p*-value
Sex (Male/Female)	15/26	12/27	15/29	0.859
Age (year)	54 (49-63)	52 (45.8, 59.5)	55 (49.5, 63.5)	0.348
Duration of diabetes (year)	9 (4.5-12)	9 (3, 11.8)	10 (6, 18)	0.284
Family history of diabetes				
Yes	334	33	33	0.520
No	7	7	11	
Marital status				
Married	41	37	41	
Single	0	3	1	
Divorced	0	0	0	0.109
Widowed	0	0	2	
Educational level				
Illiterate	7	17	14	
Primary	16	14	13	
Secondary	8	2	4	0.389
High school	4	2	5	
Diploma	5	4	7	
University	1	1	1	
Alcohol drinking				
Yes	0	4	1	0.209
No	37	32	39	
ex-drinker	4	4	4	
Smoking				
Smoker	3	4	3	0.596
Non-smoker	32	32	31	
ex-smoker	6	4	10	
Concomitant disease/disorder				
Hypertension	15	21	17	
Dyslipidemia	26	27	27	
ASCVD	5	5	5	0.924
Thyroid disorders	3	1	3	
Renal problem				
No	35	40	41	0.039
Nephropathy	6	0	3	
Oral antidiabetics (No.)				
Two	26	22	21	0.348
Three	15	18	23	
Gliptin users	27	24	32	0.456
Lipid-lowering agents	23	24	16	0.065
Antihypertensive	13	14	11	0.595
Thyroxine	3	1	4	0.448

The results are presented as median (interquartile range) and numbers. *p*-values were calculated using a non-parametric Kruskal-Wallis 1-way ANOVA, all pairs for continuous data and a Chi square test for homogeneity of categorized data. Group I: using Dapagliflozin as add-on therapy, Group II: Clinical pharmacy intervention, Group III: No intervention, and ASCVD: atherosclerotic cardiovascular disease.

Baseline characteristics were similar across groups except for significantly higher nephropathy prevalence in the dapagliflozin group. Changes in cardiometabolic indices are shown in Table 2. There was a significant reduction in fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and estimated fasting plasma glucose (eFPG) among dapagliflozin group and clinical pharmacist-led intervention group participants after 3 months. No significant difference in glycemic indices (FPG, HbA1c, and eFPG) was observed among standard therapy group participants after 3 months. Total cholesterol (TC) decreased significantly only in the dapagliflozin group, with no significant changes in the clinical pharmacist-led intervention group or standard therapy group. There was a non-significant difference regarding reduction of HbA1c and FPG in the clinical pharmacist-led intervention group -0.665% (-1.55 to -0.245) and -14.5 mg/dL (-38.75 to 6), respectively) compared to the dapagliflozin-add-on therapy group (-0.7% (-1.6 to 0.0) and -37 mg/dL (-83 to 1.0)) after three months of treatment; however, both groups caused significant reduction in HbA1c and FPG compared to the standard therapy group (+0.05% (-0.3 to 0.597) and -1.5 mg/dL (-11.75 to 30.75), respectively). Table 3, Figure 2, and Figure 3 illustrate the differences in HbA1c and FPG among different treatment modalities.

Table 2: Changes in cardiometabolic indices, including glycemic indices, lipid profile, and blood pressure

Indices	Group I (n=41)			Group II (n=40)			Group III (n=44)		
	Before	After	*p*	Before	After	*p*	Before	After	*p*
FPG	200 (170.5-257)	150 (130.5-198)	0.001	191 (160.3-220.5)	171 (133-200.8)	0.026	184 (153, 220)	190 (155-218.8)	0.919
HbA1c	8.4 (7.6-9.45)	7.6 (7-8.41)	0.001	8.64 (7.8-9.6)	7.35 (6.9-8.63)	<0.001	8.1 (7.55-8.9)	8.49 (7.62-9.18)	0.677
eFPG	194.4 (171.4-224.5)	171.4 (154.2-194.5)	0.001	201.3 (177.2-228.8)	164.2 (151.3-200.9)	<0.001	185.8 (1170-208.7)	197 (172.1-216.6)	0.677
ACGR	1.00 (0.902-1.163)	0.925 (0.784-1.116)	0.244	0.959 (0.856-1.027)	0.938 (0.837-1.098)	0.791	0.969 (0.86-1.087)	0.965 (0.856-1.098)	0.990
TC	182 (141.5-209.5)	150 (129.5-179)	0.011	165.5 (146.3-195.5)	174.5 (142.8-187.8)	0.958	185 (147.5-206.3)	167.5 (151.3-206.8)	0.633
Non-HDL	96 (68.8-122.8)	78 (62.1-96.5)	0.124	88.9 (65.1-114.7)	94.9 (66.5-116.6)	0.851	98.3 (74.1-117)	93.7 (79.7-121.1)	0.239
HDL	37 (35, 50)	39 (32-47.5)	0.114	42 (34.3-46)	38 (31-48.8)	0.421	43.5 (38.3-51.8)	42.5 (39-50)	0.368
TG	156 (103-235.5)	143 (104-169.5)	0.160	156 (109.3-213.3)	140.5 (110.8-200.3)	0.577	149.5 (106-182)	145.5 (106-172.5)	0.610
VAI	142.5 (83.7-266.3)	137 (94.7-248.9)	0.939	164.6 (107.8-234.1)	153.3 (104-246)	0.591	137.6 (87-205.6)	135.5 (85.7-202.3)	0.959
LAP	66.7 (42-112.5)	56.9 (34.7-82.7)	0.420	69.7 (47.4-101.2)	68.5 (41.1-85.3)	0.359	64.7 (44.7-93.2)	61.3 (41.2-91.8)	0.689
BP									
Systolic	130 (110-140)	120 (110-135)	0.118	120 (110-140)	120 (110-130)	0.606	120 (110-130)	130 (110-140)	0.291
Diastolic	80 (70-80)	80 (75-80)	0.922	80 (70-80)	80 (70-80)	0.683	80 (70-80)	80 (70-80)	0.896
PP	50 (40-60)	40 (40-50)	0.121	50 (40-60)	50 (40-50)	0.440	40 (40-60)	50 (40-60)	0.318
MAP	96.7 (90-103.3)	93.3 (88.3-100)	0.370	93.3 (86.7-100)	93.3 (86.7-100)	0.938	91.7 (84.2-99.2)	94.2 (90-100)	0.453
PPI	0.364 (0.34-0.429)	0.364 (0.321-0.417)	0.231	0.385 (0.333-0.426)	0.374 (0.333-0.417)	0.542	0.369 (0.333-0.426)	0.392 (0.339-0.429)	0.582

The results are expressed as median (interquartile range). P-values were calculated using a non-parametric Kruskal-Wallis 1-way ANOVA, all pairs for continuous data. FPG: fasting plasma glucose, HbA1c: glycosylated hemoglobin, eFPG: estimated fasting plasma glucose, ACGR: acute-to-chronic glycemic ratio, TC: total cholesterol, HDL: high density lipoprotein, TG: triglycerides, VAI: visceral adiposity index, LAP: lipid accumulation product, BP: blood pressure, PP: pulse pressure, MAP: mean arterial pressure, PPI: pulse pressure index.

Table 3: The difference in the HbA1c and FPG among groups of the study

	Median (IQR)	*p*1	*p*2	*p*3
HbA1c		0.547	<0.001	<0.001
Group I	-0.7(-1.6 to 0.0)			
Group II	-0.665 (-1.55 to -0.245)			
Group III	+0.05 (-0.3 to 0.597)			
FBG		0.203	<0.001	0.006
Group I	-37 (-83 to 1.0)			
Group II	-14.5 (-38.75 to 6)			
Group III	-1.5 (-11.75 to 30.75)			

The results are presented as median (IQR). P-value was calculated using an independent-samples Kruskal-Wallis test. *p*1: comparison between Group I and II, *p*2: comparison between Group I and III, and *p*3: comparison between Group II and III.

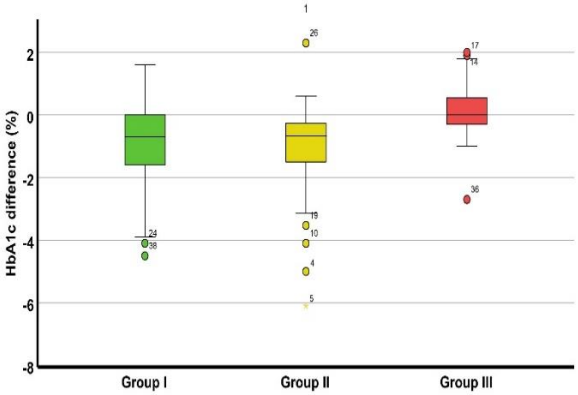

Figure 2: Boxplot shows the effects of each intervention on the changes in glycosylated hemoglobin (%). The boxplot displays the minimum, first quartile, median, third quartile, and maximum values. The outliers are the dots outside the boxplot.

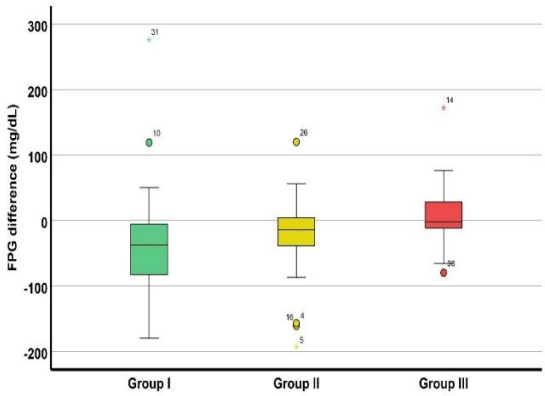

Figure 3: Boxplot shows the effects of each intervention on the changes in fasting glucose level (mg/dl). The boxplot displays the minimum, first quartile, median, third quartile, and maximum values. The outliers are the dots outside the boxplot.

Non-significant changes were observed in other cardiometabolic indices, including acute-to-chronic glycemic ratio (ACGR), high-density lipoprotein (HDL), non-HDL, triglycerides (TG), visceral adiposity index (VAI), lipid accumulation product (LAP), pulse pressure (PP), mean arterial pressure (MAP), diastolic blood pressure, and pulse pressure index (PPI). Systolic blood pressure showed a non-significant numerical decrease (-10 mmHg) in the dapagliflozin group and a non-significant numerical increase (+10 mmHg) in the standard therapy group, with no change in the clinical pharmacist-led intervention group. The incidence of adverse events across the three study groups is illustrated in Table 4.

Table 4: Side effects occurred with different treatment modalities during the treatment period

Side effects	Group I (n=41)	Group II (n=40)	Group III (n=44)
Hypoglycemia	3(7.3)	2(5)	2(4.5)
Gastrointestinal disturbances	0(0.0)	1 (2.5)	0(0.0)
Urinary tract infection (UTI)¶	3(7.3)	0(0)	0(0.0)
Diabetic ketoacidosis (DKA)	0(0.0)	0(0.0)	0(0.0)

Values were expressed as frequency and percentage. ¶One patient in the dapagliflozin-added on therapy group dropout from the study due to UTI and polyuria.

Adverse events were infrequent and generally mild. Hypoglycemia was similar among the groups, and gastrointestinal disturbances were observed in 1 participant (2.5%) in Group II; no cases were recorded in Groups I or III. Urinary tract infections (UTIs) occurred in 3 participants (7.3%) in Group I; no UTIs were reported in Groups II or III, and no cases of diabetic ketoacidosis (DKA) or any other severe complications were documented in any of the three groups during the study period. Changes in medication adherence across the three intervention groups shown in Table 5.

Table 5: Changes in medication adherence among the three intervention groups

Compliance		Group I (n=41)		Group 2 (n=40)		Group 3 (n=44)	
Category	Scoring	Before	After 3 months	Before	After 3 months	Before	After 3 months
High (Good)	≤28	35(85.4)	38(92.7)	32(80)	38(95)	38(86.4)	39(88.6)
Medium (Average)	29-42	6(14.6)	3(7.3)	8(20)	2(5)	6(13.6)	5(11.4)
Low (poor)	≥ 43	0	0	0	0	0	0
p-value		0.289		0.043		0.747	

The results are presented as a frequency and percentage (%). *p*-value was calculated using a chi-square test. The category (Low) was not included in the analysis because its number is zero.

At baseline, most participants in all groups exhibited high adherence: 85.4% (35/41) in Group I, 80% (32/40) in Group II, and 86.4% (38/44) in Group III. Notably, no participants in any group fell into the low adherence category at baseline or follow-up. After 90 days, adherence improved significantly in Group II only, with high adherence rising to 95% (38/40; p= 0.043). Non-significant small improvements occurred in Group I and Group III: Group I increased to 92.7% (38/41; p= 0.289), and Group III to 88.6% (39/44; p= 0.747). The medium adherence category decreased in all groups post-intervention, with the most pronounced reduction observed in Group II (from 20% to 5%).

DISCUSSION

This study evaluated the impact of clinical pharmacist-led intervention compared to dapagliflozin as add-on therapy and standard care in patients with type 2 diabetes mellitus (T2DM). The findings demonstrate that both clinical pharmacist intervention and dapagliflozin significantly improved glycemic control compared to standard care alone. HbA1c reduction was comparable between the clinical pharmacist-led intervention and dapagliflozin groups, suggesting that pharmacist involvement can have an effect comparable to pharmacological intensification with dapagliflozin. Therefore, in resource-limited settings, clinical pharmacist interventions can represent a cost-effective alternative to pharmacologic intensification by having a comparable effect to dapagliflozin in reducing glycemic parameters (HbA1c and FPG) and additionally reducing medication expenditures since dapagliflozin requires ongoing medication costs, while clinical pharmacist-led care is a one-time investment in human capital with broader impact. A baseline imbalance in nephropathy prevalence was observed (higher in Group I, p=0.039), representing a possible confounder since renal function may affect the impact of dapagliflozin. The significant decrease in HbA1c and FPG observed in the clinical pharmacist group aligns with multiple studies indicating that pharmacist-led services improve glycemic parameters through medication optimization, adherence reinforcement, lifestyle counselling, and early identification of drug therapy problems [24,35]. In particular, the current study's clinical pharmacist intervention included dosage modification, education on drug timing, side effect management, dietary counselling, and adherence strategies, all of which are critical in chronic disease self-management. The occurrence of side effects was minimal; 2 participants (5.0%) experienced hypoglycemia, and only 1 participant (2.5%) experienced gastrointestinal disturbance. Meanwhile, the dapagliflozin group exhibited similar glycemic improvements, consistent with prior evidence that sodium-glucose cotransporter-2 (SGLT2) inhibitors provide significant reductions in both HbA1c and FPG levels [36,37]. In this study, in the dapagliflozin add-on therapy group, 3 participants (7.3%) got UTIs, and 3 participants (7.3%) experienced hypoglycemia, while 1 participant dropped out due to UTI and polyuria. Furthermore, the addition of another medicine to patients already having 2 or 3 medications causes polypharmacy, and this can lead to medication non-adherence. Interestingly, while both interventions were effective, in other studies the pharmacist-led group demonstrated a better improvement in medication adherence scores, emphasizing the importance of patient education and engagement in treatment outcomes [22]. In our study, the adherence of patients improved significantly in group 2 only, while group 1 and group 3 showed non-significant improvements in adherence to medications. In contrast, the standard care group showed no statistically significant improvements in glycemic indices or adherence, highlighting the potential limitations of routine care without structured interventions. Our adherence assessment used the Modified Hill-Bone scale, originally validated for hypertension and adapted for diabetes. Self-reported

measures are susceptible to social desirability bias, and using a non-diabetes-specific tool may overestimate compliance. Future research should also employ objective measures (e.g., pill counts). It is noteworthy that while dapagliflozin therapy impacts biochemical markers via its pharmacodynamic action, pharmacist-led care modifies patient behavior, optimizes existing therapy, and addresses barriers to adherence, an approach that may lead to sustainable long-term benefits.

Study limitations

It is necessary to recognize certain limitations. The study duration was limited to three months, leading to short follow-up; the sample size was relatively small; and the study design is single center, using a non-validated adherence tool for T2DM with a high baseline adherence rate. A baseline imbalance in nephropathy prevalence was observed. These may possibly underestimate long-term effects and adverse events.

Conclusion

In conclusion, this study shows that both clinical pharmacist intervention and dapagliflozin add-on therapy significantly improve glycemic control in T2DM patients compared to standard care. The clinical pharmacist intervention achieved comparable, and in some cases superior, improvements in HbA1c and FPG levels while also enhancing medication adherence without the need for additional pharmacotherapy. Therefore, clinical pharmacist-led care provides comparable glycemic control as dapagliflozin at a lower cost, making it ideal for settings where medication costs and access are limited. These findings support the integration of clinical pharmacists into multidisciplinary diabetes care teams, particularly in resource-constrained settings where cost-effective, non-pharmacological interventions are essential. Future research with extended period is recommended to verify the durability of these effects and evaluate their impact on long-term complications.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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