# Safety and Efficacy of SGLT2 Inhibitors Versus DPP4 Inhibitors in Fasting Patients with T2-Diabetes Mellitus During Ramadan in Egypt (EMPA-Ramadan)

**Hesham El Hefnawy[1, *], Mohamed Abdel Hady Mashahit[2], Khaled El Sayed El Hadidy[3], Heba Ramadan[4], Athar Reda Ibrahim[1], Amany Kamel[4], Hazem Samy Matar[3], Abdelrahman Ahmed Ewaise[2]**

[1]Departement of Pediatric Endocrinology and Diabetes, National Institute for Diabetes and Endocrinology, Cairo, Egypt

[2]Department of Internal Medicine, Fayuom University Hospitals, Fayoum, Egypt

[3]Department of Internal Medicine, Beni-Suef University Hospitals, Beni-Suef, Egypt

[4]Department of Internal Medicine, National Institute for Diabetes and Endocrinology, Cairo, Egypt

**Email address:**

drhefnawy@yahoo.com (Hesham El Hefnawy), mam22@fayoum.edu.eg (Mohamed Abdel Hady Mashahit),
kshadidy@hotmail.com (Khaled El Sayed El Hadidy), hebar235@gmail.com (Heba Ramadan), athrrda@yahoo.com (Athar Reda Ibrahim),
amanykamel73@gmail.com (Amany Kamel), hazemsamy2005@yahoo.com (Hazem Samy Matar),
Aae11@gmail.com (Abdelrahman Ahmed Ewaise)

[*]Corresponding author

**Abstract:** This is a multicenter, observational, comparative, phase IV study, conducted to assess safety and efficacy of sodium glucose cotransporter 2 inhibitors (SGLT2 I) versus dipeptidyl peptidase 4 inhibitors (DPP-4 I), added to biguanides for both groups, in managing Type 2 Diabetes Mellitus (T2DM) during Ramadan fasting among Muslim Egyptian patients. All patients aged $\geq$ 18 years old, on SGLT2-inhibitor or DPP-4 inhibitor added on metformin for at least one month before Ramadan, willing to fast Ramadan. Demographic data, detailed medical history and laboratory results were collected before and after Ramadan. Out of 300 enrolled patients, three patients from group B (DPP-4 inhibitor) had mild hypoglycemic episodes and none in group A (SGLT2 inhibitor). Mean HbA1c markedly decreased after Ramadan fasting in Group A with a statistically significant difference ($p$-value = 0.021) and decreased in group B with no statistical significance ($p$-value = 0.365). Both medications demonstrated weight loss in patients, with a very highly statistically significant difference between both groups ($p$-value < 0.001). There was urinary tract infection (UTI) in both groups, with no statistical significance. No diabetic ketoacidosis was reported in the study. 6 (3.8%) of total patients in group A and 11 (7.7%) in group B had adverse events as; UTI, hypoglycemia, and genital infection. All AEs were mild to moderate and not related to medications of the trial. No serious adverse events (SAEs) were reported in the study. Both SGLT2 inhibitors and DPP4 inhibitors are safe to be used and effective in the management of T2DM during Ramadan Fasting.

**Keywords:** Ramadan Fasting, Empagliflozin, Vildagliptin

## 1. Introduction

Fasting during the Holy month of Ramadan is one of the five pillars of Islam and is obligatory for all healthy Muslim adults. Fasting Ramadan is common among people with Type 2 Diabetes Mellitus (T2DM) [1], despite the potential risk of acute complications. Diabetes is a chronic disease requiring continuous management [2]. A cornerstone of

Ramadan diabetes management is patients' education, which should include information on risks, lifestyle changes, glucose monitoring, nutrition, exercise, and medication [3, 4].

Many studies showed the Efficacy and Safety of dipeptidyl peptidase 4 inhibitors (DPP-4 I) compared to sulfonylurea (SU) in patients with T2DM during Fasting in Ramadan [5]. However, Food and Drug Administration (FDA) has found that the use of saxagliptin and alogliptin in T2DM may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. Two clinical trials were conducted in patients with heart disease "SAVOR & EXAMINE" showed that more patients who received saxagliptin or alogliptin were hospitalized for heart failure than patients who received placebo [6]. Also, many studies showed the Efficacy and Safety of sodium glucose cotransporter 2 inhibitors (SGLT2 I) in T2DM patients during Ramadan fasting [7, 8]. SGLT2 inhibitors have demonstrated a reduction in cardiovascular events and delay in the progression of kidney disease in patients with T2DM [9]. DAPA-HF trial and EMPEROR-Reduced trial evaluated the effects of dapagliflozin and empagliflozin, respectively, in patients with heart failure and reduced ejection fraction (HFrEF). Also, the recently published SOLOIST-WHF trial studied the effects of sotagliflozin in patients with HFrEF and patients with heart failure (HF). It preserved ejection fraction (HFpEF). All three trials showed a significant reduction in HF hospitalization and cardiovascular death without an increased risk of serious adverse events [10-12]. Besides, EMPA-REG OUTCOME (empagliflozin), CANVAS Program & CREDENCE (Canagliflozin), and DECLARE–TIMI 58 (dapagliflozin) studies showed that the use of SGLT2 inhibitors reduced the development of end-stage kidney disease or acute kidney injury. Also, it reduced the risk of dialysis, transplantation, or death in T2DM patients who develop kidney diseases [13-15]. According to International Diabetes Federation (IDF) and Diabetes and Ramadan (DAR) guidelines, SGLT2 inhibitors are effective in glycemic control and weight loss and have a low risk of hypoglycemia to be safe for diabetic patients during Ramadan. [16] Moreover, they have demonstrated improvements in cardiovascular and renal problems; as mentioned above, SGLT2 inhibitors are better used in T2DM patients with cardiovascular and/or renal problems. This study aimed to compare the safety and efficacy of SGLT2 inhibitors versus DPP-4 inhibitors, added to metformin in managing T2DM during Ramadan fasting among Muslim Egyptian patients.

# 2. Methods

The study is a phase IV (post-marketing) study. It was conducted in the outpatient clinics of 3 sites in Egypt: National Institute of Diabetes and Endocrinology (NIDE), Al Fayoum University Hospital, and Beni-Suef University Hospital to assess the safety and efficacy of SGLT2 inhibitors versus DPP-4 inhibitors added to biguanides for both groups, in management of T2DM during Ramadan fasting among Muslim Egyptian diabetic patients.

The study enrolled 300 Egyptian diabetic patients with T2DM receiving either SGLT2 inhibitors (empagliflozin or dapagliflozin) or DPP-4 inhibitors (sitagliptin or vildagliptin) according to their therapeutic dose as per guidelines for diabetes mellitus control, added on 2000 mg metformin daily in 2 divided doses for the two arms, for at least one month before Ramadan.

Patients were evaluated at baseline, two weeks before Ramadan, two weeks after Ramadan, and one month after the end of Ramadan (3 months from baseline visit), with a window of 2 weeks for all visits.

Patients received an education, including information on risks, lifestyle changes, self-glucose monitoring, nutrition, exercise, and medication during Ramadan fasting. Also, patients were asked to self-check blood sugar by a given glucometer at home at 7 points, as per DAR guidelines 2020. Points are: suhor (the last meal eaten by Muslims before the sun has come up, before fasting), morning, midday, midafternoon, immediately before iftar (a meal eaten by Muslims at sundown to break the daily fast during Ramadan), 2 hours after iftar, and at any time when feeling any symptoms of hypo or hyperglycemia or not feeling well).

Hypoglycemia is a clinical finding confirmed by measuring blood glucose level, according to American Diabetes and association (ADA), hypoglycemia is usually when blood glucose level is less than 70 mg/dL. Signs and symptoms of low blood glucose according to ADA include; tremors, nervousness or anxiety, sweating, chills, irritability or impatience, confusion, tachycardia, dizziness, hunger, nausea, pallor, weakness, drowsiness, blurred vision, tingling or numbness in the lips, tongue or cheeks, headache, nightmares and seizures. Presence of any symptom of them will be considered for primary endpoint and will be confirmed by self-monitoring blood glucose level.

## 2.1. Inclusion Criteria

Egyptian male and female Muslim patients, aged ≥ 18 years old. With T2DM, willing to fast Ramadan and treated with SGLT2 inhibitors (empagliflozin, dapagliflozin) or DPP-4 inhibitors (sitagliptin, vildagliptin) as an add-on to metformin for both arms, for one month before Ramadan. Willing to sign Informed Consent Form (ICF) and be ready to comply with the protocol for the duration of the study.

## 2.2. Exclusion Criteria

Subjects with uncontrolled hyperglycemia; HbA1c more than 9%, with any uncontrolled endocrine disorder except T2DM. Patients with chronic liver disease (serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase above 2 times upper limit of normal value). Patients with chronic renal disease (S creatinine above 1.5 mg/dl and/ or estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m$^2$). Patients on renal dialysis, with a history of ketoacidosis in the past six months or had a history of malignancy during the past three years. Also, subjects with strokes including transient ischemic attack (TIA), diabetic foot infection, amputation (non-

traumatic even minor), or gangrene were excluded. In addition to pregnant or breast-feeding women or subjects on any anti-diabetic treatment rather than SGLT2, DPP4 antagonist, and metformin. Besides, those who had a history of frequent urinary tract infections (UTI) were also excluded from the study.

### 2.3. Clinical Grouping

372 patients were screened, and out of them, 300 patients were enrolled in 2 groups and distributed in the three sites as follows;

Group A: 157 Patients received SGLT2 inhibitors, and Group B: 143 Patients received DPP4 inhibitors, with Metformin 2000 mg daily in both groups.

All patients completed the study without any non-compliance or dropout.

### 2.4. Statistical Analysis

Performed analysis of all efficacy variables was done for patients as they completed the study without protocol violation (as per protocol, PP) regarding primary and secondary endpoints.

#### 2.4.1. Primary Endpoints
Severe hypoglycemic episodes that might force patients to break Ramadan fasting, by symptoms of hypoglycemia mentioned by patients and to be confirmed by self-glucose measurement.

#### 2.4.2. Secondary Endpoints
1) The difference in HbA1c between patients treated with SGLT2 inhibitors and DPP-4 inhibitors added on 2000 mg metformin daily in 2 divided doses for both groups, in managing T2DM during Ramadan fasting.
2) Study Hypoglycemic and/ or hyperglycemic episodes that led to treatment shifting or dose modification during Ramadan fasting.
3) Evaluation of weight loss.
4) Evaluation of UTI.
5) Evaluation of Diabetic ketoacidosis (DKA).

6) Evaluation of serious/non-serious adverse events.

Analysis was done using IBM SPSS version 24, and all tests were performed on the 5% level of significance.

Using Chi² test for unpaired categorical variables, Paired t-test for estimating the change in numerical variables throughout the study visits, Student un-paired t-test for estimating the comparison between the subgroups for the numerical variables, P-values less than 0.05 was considered to be statistically significant.

Multivariate logistic regression was used to find regression coefficient (B) and odd ratio (OR) to fit the relationship between the group of hypoglycemic versus no hypo., change in HbA1c (divided into 3 groups; "0" is no change in HbA1c, "< 0" decrease in HbA1c and "> 0" Increase in HbA1c), change in weight (divided into three groups; "0" is no change in weight, "< 0" decrease in weight and "> 0" Increase in weight), the incidence of UTI & incidence of AE and Predictors at baseline visit such as Gender, Age, Weight, HbA1c and Treatment Group.

## 3. Ethics Statement

The study was conducted in compliance with the applicable regulatory requirements and the principles of Good Clinical Practice (GCP) and Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Teaching Hospitals (approval No. IDE 00220), IRB committee of Fayoum faculty of Medicine and approved by Research Ethical Committee of faculty of Medicine, Beni-Suef university (FM-BSU REC) and from Research and Human Development of Egyptian Ministry of Health (RHD of MOH).

## 4. Results

### 4.1. Patients' Characteristics at Baseline Visit

"Table 1" shows that males and females were equally distributed in the two treatment groups with no statistically significant difference in Gender, *p*-value = 0.488.

**Table 1.** *Patients' characteristics at baseline visit between the 2 treatment groups.*

| Patients' characteristics | Group A | Group B | P-Value [a] |
|---|---|---|---|
| N | 157 | 143 | |
| Male, N (%) | 65 (41.4%) | 58 (40.6%) | 0.488 |
| Female, N (%) | 92 (58.6%) | 85 (59.4%) | |
| Mean age (Years), (SD) | 54.35 (10.06) | 52.21 (9.54) | 0.061 |
| SBP (mm Hg), (V1) | 126.40 | 124.39 | 0.058 |
| DBP (mm Hg), (V1) | 78.92 | 77.862 | 0.060 |
| Pulse (BPM), (V1) | 81.37 | 81.71 | 0.529 |
| Body Weight (Kg), (V1) | 91.4 (13.2) | 88.8 (13.8) | 0.106 |
| BMI (kg/m$^2$) | 33.4 (4.8) | 32.3 (5.3) | 0.067 |
| HbA1c (%) | 7.19 | 6.98 | 0.060 |
| RBS (mg/dl), Mean (SD) | 147.14 (44.97) | 138.42 (45.260 | 0.105 |
| ALT (U/L), Mean (SD) | 21.80 (11.41) | 23.51 (12.66) | 0.233 |
| AST (U/L), Mean (SD) | 18.69 (11.41) | 20.35 (8.11) | 0.233 |
| S Creatinine (mg/dl), Mean (SD) | 0.84 (016) | 0.81 (0.20) | 0.165 |
| eGFR (mL/min/1.73m$^2$), Mean (SD) | 93.27 (16.51) | 96.99 (16.03) | 0.059 |

[a] Un- Paired t-test was done between main values of 2 groups.

"Table 1" shows that mean age in group A was 54.35 years and 52.21 years in group B, with no statistically significant difference in age between the 2 treatment groups, *p*-value = 0.061.

### 4.1.1. Vital Signs

"Table 1" shows that at baseline visit; there was no statistically significant difference between the two treatment groups in all vital signs, *p*-value > 0.05.
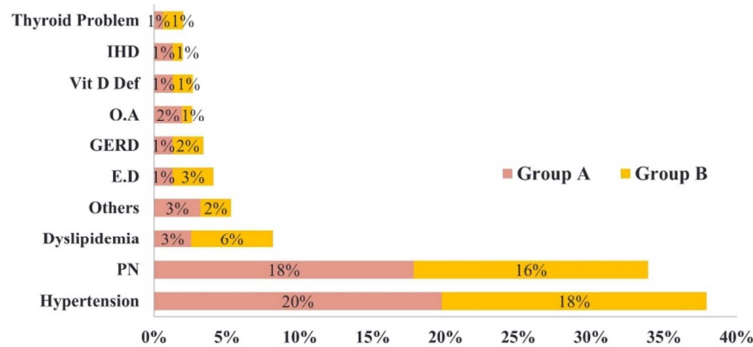
### 4.1.2. Medical History for Enrolled Patients

"Figure 1" shows patients of Group A and B had concomitant diseases; hypertension, peripheral neuritis (PN), dyslipidemia, erectile dysfunction (E.D), gastroesophageal reflux disease (GERD), osteoarthritis (O.A) and ischemic heart disease (IHD), with no statistical difference between the 2 treatment groups.



*Figure 1. Percent of medical history among 2 treatment Groups.*

### 4.1.3. Laboratory Tests

"Table 1" shows that at baseline visit; mean lab results (liver and kidney function tests) showed no statistically significant difference between the 2 treatment groups.

### 4.1.4. Diabetes Mellitus Treatment

87% of patients in Group A used medication from empagliflozin, and 13% used dapagliflozin, while 95% of patients in group B used medications from vildagliptin and only 5% used Sitagliptin, plus metformin 2000mgm daily in the two groups.

### 4.1.5. Concomitant Medications

Most enrolled patients in the study took concomitant medications at baseline visit and in the three visits of the study for; hypertension, cardiovascular protection, peripheral neuropathy, dyslipidemia, GERD, genital infection, and urinary tract infection (UTI).

### 4.2. Primary Endpoints

Hypoglycemic episodes that might force patients to break Ramadan fasting: It was reported that three patients had mild to moderate hypoglycemic episodes by symptoms in group B. Two of them had confirmed hypoglycemia by self-monitoring of blood glucose level, less than 70mg/dl. None was in group A, with no statistically significant difference between the two treatment groups (*p*-value > 0.05). Their hypoglycemic episodes led to break Ramadan fasting temporarily for the same day and then continued fasting on the same treatment without dose adjustment. Each patient had one hypoglycemic episode only.

### 4.3. Secondary Endpoints

### 4.3.1. The Difference in HbA1c Between SGLT2 Inhibitors and DPP-4 Inhibitors Added on 2000 mg Metformin Daily for Both Groups

"Table 2" shows that there was no statistically significant difference in HBA1c at baseline visit between the two groups (*p*-value = 0.060). However, there was a statistically significant difference in the percent change of HbA1c between baseline visit and end of the study in Group A (*p*-value = 0.021), no statistically significant difference in group B (*p*-value = 0.365), and no statistically significant difference between the two treatment groups (*p*-value = 0.305).

*Table 2. Average HbA1c and weight at the end of the study between the 2 treatment Groups.*

| N | Group A | Group B |
|---|---|---|
| | 157 | 143 |
| Mean (SD) HbA1c1 (%) | 7.19 (0.97) | 6.98 (0.94) |
| Mean (SD) HbA1c3 (%) | 6.99 (0.95) | 6.90 (0.91) |
| HbA1c3 – HbA1c1 | -0.2 | -0.08 |
| % Change | -2.8% | -1.1% |
| *P*-value between V1 & V3 [a] | 0.021 | 0.365 |
| *p*-value between 2 groups regarding the absolute change in HbA1c V1 to V3 [b] | 0.305 | |
| Mean (SD) Weight1 (Kg) | 91.4 (13.2) | 88.8 (13.3) |
| Mean (SD) Weight3 (Kg) | 89.4 (13.2) | 88.1 (13.6) |
| Weight3 – Weight1 | -2.05 | -0.70 |
| % Change | -2.2% | -0.8% |

| N | Group A | Group B |
|---|---|---|
| | 157 | 143 |
| *P*-value between V1 & V3 [a] | < 0.001 | < 0.001 |
| *p*-value between 2 groups regarding absolute change in weight V1 to V3 [b] | < 0.001 | |

[a] Paired t-test was done between main values of 2 groups
[b] Un- Paired t-test was done between main values of 2 groups.

### 4.3.2. Evaluation of Weight Loss

"Table 2" shows that there was no statistically significant difference in patients' body weight at baseline visit between the two treatment groups (*p*-value = 0.105). While there was a very highly statistically significant difference in the percent change of weight between baseline visit and end of the study in Group A & Group B (*p*-value < 0.001), and also in percent change from V1 to V3 between the two treatment groups (*p*-value < 0.001).

### 4.3.3. Study Hypoglycemic and/or Hyperglycemic Episodes That Led to Treatment Shifting or Dose Modification During Ramadan Fasting

Both treatment groups did not need treatment shift or dose modification due to hypo or hyperglycemia during Ramadan.

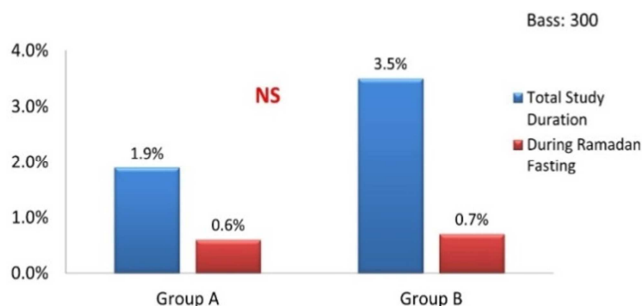### 4.3.4. Evaluation of Urinary Tract Infection (UTI)



**Figure 2.** *Percent of UTI among 2 Treatment Groups.*

The "Figure 2" shows that there was UTI in patients of group A & B by 1.9% and 3.5% respectively from the total population of the group, with no statistically significant difference in UTI during Ramadan fasting between the two treatment groups (*p*-value = 0.947) or in the entire duration of the study (*p*-value = 0.395).

### 4.3.5. Evaluation of Diabetic Ketoacidosis (DKA)

No DKA was recorded during the study in patients of the 2 treatment groups.

### 4.4. Multivariate Logistic Regression for Main Endpoints

Incidence of hypoglycemia, UTI, and AE was not associated with any predictors such as Gender, Age, Weight, HbA1c, or Treatment Group.

*Change in HbA1c:* The comparison between change in (HbA1c < 0) and change in (HbA1c = 0). Only HbA1c was a significantly predictor and negatively associated (*B*= -1.323, SE= 0.324, *p*-value < 0.001). Also, the comparison between change in (HbA1c < 0) and change in (HbA1c > 0). Again, HbA1c was a significantly predictor and negatively associated (*B*= -1.355, SE= 0.184, *p*-value < 0.001).

"Table 3" shows that change in Weight: The comparison between change in (Weight < 0) and change in (Weight = 0). Only Treatment Group was a significantly predictor and positively associated (B=0.814, SE=0.307, *p*-value = 0.008). While the comparison between change in (Weight < 0) and change in (Weight > 0); Weight was a significantly predictor and negatively associated (B=-0.042, SE=0.017, *p*-value = 0.012) and Treatment Group was a significantly predictor and positively associated (B=1.662, SE=0.490, p-value = 0.001).

**Table 3.** *Multivariate logistic regression for main Endpoints.*

| | | B | SE | *p*-value | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| | Intercept | 31.476 | 7.486 | <0.001 | | | |
| | Gender | 1.078 | 1.264 | 0.394 | 2.939 | 0.247 | 35.022 |
| Incidence of hypoglycemia [a] | Age | 0.002 | 0.064 | 0.977 | 1.002 | 0.883 | 1.136 |
| | Weight | -0.024 | 0.044 | 0.585 | 0.976 | 0.895 | 1.064 |
| | HbA1c | 1.100 | 0.864 | 0.203 | 3.003 | 0.553 | 16.314 |
| | Treatment Group | -17.153 | NA | NA | NA | | |
| | Intercept | 8.344 | 3.667 | 0.023 | | | |
| | Gender | 0.379 | 0.546 | 0.487 | 1.461 | 0.501 | 4.257 |
| Change in HbA1c [b] (Change in HbA1c = 0) | Age | -0.005 | 0.026 | 0.848 | 0.995 | 0.945 | 1.047 |
| | Weight | -0.012 | 0.020 | 0.531 | 0.988 | 0.950 | 1.027 |
| | HbA1c | -1.323 | 0.324 | < 0.001 | 0.266 | 0.141 | 0.502 |
| | Treatment Group | -0.419 | 0.529 | 0.428 | 0.658 | .233 | 1.853 |
| | Intercept | 9.656 | 2.100 | .000 | | | |
| | Gender | 0.185 | 0.296 | 0.531 | 1.204 | 0.674 | 2.150 |
| Change in HbA1c [b] (Change in HbA1c > 0) | Age | -0.013 | 0.015 | 0.395 | 0.987 | 0.959 | 1.017 |
| | Weight | 0.000 | 0.011 | 0.991 | 1.000 | 0.979 | 1.021 |
| | HbA1c | -1.355 | 0.184 | < 0.001 | 0.258 | 0.180 | 0.370 |
| | Treatment Group | -0.251 | 0.296 | 0.397 | 0.778 | 0.436 | 1.390 |

| | | B | SE | p-value | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| | Intercept | -2.527 | 2.060 | 0.220 | | | |
| | Gender | 0.352 | 0.316 | 0.265 | 1.421 | 0.766 | 2.639 |
| Change in Weight [c] | Age | 0.008 | 0.016 | 0.625 | 1.008 | 0.977 | 1.039 |
| (Change in Weight = 0) | Weight | -0.014 | 0.011 | 0.219 | 0.986 | 0.964 | 1.008 |
| | HbA1c | 0.053 | 0.159 | 0.739 | 1.055 | 0.772 | 1.441 |
| | Treatment Group | 0.814 | 0.307 | 0.008 | 2.256 | 1.236 | 4.117 |
| | Intercept | -0.468 | 2.913 | 0.872 | | | |
| | Gender | -0.024 | 0.425 | 0.956 | 0.977 | 0.424 | 2.248 |
| Change in Weight [c] | Age | 0.003 | 0.021 | 0.876 | 1.003 | 0.962 | 1.046 |
| (Change in Weight > 0) | Weight | -0.042 | 0.017 | 0.012 | 0.959 | 0.928 | 0.991 |
| | HbA1c | -0.085 | 0.222 | 0.702 | 0.919 | 0.594 | 1.419 |
| | Treatment Group | 1.662 | 0.490 | 0.001 | 5.268 | 2.016 | 13.767 |
| | Intercept | 5.473 | 5.019 | 0.276 | | | |
| | Gender | -0.731 | 0.832 | 0.380 | 0.481 | 0.094 | 2.460 |
| Incidence of UTI [a] | Age | -0.042 | 0.040 | 0.292 | 0.959 | 0.887 | 1.037 |
| | Weight | -0.015 | 0.026 | 0.560 | 0.985 | 0.937 | 1.036 |
| | HbA1c | 0.594 | 0.425 | 0.162 | 1.812 | 0.788 | 4.164 |
| | Treatment Group | -0.675 | 0.760 | 0.374 | 0.509 | 0.115 | 2.257 |
| | Intercept | 4.066 | 3.752 | 0.278 | | | |
| | Gender | -0.240 | 0.577 | 0.678 | 0.787 | 0.254 | 2.438 |
| Incidence of Adverse | Age | -0.020 | 0.029 | 0.490 | 0.980 | 0.925 | 1.038 |
| Event [a] | Weight | -0.015 | 0.020 | 0.438 | 0.985 | 0.947 | 1.024 |
| | HbA1c | 0.425 | 0.310 | 0.171 | 1.530 | 0.833 | 2.812 |
| | Treatment Group | -0.716 | 0.584 | 0.220 | 0.489 | 0.156 | 1.535 |

[a] Incidence of hypoglycemia, UTI and AE; the reference category is: Yes
[b] Change in HbA1c; the reference category is: change in HbA1c < 0
[c] Change in Weight; the reference category is: change in Weight < 0.
B: Regression Coefficient, SE: Standard Error, OR: Odd Ratio of B and p-value: significant value
Gender (for each change from male to female), age (for each increase one year), weight (for each increase 1 kg), HbA1c (for each increase of 1%), treatment group (for each change from group A to group B).

### 4.5. Adverse Events

"Table 4" shows that adverse events were in the form of UTI, hypoglycemia, genital infection, GI upset, Covid-19, and skin rash.

*Table 4. Adverse events in both treatment groups.*

| Adverse Event | Group A | | Group B | |
|---|---|---|---|---|
| N (%) | 157 | % | 143 | % |
| UTI | 3 | 1.9% | 5 | 3.5% |
| Hypoglycemia | 0 | 0% | 3 | 2.1% |
| Genital Infection | 1 | 0.6% | 1 | 0.7% |
| GI Upset | 0 | 0% | 2 | 1.4% |
| COVID-19 | 1 | 0.6% | 0 | 0% |
| Skin rash | 1 | 0.6% | 0 | 0% |
| Grand Total | 6 | 3.8% | 11 | 7.7% |

All AE were mild to moderate, and some patients with AE were given concomitant medication & resolved completely without sequelae.

There was no statistically significant difference in AE between patients in the two treatment groups (p-value = 0.148) in the study.

*No serious adverse event (SAE) was reported in the study.*

## 5. Discussion

### 5.1. Hypoglycemic Episodes That Might Force Patients to Break Ramadan Fasting

There were three patients with symptomatic hypoglycemic episodes during Ramadan fasting in group B (DPP-4 inhibitors), and none in group A (SGLT2 inhibitors). VIRTUE study showed that the vildagliptin (DPP-4 inhibitors) was associated with significantly fewer hypoglycemic episodes than SU. [17]. Devendra et al conducted an observational, nonrandomized study. They found the number of patients with hypoglycemic events during Ramadan was markedly lower in vildagliptin (DPP-4 inhibitor group) than gliclazide (SU group) [18]. As the class of DPP-4 inhibitors blocks the degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) thus, extending their actions leads to an increase in α- and β-cell sensitivity to glucose, modulation of insulin and glucagon secretion depending on the blood glucose level. Consequently, DPP-4 inhibitors are associated with a low risk of hypoglycemia [5]. S. Al Sifri et al found that switching to a sitagliptin-based regimen during Ramadan fasting decreased the risk of hypoglycemia compared with remaining on a sulphonylurea-based regimen [19].

Hypoglycemic episodes in this study occurred once in each patient during Ramadan fasting. Two of the three patients had confirmed low blood glucose levels, less than 70mg/dl. The VIRTUE study showed that many patients with hypoglycemic episodes were confirmed by blood glucose level and were once during Ramadan fasting [17].

Wan Seman et al study, which studied switching from SU to Dapagliflozin (SGLT2 inhibitors) in the fasting month of Ramadan, showed that fewer patients exhibited

hypoglycemia in the SGLT2 inhibitor group versus the SU group. The insulin-independent mechanism of SGLT2 inhibitors blocks the reabsorption of glucose in the proximal tubule of the kidneys and promotes the excretion of excess glucose in the urine. Hence, the risk of hypoglycemia is rare. [8]. A. Bashier et al, in their study, mentioned that a minority of patients broke their fast due to symptomatic hypoglycemia. However, the use of SGLT2 inhibitor was not associated with hypoglycemia unless there was concomitant use of other agents known to cause hypoglycemia, as sulfonylureas and insulin [7]. Nauck MA et al showed that use of Dapagliflozin produced much less hypoglycemia than Glipizide (3.5% of patients vs. 40.8%; *p*-value = 0.0001) in T2DM patients inadequately controlled with metformin [20].

### 5.2. The Difference in HbA1c Between SGLT2 Inhibitors and DPP-4 Inhibitors in Management of T2DM During Ramadan Fasting

HbA1c dropped by 2.8% from baseline visit to end of the study in Group A (SGLT2 inhibitors Group) and by 1.1% in group B (DPP-4 inhibitors Group), with no statistically significant difference between 2 treatment groups.

Bashier A et al study [7] showed that, HbA1c at baseline in patients treated with SGLT2-I plus oral hypoglycemics was 7.8±1.5% then markedly reduced to 7.4±1.4% (5.1% decrease rate) by end of Ramadan, with a very highly statistically significant difference (*p* < 0.001).

Results of our study reflect published data in the European Public Assessment Report (EPAR) about the Study DIA3005 of canagliflozin (SGLT2 inhibitors) on its effect in reducing HbA1c by 0.91% for 100 mg, depending on the premedication and baseline [21]. James F. List, et al study showed that A1C reduction associated with dapagliflozin (SGLT2 inhibitors) ranged from 0.55–0.90% versus placebo, based on dose, the severity of diabetes, and other patient-specific factors [22]. Serge A. Jabbour et al study; who studied the efficacy and safety of dapagliflozin as add-on therapy in patients with T2DM who were inadequately controlled with DPP-4 inhibitor with or without metformin, showed a marked reduction in HbA1c from baseline in the Dapagliflozin group compared with placebo at week 24 with; (*P*-value<0.0001). Also, there was significant reduction in HbA1c in dapagliflozin group versus placebo whether added to Sitagliptin or Metformin with; (*P*-value<0.0001) [23].

VIRTUE study compared the experience of DPP-4 inhibitors versus SU in management of patients with T2DM fasting during Ramadan fasting, the mean change in HbA1c from pre-Ramadan to study end was −0.24% in the vildagliptin group and +0.02% in the SU group (*P*-value = 0.001 between-group difference) [17].

### 5.3. Evaluation of Weight Loss

SGLT2 inhibitors specifically target the kidney by blocking the reabsorption of filtered glucose, thus leading to increased urinary glucose excretion, especially when hyperglycemia is present, which leads to weight loss [24].

Study DIA3002 showed decreased body weight with Canagliflozin groups compared to the placebo group (-2% for 100mg compared to -0.6% in the placebo group). Study DIA3009; showed a bodyweight reduction in the Canagliflozin groups compared to a weight gain in the glimepiride group. While in Study DIA3006; the DPP-4 inhibitor Sitagliptin, did not affect weight [21].

James F. List, et al study; showed that Dapagliflozin facilitates weight loss in T2DM by excretion of glucose with urinary loss of ~200-300 kcal/day. So, mean percent body weight reductions at week 12 were 2.5 to 3.4% in Dapagliflozin group, 1.2% in placebo group, and 1.7% in Metformin group. The mean percent changes in waist circumference were-1.6 to-3.5% in Dapagliflozin group, -1.2% in placebo group, and -2.2% in Metformin group, so more patients achieved >5% reduction in body weight with Dapagliflozin than with placebo and Metformin and [22].

VIRTUE study showed that in Vildagliptin group; body weight decreased by 0.76 kg versus by 0.13 kg in the Sulphonyl Urea group with *P*-value< 0.001 [18]. While, J. E. Foley et al study showed that there was weight increase by 0.8 ± 0.2 kg in the Vildagliptin group compared to 1.6 ± 0.2 kg in the gliclazide group (*p*-value < 0.01). So, there was weight gain in the SU group relative to a tendency to weight loss or less weight gain in the Vildagliptin group [25].

### 5.4. Evaluation of UTI

In Group A: 3 patients had UTI during the whole study duration, 2 of them occurred after the end of Ramadan fasting, and in Group B: 5 had UTI, 4 of them also occurred after the end of Ramadan fasting, with no study discontinuation due to UTI. Also, occurrence after Ramadan fasting is most probably related to patients' lifestyles rather than the effect of the medication during fasting.

SGLT2-inhibitors block glucose reabsorption in the proximal renal tubules, where 90% of glucose reabsorption occurs, resulting in urinary glucose, which leads to a higher risk of urinary tract infection [7], that is a common condition in patients with diabetes and is resolved with standard medical treatment [8].

Wan Seman et al study showed that UTI is slightly more increased in Dapagliflozin group than placebo group (10.3 versus 3.8%; *P*-value= 0.277) [8]. Nauck MA et al study proved that urinary tract infections occurred more frequently with patients treated with Dapagliflozin than those treated with Glipizide, but responded to standard treatment and rarely led to study discontinuation [20].

S. Al Sifri et al found while comparing safety between Sitagliptin group (DPP-4 inhibitor) and SU group that there was no UTI occurred in patients who received Sitagliptin, contrary to patients who received SU treatment, from which some cases were hospitalized and thus considered as serious adverse events [19].

### 5.5. Evaluation of DKA

No DKA was recorded during the study in patients of the

two treatment groups, with similar data in publications from Bashir et al regarding both medication groups in Ramadan [7].

Ramadan fasting in diabetic patients also poses risks of hyperglycemia and DKA due to several factors, as eating habits that are altered to include more carbohydrates, late-night eating, and elimination or adjustment of diabetes medications [7]. In this study, patients' education minimized the risk of DKA.

## 6. Safety

Kristina M. Johnsson et al study confirmed that genital infections such as vulvovaginitis in women and balanitis in men are well-known complications of T2DM [26].

Serge A. Jabbour et al study showed at week 48, genital infection was more frequent with Dapagliflozin (9.8%) than with placebo (0.4%), while urinary tract infection was equal in Dapagliflozin (6.7%) and placebo (6.2%) [23]. Increased glucosuria due to SGLT2 inhibitors increases the risk of genitourinary infections as per CANVAS program. Canagliflozin was associated with a higher risk of mycotic genital infection in women (represent 6.88%, $P < 0.001$) and infection of male genitalia (represent 3.49%, $P < 0.001$), compared to placebo [26]. However, in this study; there was only one female who suffered from genital infection (represents 0.6% of the total group population) from SGLT2 inhibitors group and one female (represents 0.7% of the total group population) from DPP-4 inhibitors group, similar to the data from Kristina M. Johnsson et al. [26].

Nauck MA et al study found that higher proportions of patients receiving Dapagliflozin suffered from genital infections or UTIs than Glipizide. About half of the genital infections were recurrent, whereas most UTIs were single episodes [20].

Virtue study during Ramadan fasting showed that 10.2% of the Vildagliptin group had adverse events versus 22.8% in SU group. And the main adverse events were hypoglycemia, nausea, vomiting, diarrhea, abdominal pain, and abdominal discomfort. One patient had a myocardial infarction resulting in death (SAE), and another had viral hepatitis [17].

All AEs occurred during this study were mild to moderate, and there was no reported SAE.

## 7. Conclusion

SGLT2 inhibitors (empagliflozin) are as safe and effective as DPP-4 inhibitors (vildagliptin) in managing diabetes mellitus type 2 during Ramadan; in decreasing HbA1C, in weight loss and did not induce hypoglycemia that stops patients from fasting or needed dose modification. The results of this research will also give attention to use this group of medications for diabetics during one day surgeries and with endoscopic examination that need long periods of fasting, to control their blood glucose without hypoglycemia or any other side effects.

## 8. Limitations

1) As the study is observational, there is no randomization.
2) Hypoglycemic episode was based on individual reporting, as one of the three patients who experienced hypoglycemic episodes, had blood glucose level more than 70mg/dl.
3) There was no specific diet or healthy lifestyle considering weight loss.

## 9. Recommendations

1) A randomized interventional study with a clear definition of the hypoglycemic episode, of adequate signs and symptoms and;
2) With a specific diet between all patients should be conducted.

## Conflicts of Interest

The authors declare that they have no competing interests.

## Author Contributions

Authors enrolled patients, collected data, carried out necessary assessments required for the study and filled in the CRFs of the patients. The corresponding author (Dr M. Hesham El Hefnawy) shared in study design and partially participated in CSR and manuscript writing.

The manuscript has been read and approved by all the authors and each author believes that the manuscript represents honest work, and the requirements for authorship have been met.

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