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**Safety and efficacy of the available oral anti diabetic drugs in treating type-2 diabetics during Ramadan1437(Hijri)fasting in Fayoum Governate**

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**ABSTRACT**

**Introduction :** Fasting in Ramadan is one of the five pillars of Islam. Without relevant medical advice and intervention, fasting can put patients with T2DM at an increased risk of serious complications. The aim of this study was to compare the effectiveness and safety of available oral anti diabetic drugs in treating type-2 diabetics during Ramadan fasting.

**Methods :** In this 16-week prospective study, data were collected up to 6 weeks before and after Ramadan fasting . Patients who had received metformin alone or with sulfonylurea (SU), DPP4-I or TZDs or any combination of the before were enrolled into the study.

**Results :** This study concluded that mean total HbA1c improved during Ramadan ( $P < 0.001$  ) . This study also found that patients treated with SUs experienced major hypoglycemic events Similarly, a fewer patients experienced weight gain when treated with TZDs. On the contrary we found that there was no evidence of hyperglycemia or hypoglycemia in patients using DPP4-I

**Conclusions:** There are several potential benefits of fasting during

Ramadan. Active glucose monitoring throughout the holy month of Ramadan enabled us to pick up more hypoglycaemic episodes. The study revealed that the preferred antidiabetic drugs during Ramadan are DPP4-I.

**Keywords: DPP4 inhibitors; hypoglycemia; sulphonylureas; type 2 diabetes mellitus; TZDs; metformin**

## INTRODUCTION

The global prevalence of diabetes is worryingly high and continues to grow, particularly in the emerging economies (1), including those with large Muslim populations. According to the International Diabetes Federation, four of the world's top 10 countries for the highest prevalence of diabetes are in the Middle East and North Africa region (2).

The prevalence of diabetes mellitus has been increasing in Egypt. In 2014, over 7.5 million people (aged 20–79 years) were suffering from diabetes in Egypt and this number is expected to increase to 13.1 million by the year 2035 [3, 4]. Approximately, over 80 million people in Egypt are Muslims and the majority of them choose to fast during Ramadan [5]

Fasting during Ramadan, a holy month of Islam, is an obligatory duty for all healthy adult Muslims, a period when adult Muslims abstain from food, water, or use of oral medications between dawn and sunset for between 29 and 30 days each year (6). Fasting is not meant to create excessive hardships for an individual; the Quran exempts some Muslims from fasting, which include pregnant or lactating women, the sick, and the elderly [7]. Consequently, both religious and medical advice suggests that people with diabetes should not fast since it could adversely affect their metabolic condition. In people with diabetes, the pattern of daytime fasting and nighttime meals, together with the use of anti-diabetic treatment, increases the risk of complications, including hypoglycaemia (8–10), which has a negative impact on morbidity, mortality and quality of life

Several Muslims are unaware of the possible complications of fasting, which include hyperglycemia, hypoglycemia, and increased risk of dehydration and thrombosis [11, 12]. The EPIDIAR study highlighted an increased risk of severe hypoglycaemia in people with T2DM fasting during Ramadan compared with other months of the year [13]. This can lead to

discontinuation of medication and/or over-compensating when fast is broken, leading to hyperglycaemia [8]. A number of clinical guidelines for people with diabetes who choose to fast have been published [8,10,14-16], but these recommendations are largely based on expert consensus and many health professionals feel poorly qualified to provide some of the recommendations. It is paramount that health professionals respect their patient's choice to fast whilst simultaneously using their knowledge, based on best evidence, to provide them with the safest management and treatment options.

The aim of this study was to evaluate the safety and efficacy of the available oral anti diabetic drugs in treating type-2 diabetics during Ramadan1437(Hijri)fasting.

## **METHODS**

### **Study Design and Patients**

This study was a prospective, observational study conducted in Egypt (fayoum) .This study included 404 subjects fulfilling the inclusion criteria that were: Type-2 DM patients Muslims aged from 18 to 65 years, who are legible to fast and willing to fast , whose disease duration ranging from 3 month up to 10 years, who are using metformin alone or with SUs, DPP4-I or TZDs or any combination of the above mentioned medications.

The study excluded: Patients with Type -1 DM. Age less than 18 years. Pregnant or lactating women. Uncontrolled type 2 diabetics (HbA1c>9). Patients with recurrent hypoglycemia or severe hypoglycemia during the last 2 months before Ramadan. High risk patients and very high risk patients . Patients using herbal therapy for diabetes treatment or those on weight loosing medications.

The study consisted of a 16-week observational period that included a fasting period of approximately 4 weeks. During this observational period, data from each patient were collected from at least two visits: at baseline (up to 6 weeks prior to the start of fasting, pre-Ramadan) , and at the end of

study (within 6 weeks after the end of fasting , post-Ramadan) . In addition, data were collected if the patient made an interim visit during the fasting period.

### **1-Before Ramadan:**

The dose of the oral medications would be modified before Ramadan to ensure better safety and efficacy during fasting .

### **Then patients categorized into 5 groups:**

**Group 1:** Patients using metformin

**Group 2:** Patients using sulphonylureas with or without metformin

**Group 3:** Patients using DPP4-I with or without metformin

**Group 4:** Patients using TZD with or without metformin

**Group 5:** Patients using any combinations of the above

At the initial visit, patient's data would be collected including age, gender, duration of diabetes, type, dosage and timing of oral medication. Also blood pressure, waist circumference and body weight would be measured and would be repeated after Ramadan. Blood sugar, HbA1c would be measured before and also after Ramadan fast.

Patients who would develop or had any of the exclusion criteria at any stage or any time of the study would be excluded.

### **2-During Ramadan:**

All patients would be advised to measure their blood sugar regularly and to record any blood sugar levels that is above 300 or below 70 or if any significant hypo or hyperglycemic symptoms (explained during the education session ). Also the patients would record any day that fast is broken and would record the cause for this.

The participants would be asked to record readings for the FBS at noon & at 6 pm and a postprandial reading 1 -2 hours after breakfast on the following days (Second day of Ramadan, mid Ramadan and near the end of Ramadan)

### **3-After Ramadan:**

Re-evaluation of the patient's blood pressure waist circumference and body weight would be done. Also, re-evaluation of Glycemic control( HbA1c ).

### **Statistical Analysis**

- Data was collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 under windows 7.
- Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test:

#### **For quantitative parametric data:**

- In-dependent student t-Test used to compare measures of two independent groups of quantitative data.

**Bivariate pear son correlation test** to test association between variables

- The level  $P \leq 0.05$  was considered the cut-off value for significance .

## **RESULTS**

### **Patient demographics and baseline characteristics**

The demographic and baseline characteristics of the patients by treatment group are presented in Table 1 . Overall ,approximately58.9% were females and 41.1% were males. Regarding the smoking, there were 1.7% of the studied population were smokers and 98.3% were nonsmoker.

Regarding the history of hypertension ,there were 31.7% of the studied population were hypertensive ,while about 3.7%of the studied population had ischemic heart disease

Regarding the obesity, there were 24.7% of the studied population were obese across subgroups of therapy type and age (**Table1**). Overall, the median daily dose of each treatment was the same at the beginning and end of Ramadan

### **Weight changes from pre to post Ramadan**

By comparing weight changes in individual groups, there was significant increase in weight (P value **0.005**) after Ramadan in group 4 while there were no significant changes among the other groups ( **Table 2**).

**Table (1): Demographic and baseline characteristics of patients**

variable	N (%) Mean ± SD
<b>Age</b>	50.7 ± 10.8
<b>Sex:</b>	
• Male	166 (41.1)
• Female	238 (58.9)
<b>Diabetes duration</b>	4.4 ± 4.3
<b>Smoking:</b>	
• Smoker	7 (1.7)
• Non smoker	397 (98.3)
<b>Co-morbidities:</b>	
• HTN	128 (31.7)
• IHD	15 (3.7)
• Obesity	100( 24.7)
<b>Hypoglycemic drugs:</b>	
• metformin	<b>64</b> ( 15.8)
• sulphonylureas with or without metformin	80( 19.8)
• DPP4-I with or without metformin	69( 17. 1)
• TZD with or without metformin	61(15.1)
• any combination of the above	130( 32.1)

**Table (2):** Weight changes from pre to post Ramadan

Variable		Group I (N=64)	Group II (N=80)	Group III (N=69)	Group IV (N=61)	Group V (N=130)
		Mean ± SD				
Weight	before Ramadan	91.66 ± 19.16	84.87 ± 15.24	95.61 ± 13.79	80.45 ± 13.79	88.81 ± 21.42
	after Ramadan	92.19 ± 18.53	84.44 ± 15.79	92.33 ± 23.42	81.87 ± 13.54	87.84 ± 18.51
P-value		0.382	0.533	0.126	<b>0.005*</b>	0.288

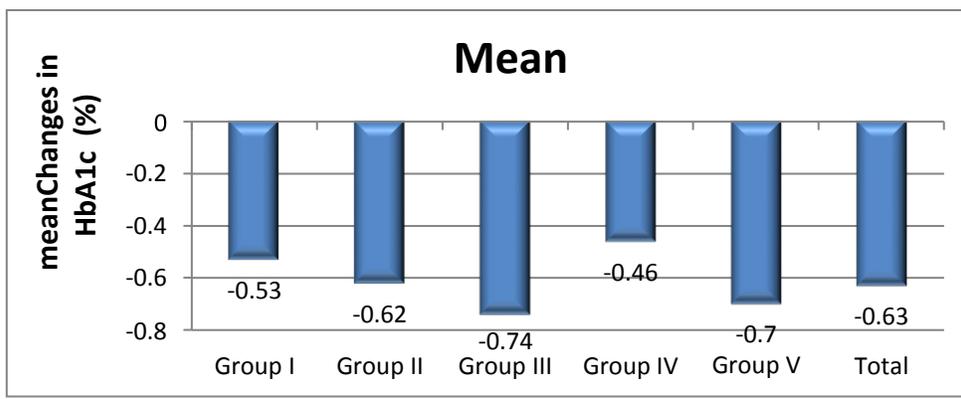
\*Significant

**HbA1c changes from pre to post Ramadan**

The study showed that mean total HbA1c improved from  $8.17 \pm 2.05$  before Ramadan to  $7.54 \pm 1.37$  after Ramadan ( $P < 0.001$ ).

Metformin, was associated with a reduction in mean (SD) HbA1c from prefasting baseline levels to the end of the study ( $-0.53$ ). In comparison, mean (SD) HbA1c at the end of the study with SU as both monotherapy and dual therapy with metformin had more reduction from baseline by ( $-0.62$ ).

While the combination of treatment and TZDs with or without metformin were associated with reduction by ( $-0.70$  and  $-0.46$ ) respectively. DPP4-I was also associated with numerically greater reductions in HbA1c ( $-0.74$ ) (Figure (1)).



**Figure (1):** the mean change in HbA1c among the study groups

## Differences in measurements of blood sugar at different times during Ramadan according to study groups

### **Pattern of measurements of fasting blood sugar**

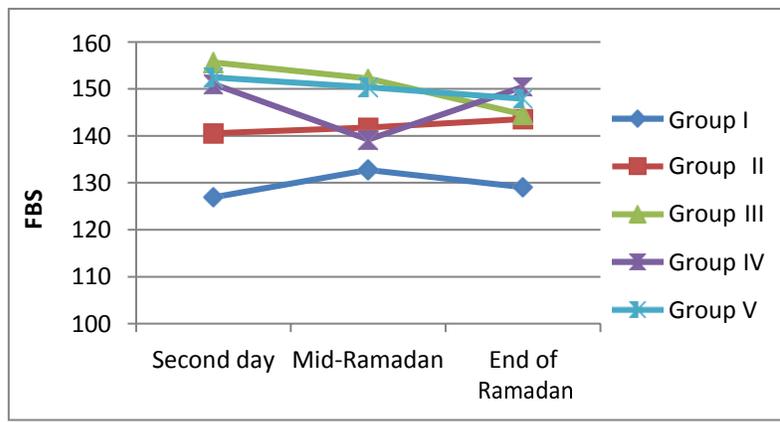
By comparing fasting blood sugar, the highest value was found in group 3 but there were significant decrease in blood glucose levels between the three days (2nd, mid, & end of Ramadan) in FBS (P value **0.031**) and the lowest value was found in group 1. There was also a significant decrease in FBS readings in group 4 from 2nd day of Ramadan to Mid Ramadan. However, these reductions were not sustained and increased in the end-Ramadan period. (P value **0.015**).

### **Pattern of measurements of before iftar blood sugar**

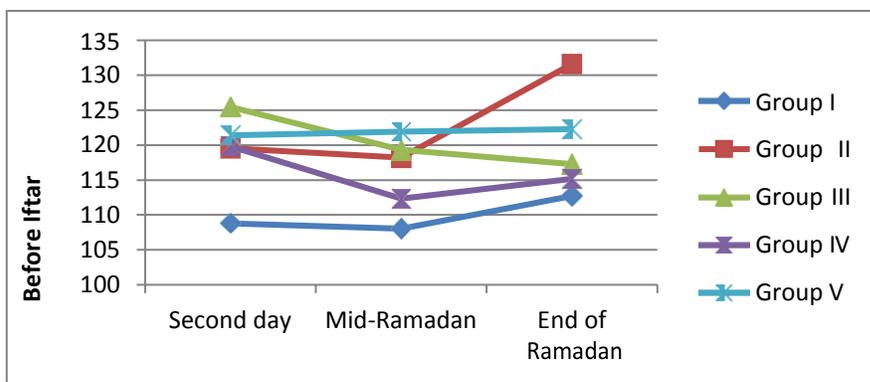
By comparing before iftar blood sugar, There were significant decrease in before iftar blood glucose levels in group 3 between the three days (2nd, mid, & end of Ramadan) (P value **0.050**), and the lowest value was found in group 1.

### **Pattern of measurements of post prandial (pp)blood sugar**

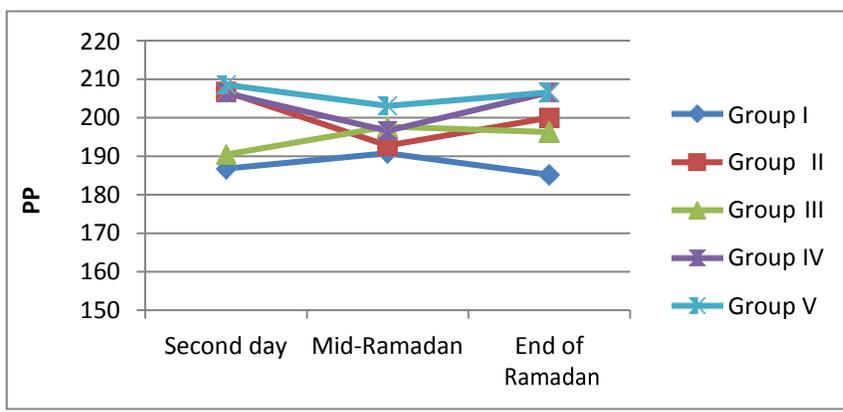
By comparing post prandial (pp)blood sugar, the highest value was found in group 5 and the lowest value was found in group 1.



**Figure (2):**Pattern of measurements of fasting blood sugar during Ramadan according to study groups



**Figure (3):**Pattern of measurements of before iftar blood sugar during Ramadan according to study groups



**Figure (4):**Pattern of measurements of post prandial (pp)blood sugar during Ramadan according to study groups

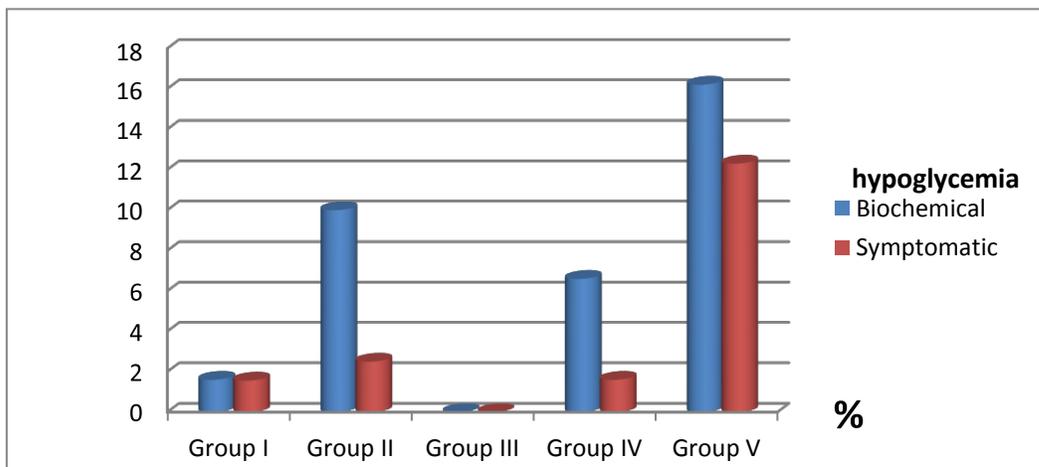
### Incidence of Hypoglycemia.

Active glucose monitoring throughout the holy month of Ramadan enabled us to pick up more hypoglycaemic episodes (34 episodes) that were asymptomatic ( biochemical) and did not require active intervention and about 20 episodes of symptomatic hypoglycaemia,

The incidence of hypoglycemia was analyzed according to the therapy type, incidence of biochemical and symptomatic hypoglycemia were higher in group 5 (16,2 %and12,3% respectively)then group2(10%and2,5%respectively), while there were no hypoglycemic events neither biochemical nor symptomatic in group3 ( **Figure 5**)

### Incidence of Hyperglycemia

Similarly, 19 episodes of hyperglycaemia were detected .The incidence of hyperglycemia was analyzed according to the therapy type ,the highest incidence of hyperglycemia occurred in group 5 ( 11 patients) and 2 patients of them had complications ,came after them patients in group 4 ( 4patients) who experienced hyperglycemia with no complication ,while in group 2 (2 patients)experienced hyperglycemia and one of them had complication. on the contrary there was no evidence of hyperglycemia in group 3(Figure 6 ).



**Figure (5):**Incidents of hypoglycemia in different groups

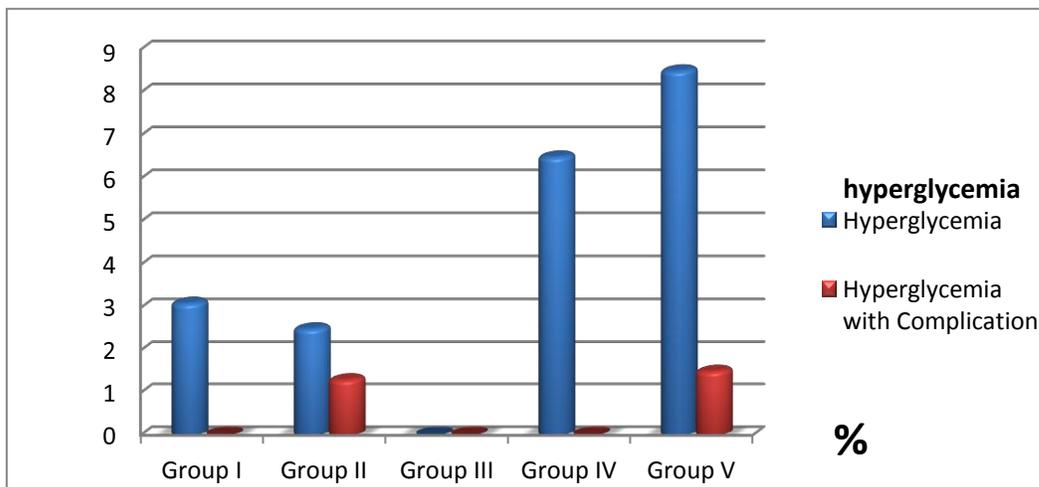


Figure ( 6):Incidents of hyperglycemia in different groups

### Percentage of patients who broke their fasting in Ramadan in different groups

Percentage of patients who broke their fasting in Ramadan in different groups was about 10.6%.the highest percentage was found in group 5,came after them group2 and the lowest percentage was found in group 1.

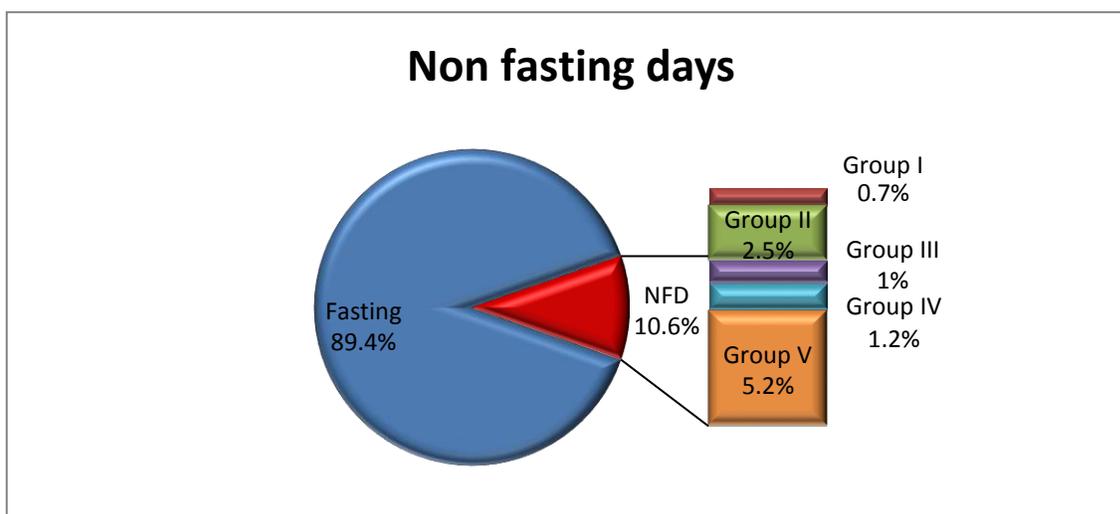


Figure (8):Percentage of patients who broke their fasting in Ramadan in different groups

### DISCUSSION

This prospective, observational study aimed to study the safety and efficacy of the available oral anti diabetic drugs in treating type-2 diabetics during Ramadan fasting.

The changes in dietary patterns during Ramadan and the short study duration make it difficult to draw definitive conclusions from body weight changes in this analysis .Nevertheless, this study showed that significant increase in weight from pre fasting baseline in Patients using TZDs with or without metformin(P value< **0.005** ) . This finding is similar to this study that

reported that Pioglitazone significantly increases body weight compared with placebo(17).

Also this study showed that no significant body weight changes among those groups of patients receiving Metformin alone or with sulphonylureas, DPP4-I or any combinations of the above (group1,2,3,5).

Similar findings have been reported with this study that reported that body weight remained unchanged in both groups that receiving sulphonylureas and DPP4-I vildagliptin(18) .

On the contrary prospective study conducted in countries in the Middle East and Asia reported that small reductions in body weight from pre fasting baseline were reported in all therapy type and age subgroups of patients receiving vildagliptin, with a trend for numerically greater reductions in body weight relative to SU treatment across all subgroups(19).

While comparing the level of HbA1c prior and post fasting we found improvement of the total mean of HbA1c from 8.17 %before Ramadan to7.54 %after Ramadan ( $P < 0.001$ ), This finding is in agreement with previous study that found that the mean HbA1c significantly improved from 8.9% before Ramadan to 8.6% during Ramadan ( $P < 0.05$ ) (20).

This study also showed that Metformin, was associated with a reduction in mean (SD) HbA1c by (-0.53 ). In comparison, mean (SD) HbA1c at the end of the study with SU as both monotherapy and dual therapy with metformin had more reduction from baseline by(- 0.62 ).

While the combination of treatment and TZD with or without metformin were associated with reduction by(-0.70 and -0.46 ) respectively. DPP4-I was also associated with numerically greater reductions in HbA1c (- 0.74%)

However, the duration of the study is rather short to firmly conclude that groups of drugs achieved its maximum HbA1c lowering effect. It is important to note that fasting can affect glycemic control too.

These results were consistent with other studies conducted in fasting patients with T2D M [ 18, 19 ].

This study illustrates that incidence of biochemical and symptomatic hypoglycemia were higher in group 5 who using any combination of therapy (16.2 % and 12.3% respectively) followed by group 2 who using SU therapy (10% and 2.5% respectively) while there was no hypoglycemic events in patients using DPP4-I.

These findings are similar to those reported in the larger pooled analysis of the VIRTU E study [5.4% vs. 19.8% with vildagliptin (n = 669) and SU (n = 621), respectively] [ 19 ]. In the randomized, controlled trial Study Evaluating vildagliptin compared to gliclazide in patients with type 2 diabetes fasting during Ramadan (STEA DFAST; Clinical Trials .gov identifier, NCT0 1758380 ), the risk of hypoglycemia was lower with vildagliptin than gliclazide; however, the difference was not statistically significant [21]. The authors attributed the small difference to the controlled conditions, where in patients received special attention in terms of good advice, treatment, and glycemic control, and therefore did not emulate a real-life setting, as observed in the VIRTU E study [19 ]. In addition, another randomized study reported no statistically significant difference (p = 0.334 ) in HEs between vildagliptin-treated patients and SU-treated patients during Ramadan which could be due to the timely follow-up with patients or change in their dietary habits during the fasting month [22 ]

The present results also concur with the findings in these studies, vildagliptin consistently showed a lower incidence of hypoglycemia compared with SUs (including glimepiride, gliclazide, glibenclamide, and glipizide). Vildagliptin also showed better treatment adherence and improved glycemic control as compared to SUs when administered as dual therapy with metformin [ 18,19,23-26 ]

DPP-4 inhibitor improves glycemic control by modulating insulin and glucagon secretion in a glucose-dependent manner and is associated with low risk of hypoglycemia and weight gain in clinical trials (27).

Similarly, the highest frequency of hyperglycaemic episodes seen in patients who had poor glycaemic control pre-Ramadan.

This study also illustrates that the highest incidence of hyperglycemia occurred in group 5 ,came after them patients in group 4 ,while in group 2 . On the contrary there was no evidence of hyperglycemia in group 3.

This results were consisted with the previous study that reported that the favorable outcome observed during fasting is due to the suppression of inappropriate glucagon secretion during hyperglycemia as well as the enhancement of glucose-dependent insulinotropic polypeptide (GIP)-mediated effect on glucagon, which results in protection against hypoglycemia. The levels of both glucagon-like peptide-1 (GLP-1) and GIP remain high during the inter-meal and overnight periods, when hypoglycemia is more likely to occur. (28).

In this study , the number of patients who breaked their fasting were 43 patients ,the majority of patients were found in group 5 followed bygroup2 On the contrary the minority of patients were found in group1&3 .This result goes with the study which found that the average number of days fasted in vildagliptin group was higher than gliclazide . (25).

### **Conclusions:**

Treatment with DPP4-I was associated with lower incidence of hypo glycemia when compared with other medications in patients who fast during month of Ramadan . Furthermore, DPP4-I showed good glycemic and weight control and was well tolerated in patients with T2 DM fasting during Ramadan .

### **CONSENT**

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

### **ETHICAL APPROVAL**

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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