# Safety and Efficacy of The Available Oral Anti diabetic Drugs In Treating Type II Diabetics During Ramadan Fasting In Sohag Governorate.

**Mahmoud Khalifa Eissa, Dr. Mohamed Abdel wahab Ezzat, Dr. Yasser Mohamed Kamal, Prof. Adel Abdel Aziz El Sayed.**
Internal Medicine Department, Faculty of Medicine, Sohag University.

## Abstract

**Objective**: to assess safety and efficacy of the available oral anti diabetic Drugs during Ramadan 2016 in Sohag Governorate .

**Methodology**: This study was conducted on 90 type II Diabetic patients attending to outpatient Endocrinology clinic in Sohag University Hospital, on oral treatment classified into 5groups,as following , 20 (22.22%)patients on Metformin(Group I),30 (33.33%)patients on Sulphonylureas with or without metformin(Group II), 18 (20%) patients on Dipeptidyl peptidase-4 inhibitors with or without metformin (Group III),12 (13.33% ) patients on Thiazolidinedoines with or without metformin (Group V),10 (10%) patients on combinations of more than two drugs (Group VI), Mean age of patients is 59.93±7.87years, (61.11%)of them were females,(38.89%) of them were male patients and Mean duration of diabetes is 4.52±2.45(range 1:10).follow up of the patient was done by Wight changes, measuring blood sugar ,asses Hba1c ,and renal function also was done before and during ramadan.

**Results**:  In this  study we found a significant decrease in Hba1c after Ramadan with Group III (DPP4I) compared  with other Groups also we found the number of hypoglycemic episodes of all groups about 10 (11.11%), more with Group II (SUs) about (9) patients developed hypoglycemia of whom 30, compared with other groups while lower number of hypoglycemia was found with Group III (DPP4I),about one patient developed hypoglycemia, also we found  the number of non fasted days more with SUs,(range 2-10) also we found no body weight changes more with Group III (DPP4I) while body weight gain occurred with Group II (SUs) about 1-4Kgs .

**In conclusion,** Ramadan represents one of challenging issues for health care providaers all over the world . DPP4 inhibitors may considered favorable for use during and after Ramadan due to their lower rate of hypoglycemic events and weight neutral/loss effect during and after Ramadan .

**Key words**: Ramadan Fasting, RBS,DPP4I ,SUS,METFORMIN ,TZD, Combinations, Wieght, Hba1c.

## Introduction

Fasting during Ramadan, a holy month of Islam, is an obligatory duty for all healthy adult Muslims. Around 9 % is the prevalence of diabetes worldwide and the estimated number of diabetic patients reached more than 4 hundred millions according to the latest edition of the IDF diabetes Atlas.   Egypt has 8th highest rate of diabetes (7.8 millions) globally and is the first in the Arab world and in Africa,(**1**).Many patients with diabetes insist on fasting during Ramadan, thereby creating a medical challenge for themselves and their physicians. It is therefore important that medical professionals be aware of

potential risks that may be associated with fasting during Ramadan(**2**).

**Aim of the study:** The aim of this study is to assess safety and efficacy of the available oral antidiabetic Drugs during Ramadan 2016 in Sohag Governorate.

**patients and Methods:** This study was included 90 patients fulfilling the **inclusion criteria** that was :

1. TypeII DM patients
2. Muslims
3. aged from18 to 65  years, who are legible to fast and willing to fast ,
4. whose disease duration ranging from 3 month up to 10 years,
5. who are using Oral Drugs as (metformin alone or with sulphonylurea,dipeptidyl peptidase-4 inhibitors or thiazoledine diones or combinations of more than two drugs)

 **Exclusion Criteria:**

1. Uncontrolled type II diabetics
2. Patients with recurrent hypoglycemia or severe hypoglycemia during the last 2 months before Ramadan.
3. High risk patients.
4. Patients with Type -1 DM.
5. Age less than 18 years.
6. Pregnant  or lactating women.
7. Patients using  Insulin therapy or herbal therapy or those on an extraordinary diet or exercise or those on weight loosing medications.

Patients' selection and enrolment (after obtaining informed written consent) started before the start of next Ramadan fast in Ramadan 2016.

**1-Before Ramadan:**  All participants had a structured educational session targeting safe fast.  All patients were given a diary to facilitate recording of blood glucose readings and adverse events and also aglucometer for self blood glucose monitoring. The dose,the oral medications were modified just before Ramadan to ensure better safety and efficacy during fasting .  All the patients were  instructed clearly to break or to stop fast if the blood glucose is lower than 70 mg / dl  (or there significant hypoglycemic symptoms) also if the blood sugar is more than 300 mg / dl  or if there is any chest pain , dyspnea, palpitation .

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

**Group** I: Patients using metformin alone

**Group** II**:** Patients using  sulphonylurea with or without Metformin

**Group** III**:** Patients using Dipeptidyl peptidase-4 inhibitors

**Group** V**:** Patients using Thiazolidinedoines with or without Metformin

**Group** VI**:** Patients using combinations of more than two drugs .

At the initial visit, patient's data was collected including age, gender, duration of diabetes, type, dosage and timing of oral medication .  Also blood pressure, waist circumference and body mass index was  measured and was repeated after Ramadan. Blood sugar, Hba1C and serum creatinine was measured before and  also after Ramadan fast.. Patients who developed or had any of the exclusion criteria at any stage or any time of the study was excluded.

**2-During Ramadan:** All patients were advised to measure their blood sugar regularly and to record any blood sugar levels that is above 300mg/dl or below 70 mg/dl or if any significant hypo or hyperglycemic symptoms (explained during the education session ). Also the patients recorded any day that fast was broken and recorded the cause for this. The participants were asked to record readings for the FBS at noon & at 6 pm and postprandial reading 2hours 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 mass index was done. Also re-evaluation of Glycemic control, HbA1c,serum creatinine .

## Results

The Study was conducted on 90 type Diabetic patients attending to outpatient Endocrinology clinic in Sohag University Hospital, on oral treatment classified into 5groups,as following ,20 patients (22.22%) on Metformin (group I),30 patients (33.33%) on Sulphonylureas with or without metformin (Group II), 18 patients (20%) on Dipeptidyl peptidase-4 inhibitors with or without metformin (Group III),12 patients (13.33% ) on Thiazolidinedoines with or without metformin (Group IV),10 patients (10%) on combinations of more than two drugs (Group V), As showing in table(1) ; Mean age of patients is 59.93±7.87years, (61.11%)of them were females,(38.89%) of them were male patients and Mean duration of diabetes is 4.52±2.45(range 1:10) .

**by assessing weight before and after Ramadan in all groups but there wasn't any significant changes in body weight except in group II and group V as showing in table (1)Table (1)Comparison among different groups according to weight**

| Variable | Group I | Group II | Group III | Group V | Group VI | Total |
|---|---|---|---|---|---|---|
| Weight before Ramadan Mean ± SD Median | 82.65±7.16 85 | 80.7±9.82 80 (65:95) | 78.06±6.47 75.5 | 85.92±11.27 90 (65:97) | 78.2±8.78 85 | 81.01±8.96 82.5 |
| Weight after Ramadan Mean ± SD Median | 82.45±7.46 85 | 81.07±9.74 80.5 | 78.17±6.59 75 | 85.08±11.89 90) | 79.6±8.30 85 | 81.17±8.95 82.5 |
| P comparing before & after | 0.16 | 0.09 | 0.43 | 0.17 | 0.001 | 0.24 |
| Change in weight Mean ± SD | -0.2±0.62 0 (-2:1) | 0.4±1.25 0 (-2:3) | 0.11±0.58 0 (-1:2) | -0.83±1.95 0 (-5:0) | 1.4±0.97 2 (0:2) | 0.16±1.25 0 (-5:3) |

by assessing  HbA1C before and after Ramadan in all groups and by compare different pairs of groups according to HbA1C change there was significant changes at group Ⅴ by comparison with group Ⅰ and group Ⅱ**.** Also there was slightly significant changes at group Ⅵ by comparison with group Ⅰ and group Ⅱ as showing in  table  (2).Table  (2)Comparison different  groups  according  to Hba1c

| Variable | Group I | Group II | Group III | Group V | Group VI | Total |
|---|---|---|---|---|---|---|
| HbA1C  before Ramadan Mean ± SD Median | 7.57±1.29 7.2 (5.7:10.5) | 8.69±2.11 8.2 (5.6:14.5) | 7.2±1.03 7 (6:10.5) | 8.33±1.81 7.6 (7:11.3) | 6.94±1.38 7 (5.2:8.6) | 7.9±1.75 7.3　(5.2 :14.5) |
| HbA1C    after Ramadan Mean ± SD Median | 7.60±1.24 7.3 (5.9:10.3) | 8.73±2.07 8.2 (5.7:14.5) | 7.04±0.95 6.95 (6:10) | 8.30±1.83 7.5 (6.9:11.3) | 6.87±1.27 6.9 (5.3:8.4) | 7.88±1.74 7.3 (5.3:8.4) |
| P    comparing before & after | 0.25 | 0.11 | 0.02 | 0.04 | 0.11 | 0.19 |
| Change    in HbA1C Mean ± SD Median | 0.03±0.11 0 (-0.2:0.2) | 0.04±0.13 0 (-0.2:0.3) | -0.16±0.25 -0.1　(-0.5:0.4) | -0.03±0.05 0 (-0.1:0) | -0.07±0.13 -0.1　(-0.2:0.1) | -0.02±0.17 0 (-0.5:-0.4) |

And by comparison among all groups according to non-fasting day and complications as hypoglycemia was found that occurrence of them with group Ⅱ more than with others groups as showing in table (3,4)

Table(3)Comparison among different groups according to non-fasting day and complications

| Variable | Group I | Group II | Group III | Group V | Group VI | Total | P value |
|---|---|---|---|---|---|---|---|
| Non    fasting days Mean ± SD | 4.0±1.41 | 4.57±2.88 | 1.5±0.71 | 2.0±0 | 0 | 3.5±2.4 | 0.053 |
| Hypoglycemia No Yes | 20 (100%) 0 | 21 (70.00%) 9 (30.00%) | 17 (94.44%) 1 (5.56%) | 12 (100%) 0 | 10 (100%) 0 | 80 (88.89%) 10 (11.11%) | 0.002 |
| Hyperglycemia No Yes | 18 (90.00%) 2 (10.00%) | 27 (90.00%) 3 (10.00%) | 16 (83.33%) 2 (11.11%) | 10 (83.33%) 2 (16.67%) | 6 (60.00%) 4 (40.00%) | 77 (85.56%) 13 (14.44%) | 0.18 |

**Table (4)**P values of comparison of different pairs of groups according to Hypoglycemia

|  | **Group** I | **Group** II | **Group** III | **Group** V | **Group** VI |
|---|---|---|---|---|---|
| **Group** I | 1.00 |  |  |  |  |
| **Group** II | 0.007 | 1.00 |  |  |  |
| **Group** III | 0.47 | 0.07 | 1.00 |  |  |
| **Group** V | 1.00 | 0.04 | 1.00 | 1.00 |  |
| **Group** VI | 1.00 | 0.08 | 1.00 | 1.00 | 1.00 |

## *Discussion:*

This study was conducted on 90 type II Diabetic patients attending to outpatient Endocrinology clinic in Sohag University Hospital, on oral treatment classified into 5groups,as following , 20 (22.22%)patients on Metformin(**Group**I),30 (33.33%)patients on Sulphonylureas with or without metformin(**Group** II), 18 (20%) patients on Dipeptidyl peptidase-4 inhibitors with or without metformin (**Group** III),12 (13.33% ) patients on Thiazolidinedoines with or without metformin (**Group** V),10 (10%) patients on combinations of more than two drugs(**Group** VI), Mean age of patients is 59.93±7.87years, (61.11%)of them were females,(38.89%) of them were male patients and Mean duration of diabetes is 4.52±2.45(range 1:10) .

In this study we found a significant decrease in Hba1c after Ramadan with **Group** III (DPP4I) compared with other Groups also we found the number of hypoglycemic episodes of all groups about 10 (11.11%), more with **Group** II (SUs) about (9) patients developed hypoglycemia of whom 30, compared with other groups while lower number of hypoglycemia was found with **Group** III (DPP4I),about one patient developed hypoglycemia, also we found the number of non fasted days more with SUs,(range 2-10) also we found no body weight changes more with **Group** III (DPP4I) while body weight gain occurred with **Group** II (SUs) about 1-4Kgs .

This study supported with the same result as was in :

In STEADFAST study (randomized study)**,(3).**that was done on 557 pts in Middle East(>50%) ,in 2010, Europe and Asia this study showing good control of HBA1C with vildagliptin (DPP4I) rather than sulfonylurea with or without metformin and hypoglycemic event more with Sus .this study comparison only between DPP4I and Sulphonylureas with or without metformin , also other studies showing the same results as in,

In Diabetic patient fasting during Ramadan (TEN YEARS OVER VIEWS STUDIES) **,(3,4,5,6,7,8,9,10)**.( 5 studies non randomized was done in Isreal 2005 to 2015,showing comparison only between DPP4I and Sulphonylureas.,

In VECTOR study**,(11)**.(Seventy-two patients were enrolled (vildagliptin, n = 30; SU, n = 41; no treatment, n = 1),in 2011 ,of whom 23 (76.7%) and 36 (87.8%), respectively, completed the study. With vildagliptin, there were no HEs(hypoglycemic events) or severe HEs, compared with 34 HEs (15 patients, 41.7%) and one severe (grade 2) HE with SUs. The mean between-group difference in the proportion who experienced at least one HE was −41.7% (95%CI −57.8%, −25.6%), p = 0.0002. Vildagliptin lowered mean HbA1c from 7.6% (SD 0.9%) at baseline to 7.2% (SD 0.7%) post-Ramadan, where as SUs had no

effect (7.2% [SD 0.6%] vs 7.3% [SD 0.7%]; mean between-group difference −0.5% [95% CI −0.9%, −0.1%], p = 0.0262). The mean number of missed doses was markedly lower with vildagliptin (0.2 [SD 0.8] vs 7.6 [SD 14.9]; mean between-group difference −7.4 [95% CI −13.7, −1.20] doses; p = 0.0204). Body weight remained unchanged in both groups),

In aFive –country observational study,**(12)**.(was done in 2009 in India, Malaysia. ,Isreal, United Arab Emirates and Saudi Arabia), Of the enrolled subjects (N = 1397), 1378 returned their diary cards at study end and were included in the analysis. Overall, 89% of subjects who expressed their intention to fast prior to Ramadan reported that they observed the fast during Ramadan. A total of 271 subjects (19.7%) experienced one or more symptomatic hypoglycaemic events during Ramadan, with incidences of 25.6%, 16.8%, and 14.0% observed in subjects treated with glibenclamide, glimepiride, and gliclazide, respectively. By country, the highest incidence of hypoglycaemia was reported by subjects from Israel (40%) followed by those from Malaysia (24%), the UAE (18%), India (13%), and Saudi Arabia (10%). The overall incidence of severe hypoglycaemic events (i.e., events requiring medical or non-medical assistance) was 6.7%, with the highest incidence occurring in the glibenclamide group) ,this study differ from our study in , this study was done only on one group,(patients using sulphonylureas with or without metformin),while this study was done on 5 groups (patients using metformin ,sulphonylureas ,DPP4I,TZDS,and combination of more than two drugs ).

In vildagliptin therapy and hypoglycemia in Muslims type II during Ramadan study. **(13)** ,( during Ramadan , in North West London 2009

,at least one hypoglycaemic event (defined as blood glucose < 3.5 mmol/l with or without symptoms) was recorded in two patients receiving vildagliptin (7.7%) and 16 patients receiving gliclazide [61.5%; difference between groups −53.8%, 95% confidence interval (CI) −74.9 to −26.3, p < 0.001]. Vildagliptin was associated with a reduction in the mean number of hypoglycaemic events during Ramadan compared with before Ramadan, whereas gliclazide was associated with an increase (least squares mean difference between groups −0.66, 95% CI −1.20 to −0.13, p = 0.0168). Both gliclazide and vildagliptin were associated with similar reductions in Hba1c and a small, but insignificant, increase in weight).

In study of safety and efficacy of dpp4i and metformin as initial combination therapy and as a mono therapy in patient with type II DM,(14) China 2013, showing more reduction in Hba1c , body weight and no hypoglycemic event with combination therapy than metformin alone .,

in this study we found no changes in Hba1c ,body weight with metformin alone and we found low significant reduction with combination may be due to miss use of drugs during Ramadan , this study differ in which not in fasting days not in Ramadan,

In EPIDIAR study ,**(15).** (this study on type I and type II diabetes patients ,using insulin and oral therapy ) Investigators recruited 1,070 (8.7%) patients with type 1 diabetes and 11,173 (91.3%) patients with type 2 diabetes. During Ramadan, 42.8% of patients with type 1 diabetes and 78.7% with type 2 diabetes fasted for at least 15 days. Less than 50% of the whole population changed their treatment dose (approximately one-fourth of patients treated with oral anti

**388**

diabetic drugs [OADs] and one-third of patients using insulin). Severe hypoglycemic episodes were significantly more frequent during Ramadan compared with other months (type 1 diabetes, 0.14 vs. 0.03 episode/month, P = 0.0174; type 2 diabetes, 0.03 vs. 0.004 episode/month, P < 0.0001). Severe hypoglycemia was more frequent in subjects who changed their dose of OADs or insulin or modified their level of physical activity).this study differ from our study ,this study was done on patients using insulin and oral drugs.

In this study there was no significant changes in diastolic or systolic blood pressure pre or post Ramadan fasting as this result not studied drugs affect blood pressure .

in this study there is no significant changes in s. creatinine except with group3 and group4 may be due to dehydration and summer.

Many of previous studies  discuss comparisons between safety and efficacy of DPP4I and sulphonylureas during Ramadan ,while this study discuss safety and efficacy mostly of oral drugs as (METFORMIN ,DPP4I ,TZD ,SULPHONYLUREAS AND COMBINATIONS). In this  study TZD not as same as DPP4I but showing reduction in HBA1C after Ramadan, also patients on combination therapy showing weight body reduction after Ramadan .

in this study hyperglycemia was observed with all groups about 13 (14.44%).

In a study of Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations ,(16), in 2011 ,in Europe,  showing more reduction in Hba1c with combination therapy  than mono therapy  also weight reduction and hypoglycemia , as  in this study

showing Hba1c showing reduction with combination therapy .

**Limitations:** This was an observational study and as such subjects were not randomized to treatments. While baseline measures appeared comparable, it is possible that differences in measured and unmeasured patient characteristics (e.g., measures of glycemic control) could partially explain these results. this study leak observation and follow up of diet and exercise and there effect on diabetic patients during Ramadan, also our study included small number of patients .

**Conclusion:** Ramadan represents one of the challenging issues for health care providers all over the world. DPP-4 inhibitors may considered  favorable for use during and after Ramadan due to their lower rate of hypoglycemic events and weight neutral/loss effect during and after Ramadan. ,estimate significant abnormality. As regard number of hypoglycemic events mostly in group II (sulphonylureas) 9 patients have hypoglycemia from30 patients and range of non-fasted days with the same group was (2:10).also hyperglycemia was found with all groups ,13patients (14.44%) . with analysis of   HBA1C ,improvement mostly was group 3 more than other groups. also with analysis body weight change,   showing   little   changes especially with group 2 (SUs) on other hand about 80%  no body changes with other   groups.   with   analysis   of s.creatinine   significant   changes occurred with dpp4i and combinations drugs

# References:

1.  Diabetes Atlas 7th Edition , December 2015   (IDF congress, Vancouver , Canada)
2.  Al-Arouj M, RadhiaBouguerra, JohnBuse, SherifHafez,et   al.,Recommendations for   Management   of   DM   During

Ramadan Diabetes Care ( 2005 )vol. 28 no. 9 2305-231

3. Hassanein M, AbdallahK ,Schweizer et al ,A.A double-blind, randomized trial, including frequent patient-physician contacts and Ramadan focused advice, assessing vildagliptin and gliclazide in patients with type 2 diabetes fasting during Ramadan: the STEADFAST study. Vasc. Health. Risk.Manag.28(10), 319-326(2014), Pages 1446–1450

4. Al Sirifi et al, .Randomized, open-label Patients treated with SU +/- Met. Were given Sita+/- Met.

5. Aravind et al., Randomized, open-label Patients treated with SU +/- Met. Were given Sita+/- Met.

6. Al-Arouj et al. Nonrandomized, Observational , open-label study Patients prescribed Vilda/SU +/- Met. Before study start, treatment continued during the study,p344,378.

7. Halimi et al,.Non-randomized, Observational, open-label study. Patients prescribed Vilda + Met. /IS* + Met. Before study start, treatment continued during the study,p112,145.

8. Shete et al. Nonrandomized, Observational, open-label study. Patients prescribed Vilda/SU +/- Met. Before study start, treatment continued during the study,p21,28.

9. Hanif et al. Non-randomized, Observational, open-label study. Patients prescribed Vilda/Gliclazide + Met. Before study start, treatment continued during the study p555,570.

10. Devendra et al. Nonrandomized, Observational, non-interventional study. Patients prescribed Vilda/Gliclazide add on Met. Before treatment study,p412,420

11. Hassanein M1, Abdallah K2, Schweizer A3 et al. . Randomized,double-blined. Patients prescribed Vilda/Gliclazide add on Met. Before treatment study,p33,40

12. Mohamed Hassanein, Wasim Hanif ,Nicola Lister, et al, results of the VECTOR study, Pages 1367-1374 | Accepted 07 Apr 2011, Published online: 16 May 2011.

13. Aravind SR1, Al Tayeb K, Ismail SB et al, Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: a five-country observational study, Curr Med Res Opin. 2011 Jun;27(6):1237-42. doi: 10.1185/03007995.2011.578245. Epub 2011 Apr 20.

14. D. Devendra, B. Gohel, V. Bravis , Vildagliptin therapy and hypoglycaemia in Muslim type 2 diabetes patients during Ramadan , 12 August 2009 , DOI: 10.1111/j.1742-1241.2009.02171.x.

15. Salti I1, Bénard E, Detournay B et al, (EPIDIAR) stud,. Diabetes Care. 2004 Oct;27(10):2306-11.p312.

16. Wendy L. Bennett, MD, MPH et al , Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations, Published online 2011 Mar 14. doi: 10.7326/0003-4819-154-9-201105030-p55,60.