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

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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 5 groups, 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 Thiazolidinediones 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 ± 7.87 years, (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 weight changes, measuring blood sugar, as well as 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 providers 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, Weight, 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, (I). 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. Type II DM patients
2. Muslims
3. aged from 18 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 thiazolidinediones 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 glucometer 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 Thiazolidinediones 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 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 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 5 groups, 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±7.87 years, (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>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group V</th>
<th>Group VI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight before Ramadan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>82.65±7.6</td>
<td>80.7±8.2</td>
<td>78.06±6.47</td>
<td>85.92±11.2</td>
<td>78.2±8.78</td>
<td>81.01±8.96</td>
</tr>
<tr>
<td>Median</td>
<td>85</td>
<td>80</td>
<td>75</td>
<td>90</td>
<td>85</td>
<td>82.5</td>
</tr>
<tr>
<td>Weight after Ramadan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>82.45±7.6</td>
<td>81.07±9.7</td>
<td>78.17±6.59</td>
<td>85.08±11.8</td>
<td>79.6±8.30</td>
<td>81.17±8.95</td>
</tr>
<tr>
<td>Median</td>
<td>85</td>
<td>80.5</td>
<td>75</td>
<td>90</td>
<td>85</td>
<td>82.5</td>
</tr>
<tr>
<td>P comparing before &amp; after</td>
<td>0.16</td>
<td>0.09</td>
<td>0.43</td>
<td>0.17</td>
<td>0.001</td>
<td>0.24</td>
</tr>
<tr>
<td>Change in weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>-0.2±0.62</td>
<td>0.4±1.25</td>
<td>0.11±0.58</td>
<td>-0.83±1.95</td>
<td>1.4±0.97</td>
<td>0.16±1.25</td>
</tr>
<tr>
<td>(range)</td>
<td>(-2:3)</td>
<td>(0:2)</td>
<td>(0:1.2)</td>
<td>(-5:0)</td>
<td>(0:2)</td>
<td>(-5:3)</td>
</tr>
</tbody>
</table>
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

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

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)

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group V</th>
<th>Group VI</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non fasting days</td>
<td>4.0±1.41</td>
<td>4.57±2.88</td>
<td>1.5±0.71</td>
<td>2.0±0</td>
<td>0</td>
<td>3.5±2.4</td>
<td>0.053</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>20 (100%)</td>
<td>21 (70.00%)</td>
<td>17 (94.44%)</td>
<td>12 (100%)</td>
<td>10 (100%)</td>
<td>80 (88.99%)</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>0 (30.00%)</td>
<td>9 (33.33%)</td>
<td>1 (5.56%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>10 (11.11%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (90.00%)</td>
<td>27 (83.33%)</td>
<td>16 (83.33%)</td>
<td>10 (60.00%)</td>
<td>6 (30.00%)</td>
<td>77 (85.56%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (10.00%)</td>
<td>3 (16.67%)</td>
<td>2 (12.50%)</td>
<td>2 (12.50%)</td>
<td>4 (20.00%)</td>
<td>13 (14.44%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (90.00%)</td>
<td>27 (83.33%)</td>
<td>16 (83.33%)</td>
<td>10 (60.00%)</td>
<td>6 (30.00%)</td>
<td>77 (85.56%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (10.00%)</td>
<td>3 (16.67%)</td>
<td>2 (12.50%)</td>
<td>2 (12.50%)</td>
<td>4 (20.00%)</td>
<td>13 (14.44%)</td>
<td></td>
</tr>
</tbody>
</table>
Table (4) P values of comparison of different pairs of groups according to Hypoglycemia

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group V</th>
<th>Group VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II</td>
<td>0.007</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>0.47</td>
<td>0.07</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group V</td>
<td>1.00</td>
<td>0.04</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Group VI</td>
<td>1.00</td>
<td>0.08</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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 5 groups, 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 ± 7.87 years, (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 1-4 Kgs.

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 a five-country observational
study,(12) (was done in 2009 in India,
Malaysia, Israel, 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 glibencamide, 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
glibencamide 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
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 from 30 patients and range of non-fasted days with the same group was (2:10). also hyperglycemia was found with all groups ,13 patients (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.

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