Diabetic Patients Fasting During Ramadan: Ten Years Overview

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ABSTRACT

Aim: Many diabetic patients insist on fasting in Ramadan despite the potential risks of hypoglycemia, hyperglycemia, diabetic ketoacidosis and diabetic hyperosmolar coma. These patients represent a challenge not only for themselves, but also for the professional care providers during this period that lasts a full month. Aim of this review to provide health care practitioners with new data published in the last ten years regarding the impact of new therapeutic modalities during Ramadan focusing on hypoglycemic events and weight change.

Methods: A Pubmed search was conducted using the search terms: " Ramadan, fasting and diabetes, incretin-based therapy, insulin and fasting Ramadan, oral hypoglycemic agents, Ramadan fasting and hypoglycemia". Our search has been restricted for the last ten years between 2005-2015 frame times, English Language. All randomized and observational trials in patients with type 2 diabetes fasting during Ramadan have been included in this Review.

Results: The database search disclosed the importance of pre Ramadan period focusing on structured diabetes education, the introduction of the Managing Diabetes Ramadan Conversation Map TM by Eli Lilly company, representing one of the important tools that help health care providers and patients manage a safer Ramadan fasting.

Most of the recent trials focused mainly on incretin-based therapy during Ramadan fasting, taking into account their low risk of hypoglycemic events and a weight neutral/reduction effect. Sitagliptin and vildagliptin were the only two drugs evaluated during Ramadan. The rate of hypoglycemic events was lower using these two agents in comparison with sulfonylureas. Weight reduction was observed with vildagliptin, whereas this parameter was not assessed in sitagliptin trials. Liraglutide was the only glucagon like peptide receptor agonist studied during Ramadan with its beneficial effect on glycated hemoglobin A1c, weight reduction and less hypoglycemic events. Treatment with Glilazide is safer than other sulfonylurea agents. The use of insulin analogues in the last ten years is better than human insulin during Ramadan fasting.

Conclusion: Dipeptidyl peptidase inhibitors and glucagon like peptide-1 receptor agonists are 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. This Review and for the first time highlights the weight changes that occur during Ramadan treatment in type 2 diabetic patients treated with dipeptidyl peptidase inhibitors.

Gliclazide treatment with its lower rate of hypoglycemic events might be a suitable option for patients who fast Ramadan.

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KEYWORDS

- ramadan
- diabetes
- incretin-based therapies
- insulin
- oral hypoglycemic agents

ABBREVIATIONS

- SU: Sulfonylurea
- Met: Metformin
- Sita: Sitagliptininsulin
- Vilda: Vildagliptin
- IS: Insulin Secretagogue (SU or glinide)

Introduction

Ramadan is the ninth month of Islamic calendar, representing one of the five main pillars in Islam. Fasting during Ramadan is obligatory for all healthy adult Muslims and it requires abstinence for eating, drinking and smoking from sunrise to sunset. Since the timing of Ramadan follows the Islamic lunar calendar, which is 11-12 days shorter than the solar year, the period of the month of Ramadan varies each year and moves through the seasons. Therefore, the fasting hours vary from 10-20 hours; on average, fasting lasts 15 hours depending on the geographical location and time of Ramadan in the seasonal cycle.

During Ramadan people consume two main meals; one is a predawn meal (Suhur) followed by a long fast and the second is a fast breaking meal after sunset (Iftar). The world's Muslim population is expected to increase by about 35 percent in the next 20 years, rising from 1.6 billion in 2010 to 2.2 billion by 2030, according to a new population projection by Pew Research Center's Forum on Religion and Public Life. This increase is driven primarily by differences in fertility rates and the size of youth population.

The majority lives in Asia-Pacific, Middle East and North Africa, relatively small minority lives in Europe, North and South America [1]. The prevalence of diabetes keeps growing rapidly amounting to 382 million patients at 2014. It is estimated to rise to 592 million by the year 2035. The estimated global prevalence of type 2 diabetes is 8.3% among adults. It can be estimated that there are at least 132 million Muslims worldwide with diabetes, of whom more than 78.7% (100 million) with type 2 diabetes fasted for at least 15 days during Ramadan [2].

Furthermore, about 80% of people with type 2 diabetes live in low and middle income countries, particularly in those regions of the world with large Muslim populations [3].

Major Risks Associated with Fasting in Ramadan

Hypoglycemia and weight gain were the most evaluated risks, therefore our review focuses upon these two risks.

■ Hypoglycemia

One of the major risks associated with fasting during Ramadan includes hypoglycemia, which is multi-factorial, due to abstaining food intake, unadjusted anti-diabetic agents (secretagogous agents and insulin therapy) and fasting during Ramadan without pre-Ramadan instructions. A recently published multi-country retrospective observational study of the management and outcome of patients with diabetes during Ramadan study (CREED study) [4] described the characteristics and management of patients with diabetes type 1, type 2 and gestational diabetes who were ≥ 18 years old on the first day of Ramadan 2010. A total of 508 physicians in 13 countries enrolled 3777 patients and a total of 3394 cases were analyzed.

At least one episode of hypoglycemia was reported in 8.8% of patients during Ramadan (mean 1.8, range 1–9 events). Most of the episodes required either assistance (51.4%) and/or stopping the fast (47.8%).

Hospitalization during Ramadan was rare. 15 patients reported one hospitalization during the month, with only seven of those being related to diabetes. The authors conclude that physicians have increasingly adopted multiple approaches to the management of fasting during Ramadan, including the adoption of international and/or national guidelines, providing fasting-specific advice and adjusting treatment regimens, so that patients were able to fast for a greater number of days without acute complications.

The Ramadan Education and Awareness in Diabetes study READ [5] was a UK retrospective study to assist the safety of fasting Ramadan among Muslims with type 2 diabetes who attended a structured educational program, which included education regarding physical activity, meal planning, glucose monitoring, hypoglycemia (defined as home blood glucose <63 mg/dl, 3.5 mmol/l), dosing and timing of medication. The study disclosed a significant decrease in total number of hypoglycemic events in group A, from 9 to 5 compared with an increase in group B from 9 to 36 ($p < 0.001$), at 12 months after attending the program, glycated hemoglobin A1c reduction was sustained in group A. Therefore, education in the pre-Ramadan period seems to represent a pivotal time frame in preventing undesired hypoglycemia.

■ Weight gain

The recent published data disclosed less weight gain since the introduction of educational instructions program, Ramadan conversation maps and the use of incretin- based therapy. Compared to pre-Ramadan weight, in the READ study during the month of Ramadan, the

patients in the control group gained about 0.6 Kg, while the education group reduced about 0.7 Kg (P < 0.001) [5].

Management of Diabetic Patients during Pre-Ramadan Period

One of the most important periods of Ramadan is the pre Ramadan assessment period, where patients with diabetes who wish to fast during Ramadan should be prepared and engaged in a structured education program in order to pass Ramadan safely without hypoglycaemic events and weight gain.

One of the recent advances in this field is the introduction of the Managing Diabetes Ramadan Conversation MapTM created by healthy interaction in collaboration with the IDF and supported by Lilly Diabetes Company launched in June 2013 in and already used in many countries including Egypt, Morocco, Algeria, Gulf States, Saudi Arabia, Lebanon, South Africa, Sub-Saharan Africa, Malaysia, Indonesia, Pakistan, Netherlands, Switzerland and Israel.

Previous data showed the efficacy of diabetes conversation map education for better management of diabetes, a prospective two phase, one group, mixed method using Modified American Association of Diabetes Educator (AADE) showed significant improvement in diabetes knowledge test ($p < 0.5$), including significant improvement in blood glucose monitoring ($p= 0.01$), foot care ($p = 0.03$), and taking medication ($p = 0.09$) [6,7].

This tool is also efficacious during Ramadan and recommended for use in the pre-Ramadan period [8,9]. The aim of this Map is to help people with diabetes experience healthier Ramadan with less hypo hyperglycemia and weight gain.

A multinational prospective study recently published disclosed the impact of individualized education before Ramadan in type 2 diabetic patients who intended to fast during Ramadan. 515 received individualized education addressed meal planning; physical activity, blood glucose monitoring and 259 received usual care. The results reveal that patients who received individualized education were more likely to modify their diabetes treatment plan during Ramadan (97% vs. 88%, $p <0.0001$), to perform self-monitoring of blood glucose at least twice daily during Ramadan (70% vs. 51%, $p <0.0001$), and to have improved knowledge about hypoglycemic signs and symptoms ($p=0.0007$). Those who received individualized education also reduced their body mass index (-1.1 ± 2.4 kg/m^2 vs. -0.2 ± 1.7 kg/m^2), $p<0.0001$) and glycated haemoglobin (-0.7 ± 1.1% vs. -0.1 ± 1.3%, $p<0.0001$) during Ramadan compared to those who received usual care. There were more mild (77% vs. 67%, $p=0.0031$) and moderate (38% vs. 19%, $p < 0.0001$) hypoglycemic events reported by participants who received individualized education than those who received usual care, but fewer reported severe hypoglycemic events during Ramadan (23% vs. 34%, $p=0.0017$) [10].

Drug Management during Ramadan

This article reviews all published clinical trials - randomized and observational-for treatment of type 2 diabetic patients during Ramadan for the last ten years.

The arsenal of drugs for type 2diabetes increased in the last ten years with the introduction of DPP-4 inhibitor, GLP-1 Rc agonists, and recently the sodium glucose co transporters SGLT2 inhibitors.

Incretin-Based Therapy

■ Dipeptidyl peptidase - 4 inhibitors (DPP-4 Inhibitors)

This group of agents act by blocking the degradation of endogenous glucagon-like peptide-1, thus its action will be prolonged; the manner of action of these agents is glucose dependent modulation of insulin and glucagon secretion [11]. It is well known that DPP-4 inhibitors are well tolerated among the majority of patients with diabetes.

The low rate of hypoglycemic events and the neutral weight effect make this group of agents favorable for use during Ramadan. This review discusses the experience with DPP-4 inhibitors and glucagon like peptide1 receptor agonists (GLP-1Rc agonists) in type 2 diabetic patients fasting during Ramadan and it focuses on two important issues: hypoglycemia and weight.

Our search discloses two randomized open label studies for sitagliptin, six clinical trials for vildagliptin, (one randomized open label study and five non randomized, observational open label studies) and only one recent trial using GLP1-Rc agonist Liraglutide.

The first of the two studies published recently [12] was conducted in different countries, it assessed sitagliptin treatment during Ramadan comparing the incidence of hypoglycemia in

Muslim patients with type 2 diabetes treated with sitagliptin or sulfonylurea (SUs).

Patients were randomized in 1:1 ratio to either sitagliptin 100 mg per day (507 patients) or remain on their sulfonylurea with or without metformin (514 patients).

The results of the study showed that overall symptomatic hypoglycemic events during Ramadan were lower in the sitagliptin group (6.7%; 128 events in 34 patients) in comparison with the sulfonylurea group (13.2%; 195 events in 68 patients), resulting in a risk reduction ratio of 0.5 (95% CI, 0.34-0.75; p<0.001). The proportion of hypoglycemia was lower with gliclazide relative to the other sulfonylurea agents administrated in this study (6.6% (10/156 patients) and there were no reported events that required medical assistance. However, a low percentage of patients (0.2% in the sitagliptin group and 0.8% in the SUs group) had hypoglycemic events required non-medical assistance. Measurement of weight change was not assessed. A second, similar study evaluated sitagliptin in patients with type 2 diabetes fasting during Ramadan from Asia. This multicenter, randomized open label trial enrolled 870 patients. Patients treated with a stable dose of sulfonylurea with or without metformin were randomized to either remain on their pre-study SU (434 patients) or switch to sitagliptin 100 mg once daily (436 patients). 97% of the randomized patients indicated that they did not break the fast for reasons other than threatening hypoglycemia. Fewer patients in the Sitagliptin group (3.8%, 22 events in 16 patients) reported at least one symptomatic hypoglycemic event during Ramadan compared with the SU group (7.3%; 63 events in 31 patients), resulting in a risk ratio of 0.52(95% CI, 0.29-0.94; p=0.028). A lower rate of hypoglycemic events (3.8%) was observed in the gliclazide group [13]. Weight measurement was not assessed as well.

In these two randomized studies, the incidence of symptomatic hypoglycemia during Ramadan was reduced by about 50% with Sitagliptin compared to SUs treatment, except for Gliclazide treatment subgroup, which was with lower incidence rate, similar to Sitagliptin.

Vildagliptin was first evaluated in patients with type 2diabetes during Ramadan in two studies conducted in UK. An observational, non-randomized, non-interventional study, collecting data from primary care practices in North West London was conducted by Devendra et al. [14]. A total of 52 uncontrolled type 2 diabetic patients treated with Metformin were treated either with vildagliptin 50 mg BID (26 patients) or gliclazide 80 mg BID (26 patients) titrated to 160 mg bid if fasting glucose was >7 mmol/L on day 8. The number of patients experiencing hypoglycemic events (defined as blood glucose < 3.5 mmol/L with or without symptoms) was markedly lower with Vildagliptin (7.7%; 2 patients experiencing 2 events) than gliclazide (61.5%; 16 patients experiencing 24 events; p<0.001. There were no severe hypoglycemic events reported in the vildagliptin group, and only one event was reported in the gliclazide group. Minimal weight changes were observed over the same period (mean change of +0.12 kg with vildagliptin and + 0.38 Kg with gliclazide; p = 0.4709).

The VIRTUE (Vildagliptin experience compared with sulphonylUreas observed during Ramadan) a real world setting study compared the effect of vildagliptin with sulphonylurea treatment on hypoglycemia in Muslim patients with type 2 diabetes fasting during Ramadan was published recently [15]. For the primary end point defined as any reported symptoms of hypoglycemia by the patient and/or any blood glucose measurement <3.9 mmol/L (70 mg/dL), fewer significantly patients reported hypoglycemic events with vildagliptin (36 events/669, 5.4%) compared with SUs (123 events/621, 19.8%) [OR (95% CI) = 0.23 (0.156; 0.340, p<0.001]. No patients reported severe hypoglycemia with vildagliptin whereas four patients in the SUs group reported such an event. Furthermore, weight changes pre Ramadan to post-Ramadan were –0.76 kg with vildagliptin compared with –0.13 kg with SUs, representing a mean change difference of –0.63 kg (p < 0.001).

The STEADFAST study represents the first multiregional, double-blind randomized study published recently [16]. 557 patients with type 2 diabetes treated previously with metformin and any sulfonylurea were included in the study. 279 patients received vildagliptin (50 mg twice daily) and 278 gliclazide. The proportion of patients reported confirmed hypoglycemic events (defined <3.9 mmol/L and/or severe) during Ramadan was 3.0% with vildagliptin and 7.0% with gliclazide (P=0.039; one-sided test), and this was 6.0% and 8.7%, respectively, for any hypoglycemic events (P=0.173). In both groups, the adjusted mean decrease in weight was –1.1 ± 0.2 kg (P = 0.987). Overall safety was similar between the treatments. Other three small studies published compared the use of DPP-4 inhibitors during Ramadan showed similar results [17-19]. Table 1

Table 1: Summarizes recent studies using DPP-4 inhibitors during Ramadan.

Name of drug and Author Sitagliptin	Study design	Number of patients	Symptomatic Hypoglycemic events. DPP-4 Inhibitor vs. comparator	Hypoglycemic events -Statistical significance	Body weight change
Al Sirifi et al.	Randomized, open- label Patients treated with SU +/- Met. Were given Sita+/- Met.	1021	6.7% vs. 13.2% 128 vs. 195 events	RR 0.5 (95%CI, 0.34-0.75; P < 0.001)	No data
Aravind et al.	Randomized, open- label Patients treated with SU +/- Met. Were given Sita+/- Met.	848	3.8 % vs.7.3% 22 vs. 63 events	RR 0.52 (95% CI, 0.29–0.94; P = 0.028)	No data
Vildagliptin Al-Arouj et al.	Nonrandomized, Observational , open-label study Patients prescribed Vilda/SU +/- Met. Before study start, treatment continued during the study.	1315	5.4 % vs. 17.9% 36 vs.123 events	P < 0.001	-0.76 Kg Vilda Vs -0.13 Kg SU P < 0.001
Halimi et al. .	Non-randomized, Observational, open-label study. Patients prescribed Vilda + Met. /IS* + Met. Before study start, treatment continued during the study.	198	7.5% vs.17.9% 13 vs. 22 events	P = 0.025	-0.7 Kg Vilda Vs. -0.5Kg SI*
Shete et al. .	Nonrandomized, Observational, open-label study. Patients prescribed Vilda/SU +/- Met. Before study start, treatment continued during the study.	97	0.0% vs.4.8% 0 vs. 2	P = 0.104	-1.2 Kg Vilda Vs. -0.03 Kg SU P = 0.011
Hanif et al. .	Non-randomized, Observational, open-label study. Patients prescribed Vilda/Gliclazide + Met. Before study start, treatment continued during the study.	59	0.0% vs.41.7% 0 vs. 34 events	P = 0.0002	No change
Devendra et al. .	Nonrandomized, Observational, non-interventional study. Patients prescribed Vilda/ Gliclazide add on Met. Before treatment study.	52	7.7% vs. 61.5% 2 vs. 24 events	P < 0.001	+0.12 Kg Vida Vs. + 0.38 P = 0.4709
Hassanein et al. .	Randomized,double-blined. Patients prescribed Vilda/ Gliclazide add on Met. Before treatment study.	557	6% vs. 8.7% (events-no data)	P = 0.173	-1.1 ± 0.2 Kg (in both groups)

summarizes studies in this group of agents with a focus on the weight changes in addition to hypoglycemic events and hemoglobin A1C reduction.

Glucagon like Peptide 1 Receptor Agonists (GLP1-Rc Agonists)

This group of agents includes several drugs already on the market and others in advanced development stages. The mechanism of action of these agents is by increasing insulin secretion in a glucose dependent manner, reducing glucagon secretion, slowing gastric emptying and decreasing appetite [20]. Only one comparative study between sulfonylurea and liraglutide in type 2 diabetes patients was published recently [21]. Baseline data was collected ≥ 14 days prior to Ramadan and at 3 and 12 weeks after Ramadan in 99 patients intending to fast Ramadan, the patients were randomized in two UK sites. At 12 weeks, more patients in the liraglutide group compared with the sulfonylurea group achieved a composite endpoint of hemoglobin A1c less than 7%, no weight gain and no severe hypoglycemia, this composite end point did not reach statistically significance 95% confidence interval (CI 0.97, p = 0.06). No change in hemoglobin A1c was observed between the two groups, not only in the baseline visit but also at 12 weeks. Significant reductions were observed in weight

and diastolic blood pressure in the Liraglutide group compared with sulphonylurea group. There were no episodes of severe hypoglycemia in either group; however, self-recorded episodes of blood glucose monitoring ≤ 3.9 mmol/l were significantly lower with Liraglutide p < 0.0001). The LIRA-Ramadan study recently completed aimed to evaluate the efficacy and safety of Liraglutide versus sulfonylurea both in combination with metformin during Ramadan. The data was presented in EASD 2015.

It is important to stress that GLP-1 Rc agonists should be initiated in the pre Ramadan period defined as 1-2 months before Ramadan, taking into consideration the drug titration period in order to achieve a therapeutic steady state concentration and to minimize gastrointestinal side effects.

Other Oral Hypoglycemic Agents

Sulphonylurea agents and other insulin secrtagogue still represent one of the treatment modalities in Ramadan despite the hypoglycemia and weight gain effect. Our database search disclosed four small clinical studies [22-25].

The study reported by Zarger et al. [23]. Assessed whether switching to an evening administration of a long acting sulfonylurea - gliclazide modified release (MR) - during the 29 days can maintain glycaemic control in patients with type 2 diabetes. Male type 2 diabetic patients from Bangladesh, Pakistan and India, under glycemic control with gliclazide modified release (MR) 60 mg monotherapy, switched to evening administration of the same dose during Ramadan, and reverted to the morning schedule thereafter. The primary outcome was the difference in fasting plasma glucose (FPG) before and after Ramadan. In 136 patients, mean (95% CI) FPG decreased by 0.01 mmol/l (0-0.2, p = 0.3) with evening medication by the end of the fast, and increased by 0.2 mmol/l (0.1-0.3, p = 0.01) after reverting to morning medication 20 days later. There were 5 (3.7%) hypoglycaemic events before, 3 (2.2%) during and 2 (1.5%) after Ramadan. The authors concluded that male type 2 diabetic patients undertaking the Ramadan fast can safely maintain glycaemic control with evening administration of gliclazide MR 60 mg during the fast, and reverting to a morning schedule thereafter.

Insulin Treatment during Ramadan

■ Long acting insulin analogues

Our search discloses two trials using long acting insulin analogue. The first study reported by Salti and Ramadan Study Group aimed to determine the safety and efficacy of insulin glargine and glimepiride in patients with Type 2 diabetes before, during and after Ramadan [22].

In this open, descriptive, multi-centre, prospective study, insulin-naïve (n = 100) or previously insulin-treated (n = 249) patients with Type 2 diabetes received insulin glargine the number and type of hypoglycaemic episodes and glycaemic control were assessed before, during and after Ramadan. The results showed only one episode of severe hypoglycaemia in each time periods. Mild hypoglycaemic episodes increased from 156 pre Ramadan to 346 during Ramadan (P < 0.001) and decreased to 153 post-Ramadan (p = 0.0002). The increase during Ramadan was mainly attributed to increased symptomatic hypoglycaemic episodes. FBG and glycated haemoglobin improved during the titration period and did not change during the rest of the study. Risk of hypoglycaemic events during Ramadan was higher in countries where fasting is strict (odds ratio (OR) 3.69 (2.06-6.63), p < 0.0001). Lower weight (<70.0 Kg; OR 2.56 (1.46-4.48), p = 0.001) and waist circumference (< 90 cm; OR 3.06 (1.62-5.78), p = 0.001) increased the risk of hypoglycaemia during Ramadan, whilst FBG > 6.7 mmol/l (OR 0.3 (0.17-0.54), P < 0.0001) had a protective effect.

The authors concluded that a combination of insulin glargine and glimepiride may be used during Ramadan in patients with Type 2 diabetes who wish to fast. Glimepiride is provided at the time of breaking the fast and insulin glargine titrated to provide FBG > 6.7 mmol/l. The second study was a comparative one which evaluated glycemic effects of glimepiride, repaglinide and insulin glargine in type 2 diabetes mellitus during Ramadan fasting [23]. The results disclosed no significant difference between the three drug therapies regarding glucose metabolism and rate of hypoglycemia.

Human Insulin Premixes vs. Insulin Analogue Premixes

A comparative study conducted by Devendra et al. in North-West London showed that Muslim patients with Type 2 diabetes attending primary care practices treated with mixtard 30 HM insulin twice daily before Ramadan achieved a reduction in hemoglobin A1c of 0.48% (P = 0.0001) before and after Ramadan in group 1 which changed the evening insulin to humalog

mix 50 (n = 26) 2 weeks before Ramadan, whereas group 2 that continued with mixtard 30 HM had a mean hemoglobin A1C increase of 0.28% (P= 0.007). Group 1 was associated with a small reduction of 0.04 (p = 0.81) in the mean number of hypoglycemic events during Ramadan compared to pre-Ramadan period, whereas group 2 was associated with an increase of 0.15 (p = 0.43). Although these differences between the groups were not statistically significant following adjustment for baseline factors (LSM difference between groups = 0.135, p = 0.36, 95% confidence limits (-0.16, 0.43)). The authors concluded that changing to humalog mix 50 during Ramadan resulted in an improvement in glycemic control without increasing the incidence of hypoglycemia [26]. There is an evidence previously reported (data not included in our search) suggesting that the use of insulin analogue lispro and humalog mix 25instead of human insulin in patients with type 2 diabetes during Ramadan fasting is associated with less hypoglycemic events and less postprandial hyperglycemia.

Insulin Pump

For Insulin pump use during Ramadan, four studies were reported in the last ten years with a very small number of patients with type 1 diabetes.

The study reported by Benbarka et al. included a total of 49 out of 63 patients (aged 22 +/- 7) with type 1 diabetes using an insulin pump fasted during Ramadan. Outcome measures included: The number of days fasted, hypoglycemia, unusual hyperglycemia, and the number of emergency hospital visits [26].

Thirty patients (61.2%) fasted the whole month with no problems, nine (18.4%) fasted 27-28 days, eight (16.3%) fasted 24-25 days, and two (4.1%) fasted 23 days. Nearly half of the patients decreased their basal insulin by 5-50% of their pre-fasting doses. Seventeen patients had hypoglycemia requiring breaking the fast. Unusual hyperglycemia was reported in nine patients (18.4%). It is important to note that patients with type 1 diabetes represent a high risk category for fasting during Ramadan. Therefore, fasting is not recommended for type 1 diabetes.

Sodium Glucose Co-transporter 2 (SGLT2) Inhibitors

A new class of agents was recently introduced in the management of type 2 diabetic patients. It represents a unique class because of its insulin independent mechanism of action. These agents increase glucose excretion due to selective inhibition of SGLT2 on the first segment of the proximal tubule of the nephron [27].

A recent 12 weeks, randomized, open-label, two arm parallel group study assessed dehydration parameters with dapagliflozin in patients with type 2 diabetes during Ramadan fasting month, it included 119 patients with T2DM on sulfonylurea(SU) and metformin therapy randomized to either switch to dapagliflozin 10 mg (n=58) or remain on pre-study therapy sulfonylurea (n=52). The primary end point was to assess the proportion of patients with dehydration, defined as loss of 1.8% of body weight within 13 hour of fasting. The results of the study revealed no difference in the proportion of patient with dehydration 73.1% (n=38) vs. 81.6% (n=38); p = 0.258 in both dapagliflozin and sulfonylurea group. More patients in the dapagliflozin group, 43.1% (n=25) vs. 23.1% (n=12); p=0.026 complained of thirst sensation. (A poster presented on EASD 2015, yet to be published). Taking into consideration the insufficient Clinical data regarding this group of agents, a cautious use is recommended during Ramadan especially with elderly patients, until new data will be published.

Discussion

This Review shows the importance of pre Ramadan assessment period for a better management of fasting during Ramadan focusing on individualized education for achieving weight loss and less hypoglycemic events during fasting. In the last ten years and with the increased arsenal of drugs for diabetes management, incretin based therapy represents one of the important modalities for therapy during the Ramadan fasting in type 2 diabetic patients with less hypoglycemic events and weight neutral/ loss effect using DPP-4 inhibitors and GLP1-Rc Agonists. Out of this group, Sitagliptin and Vildagliptin are the only two DPP-4 inhibitors that have been reported during Ramadan treatment.

Concerning sitagliptin, in both studies presented in this Review, patients treated with gliclazide, as a comparator, were with a lower rate of hypoglycemic events than other SUs agents used in these trials. Unfortunately, weight change was not assessed in both studies. Taking into consideration that SUs agents are still largely administrated in type 2 diabetes in many countries and according to these re-

sults, gliclazide seems to be safer for use in patients fasting Ramadan than other SUs.

Six studies have been reported with vildagliptin, five of them have been non randomized open label studies and only one randomized double blind study recently reported by Hassanein et al. . In all six studies fewer hypoglycemic events were reported in patients treated with vildagliptin, it is worthy of mention that in all the studies weight changes were reported (see table1). In the STEADFAST study which represents the only randomized study using Vildagliptin, the proportion of patients with hypoglycemic events between treatment groups did not reach statistically significant results. Liraglutide is the only GLP1-Rc agonist evaluated during Ramadan period with favorable effect on weight loss and less hypoglycemic events.

Insulin analogues appear to be better for use during Ramadan than human insulin. This Review shows the use of different regimens including premixes during Ramadan. Clinical care practitioners should be aware for the need of drug evaluation and dose adjustment especially in this group of patients in the pre Ramadan period. Clinical data still needed for the use of SGLT2 inhibitors during Ramadan, the newly published data regarding the cardiovascular safety and superiority of empagliflozin (not reported in our review) are encouraging for considering this group of agents for use in the future.

Conclusion

Ramadan represents one of the challenging issues for health care providers all over the world. DPP-4 inhibitors and GLP1-Rc agonists are 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.

This Review and for the first time highlights the weight changes that occur during Ramadan treatment in type 2 diabetic patients treated with DPP-4 inhibitors. Gliclazide treatment with lower hypoglycemic events in comparison with other SUs agents might be a suitable option for patients who fast Ramadan and are unable to secure permanent treatment with other agents due to lower socioeconomic status. The month of Ramadan represents a golden opportunity for a better management of diabetic patients and drug intensification including insulin treatment, not only during Ramadan but also throughout a patient's entire life.

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