

## Newer antidiabetic drugs in Ramadan

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### Abstract

The management of diabetes in the month of Ramadan can be very challenging. On one hand there is the issue of fasting associated hypoglycaemia, and on the other, fasting as well as post prandial hyperglycaemia. Under such circumstances, a planned regimen needs to be followed to keep the blood glucose levels under control. The same oral antidiabetic agents that were used prior to the fast are used during Ramadan with modification in dosage and timing. With the advent of newer antidiabetic agents, there is a good scope for better control and reduced complications.

**Keywords:** Ramadan, diabetes, DPP-IV inhibitors, GLP-1 agonists, SGLT-2 inhibitors, hypoglycaemia.

### Introduction

Fasting in Ramadan is one of the five main pillars of Islam and is passionately practiced worldwide by Muslims. Around 18-25% of the world population comprise of Muslims. Considering the global prevalence of diabetes, an estimated 40-50 million diabetics worldwide are presumed to fast during Ramadan.<sup>1</sup> The rigorous fast includes total abstinence from food, drinks and even medications, from sunrise to sunset. Although the Koran exempts the sick from fasting, many diabetic patients insist on observing it, creating a challenge for both themselves and the physician. It is necessary for medical professionals to be aware of the problems associated with fasting and the solutions to it.

### Management of Diabetes in Ramadan: Newer Antidiabetic Agents

Various recommendations have been proposed for the management of diabetes in Ramadan.<sup>2-4</sup> Overall, major emphasis needs to be laid on risk stratification, individualization of treatment, frequent monitoring of blood glucose levels and Ramadan structured diabetes education.

The two major meals in Ramadan are the post-sunset Iftar and the pre-dawn Suhur. The timing and dosage of antidiabetic agents are hence to be modified as per the

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intake of meals. The agents that act by increasing insulin sensitivity are associated with a significantly lower risk of hypoglycaemia than compounds that act by increasing insulin secretion.

### Gliptins or Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors:

#### Mechanism of action

These are new oral hypoglycaemic agents which act on the enzyme DPP-IV, inhibiting it to enhance endogenous incretin activity by preventing the rapid degradation of the incretin hormones, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). This in turn inhibits glucagon release, increases insulin secretion and decreases gastric emptying leading to overall lowering of blood glucose levels. DPP-IV inhibitors are among the best tolerated drugs for the treatment of diabetes. They cause a moderate HbA1c reduction and are weight neutral. Their more physiological mechanism of action with lesser side effects provides an attractive option for use during Ramadan where hypoglycaemia is a serious concern.

The incretin hormones, GLP-1 and GIP increase the sensitivity of the  $\alpha$ - and  $\beta$ -cell to glucose, resulting in glucose-dependent secretion of insulin and glucagon, which underlie their low propensity to cause hypoglycaemia. When glucose levels fall in the hypoglycaemic range, this leads to a more rapid and pronounced decrease in insulin release and a similar increase in glucagon. This preserved glucagon counter-regulation has specifically been shown for the DPP-4 inhibitor vildagliptin in placebo-controlled crossover studies both in diet- and insulin-treated patients with T2DM as well as in patients with T1DM.<sup>5,6</sup> While vildagliptin suppresses the inappropriate glucagon secretion during hyperglycaemia, it sustains or even enhances the glucagon response to hypoglycaemia.

### Vildagliptin in Ramadan

Various studies have compared the use of gliptins and sulfonylureas (SUs) during fasting in Ramadan. In a study conducted among 52 Muslims in North West London, 26 were given vildagliptin as add on therapy with 2g metformin and the remaining 26 were given gliclazide.<sup>7</sup> During Ramadan, at least one hypoglycaemic event (defined as blood glucose < 63 mg/dl (3.5 mmol/l) with or

without symptoms) was recorded in two patients receiving vildagliptin (7.7%) and 16 patients receiving gliclazide. Moreover 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. Similarly, in a UK observational study of South Asian patients, VECTOR, none of the 23 patients treated with vildagliptin as add-on to metformin reported hypoglycaemia during Ramadan, in contrast to the 15 (41.7%) patients receiving SU therapy.<sup>8</sup>

A much larger Vildagliptin experience compared with sulfonylurea observed during Ramadan (VIRTUE) study was conducted enrolling Muslim patients from 10 countries in the Middle East and Asia.<sup>9</sup> Significantly fewer patients experienced hypoglycaemia with Vildagliptin (n=684) (5.4%) compared with SU (n=631) (19.8%). In another study among 198 subjects, the Vildagliptin Experience during Ramadan in patients with Diabetes (VERDI), limited to a population originating mostly from the Maghreb region in France, the frequency of hypoglycaemia was found to be 7.5% in the vildagliptin arm compared to 17.9% in the SU arm.<sup>10</sup>

A similar study conducted in India recruited 55 patients undertaking Ramadan fast in the Vildagliptin group and 42 in the SU group and compared the effects of both drugs.<sup>11</sup> Hypoglycaemic events were low in both groups, but the Vildagliptin group showed greater reductions in HbA1c compared with the SU group. The Vildagliptin group also showed a significant but modest reduction in the body weight compared with the sulfonylurea group. The benefits extend beyond minimizing adverse effects to better glycaemic control and body weight reduction.

In a multiregional, double-blind randomized trial, the STEADFAST study, 557 patients with T2DM who were previously treated with metformin and any sulfonylurea were given either Vildagliptin or gliclazide plus metformin.<sup>12</sup> The proportion of patients reporting measured hypoglycaemic events during Ramadan was 3.0% with Vildagliptin and 7.0% with gliclazide and this was 6.0% and 8.7%, respectively, for any hypoglycaemic event. The adjusted mean change pre- to post-Ramadan in HbA1c was 0.05%±0.04% with Vildagliptin and 0.03%±0.04% with gliclazide, from baselines of 6.84% and 6.79%, respectively. Vildagliptin was shown in this interventional study to be an effective, safe, and well-tolerated medication in patients with T2DM fasting during Ramadan, with a consistently low incidence of hypoglycaemia across studies, accompanied by good glycaemic and weight control.

### Sitagliptin in Ramadan

A similar study was conducted with sitagliptin instead of Vildagliptin and the frequency of hypoglycaemic events was compared with SUs among 1021 subjects undergoing Ramadan fast.<sup>13</sup> The proportion of patients who recorded one or more symptomatic hypoglycaemic events during Ramadan was found to be lower in the sitagliptin group (6.7%) compared with the SU group (13.2%). The risk of symptomatic hypoglycaemia was significantly decreased with sitagliptin relative to SU treatment. In another study involving 848 patients who fasted in Ramadan (421 on sitagliptin and 427 on SU) symptomatic hypoglycaemic events during Ramadan were lower with sitagliptin (3.8%) compared to SUs (7.3%).<sup>14</sup> Switching antihyperglycaemic treatment to sitagliptin from a SU reduced the risk of symptomatic hypoglycaemia by approximately 50% in patients who fasted during Ramadan.

### Saxagliptin, Alogliptin & Linagliptin in Ramadan

Though, there are no published data on any of the other gliptins' usage in Ramadan, the lack of hypoglycaemia risk does indicate that it may be safe to add any dipeptidyl peptidase-4 inhibitor to patients who are planning to fast during Ramadan, but are not well controlled when taking metformin alone.

### GLP-1 Agonists: Mechanism of action

GLP-1 is an incretin hormone secreted from the L cells of the intestine, which has been considered as a new and promising treatment for type 2 diabetes. It stimulates endogenous insulin secretion when plasma glucose levels are elevated and also decreases glucagon secretion. It also decreases gastric motility, which delays gastric emptying and leads to reduced appetite and food intake. Exenatide and the longer acting liraglutide are the two drugs available in this class. In the LEAD trials, treatment with liraglutide presented a lower risk of hypoglycaemia, as liraglutide stimulated insulin secretion in a glucose-dependent manner and had no effect on glucagon secretion when plasma glucose was low.<sup>15</sup> GLP-1 analogues are therefore very useful agents for management of diabetes, particularly in the setting of Ramadan. They can be combined with the insulin sensitizers which also have a very low risk of hypoglycaemia.

### Liraglutide in Ramadan

The Treat 4 Ramadan Trial was undertaken to compare sulphonylurea with liraglutide in combination with

metformin in patients on mono/dual oral therapy with established type 2 diabetes, fasting during Ramadan.<sup>16</sup> Ninety-nine adults intending to fast during Ramadan were followed up for 12 weeks. More patients in the liraglutide compared with the SU group achieved a composite endpoint of HbA1c < 7%, no weight gain and no severe hypoglycaemia, although this did not reach statistical significance. Significant reductions were also observed in weight and diastolic blood pressure (BP) in the liraglutide compared with the SU group. Treatment satisfaction was comparable across the treatment groups. There were no episodes of severe hypoglycaemia in either group; however, self-recorded episodes of blood glucose  $\leq 70$  mg/dl (3.9 mmol/l) were significantly lower with liraglutide.

### Exenatide in Ramadan

Exenatide has a short half life and is given in a twice daily regimen. A newer once weekly Exenatide will also be available in the near future. Though, there is currently no published data available, Exenatide also has a potential for safe use in Ramadan due to its negligible risk of hypoglycaemia. Studies in this group would be welcome.

### South Asian Guidelines on GLP1RA in Ramadan

A consensus statement by the South Asian Guidelines for Management of Endocrine Disorders in Ramadan describes the pre-Ramadan assessment, planning, prescription and management and monitoring of patients who are on GLP-1 analogues, with or without other anti-diabetic therapies.<sup>17</sup> As per its recommendations, a patient on liraglutide should continue on the same dose, but preferably taken during iftar. In case of exenatide, the morning dose should be same at iftar and the evening dose should be same at suhur. For those on the once-weekly exenatide (extended release preparation), it should be continued as such during Ramadan. A point to be noted by patients on GLP-1A is to ensure adequate fluid intake during Ramadan.

### Sodium-Glucose Co-Transporter 2 Inhibitors: Mechanism of action

Sodium-glucose co-transporter 2 (SGLT2) inhibitors form the latest class of oral antidiabetes medication available for type 2 diabetes. To date, no studies have been reported of their use during Ramadan. These drugs competitively inhibit the SGLT2 co-transporter in the kidney and block the reabsorption of glucose; thus the risks of inducing hypoglycaemia is low because of their insulin-independent action and hence form an attractive prospect for managing diabetes in Ramadan. However,

there are a few things to be considered. SGLT2 inhibitors should be initiated 2-4 weeks prior to the fast so that the patients get acclimatized to the unique mechanistic and side effect profile of these molecules. Patients may need reassurance that the polyuria and glycosuria are a consequence of its mechanism of action resulting in diuresis and fluid loss and are not indicative of poor glycaemic control. They also need to watch out for dehydration, especially in the setting of absence of fluid intake during fasting and should also be acquainted with the risk of genital tract infections.<sup>18</sup>

### Conclusion

Improved glycaemic control without hypoglycaemia and weight gain is the key goal in the management of diabetes but achieving this goal is challenging in patients with diabetes, especially who are fasting. Newer anti-diabetics like the incretins, which maintain glycaemic control in a glucose-dependent manner, provide a safe alternative therapeutic option during Ramadan, although cost effectiveness can be a major hindrance. Further studies need to be done to concretely establish their efficacy and lower adverse effect profile in fasting during Ramadan.

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