South Asian Guidelines for Management of Endocrine Disorders in Ramadan

Role of oral hypoglycemic agents in the management of type 2 diabetes mellitus during Ramadan

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ABSTRACT

It is obligatory for all adult Muslims to observe fast during the holy month of Ramadan, but sick individuals including those with diabetes mellitus are exempted from the duty of fasting. Specific medical advice must be provided to individual patients concerning the potential risks they must accept if they decide to fast. Any alteration in medications deemed necessary to provide an effective and safe antidiabetic regimen should be instituted well before the start of Ramadan. Diet-controlled patients and those well controlled on insulin sensitizers have low risk of hypoglycemia and may safely fast with some modification in the timing of the doses. Newer generation sulfonylureas (gliclazide MR and glimepiride) have reasonable safety profile during Ramadan fasting and are economical options for a large number of diabetics worldwide, especially in the developing countries; older, long acting sulfonylureas like glibenclamide and chlorpropamide should be avoided during fasting. Oral DPP-IV inhibitors are important substitutes to sulfonylureas for patients with diabetes mellitus during fasting owing to their glucose-dependent mechanism of action, efficacy, and tolerability. This group of drugs causes a moderate A1c reduction, are weight neutral, and have a very low risk of hypoglycemia. Short-acting insulin secretagogues are an option in the subset of fasting diabetic patients who have predominantly post-prandial hyperglycemia.

Key words: Gliptins, hypoglycemia, insulin sensitizers, Ramadan fasting, sulfonylureas

Introduction

There are about 1.57 billion Muslims in the world comprising 23% of the world's population of 6.8 billion. One of the five pillars of Muslim faith is fasting during the month of Ramadan (the 9th month of the Islamic calendar). Muslims who fast during Ramadan abstain from food and drinks (including use of oral medications) and smoking from predawn to dusk. The duration of fasting may range from a few to more than 20 h depending on the geographic location and the season of the year. Most Muslims consume two major meals a day during this month, one after the sunset, referred to in Arabic as Iftar (breaking of the fast meal), and the other before dawn, referred to as Suhar (predawn). The population-based Epidemiology of Diabetes and Ramadan (EPIDIAR) study conducted in 13 Islamic countries showed that about 43% and 79% respectively of Muslims with type 1 and type 2 diabetes mellitus (T2DM) fast during Ramadan meaning

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that more than 50 million individuals with diabetes fast during Ramadan.[1]

Religious fasting is meant to inculcate discipline in an individual and is not meant to impose excessive hardship; in fact, the Holy Koran specifically exempts the sick from the obligation of fasting if fasting might have an adverse effect on the individual. People with diabetes mellitus fall in this category of individuals exempted from fasting because marked departures from the usual amount and pattern of food and fluid intake required during Ramadan fasting carries the risk of acute metabolic decompensation. Notwithstanding this relaxation, many diabetic patients insist on fasting during Ramadan giving rise to a medical challenge for themselves and for the physicians caring for them.

Management of Diabetes Mellitus During Ramadan

All diabetics desiring to fast during Ramadan should be well prepared to make fasting as safe as possible. Specific medical advice must be provided to every diabetic patient concerning the potential risks they must accept if they decide to fast.

Pre-ramadan medical assessment

This should take place 30 to 60 days before Ramadan and focus specifically on patients' overall wellbeing and control of blood glucose, hypertension, and dyslipidemia. Individual assessment for each patient is essential and emphasis should be on preventing the occurrence of hypoglycemic events. Appropriate investigations should be carried out to document complication status, and necessary changes in lifestyle, and diet, affected. Any change in medication, if required, should be instituted at this stage, so as to establish a safe and effective antidiabetic regimen and provide a stable glycemic control prior to the start of Ramadan fast. Risk stratification of diabetic patients who are planning to fast is recommended based on the presence of various risk factors.[2]

Educational counseling

Each individual needs to be counseled about the essential elements necessary to render fasting safer. These include the importance of glucose monitoring during fasting and nonfasting hours, when to stop the fast, meal planning to avoid hypoglycemia and dehydration during prolonged fasting hours, and the appropriate meal choices to avoid postprandial hyperglycemia. The educational program should include advice on the timing and intensity of physical activity during fasting as well. The caregivers (medical professionals/family members) need to be made aware of the potential problems that fasting during Ramadan may create.

Breaking the fast

Patients must immediately break the fast if hypoglycemia (blood glucose <60 mg/dl) occurs at any time during the fast or if blood glucose exceeds 300 mg/dl. In case blood glucose drops to less than 70 mg/dl in early hours of the fast, particularly if sulfonylureas or insulin have been taken at predawn, the fast should be terminated. Fasting should be avoided on "sick days."

Oral Hypoglycemic Agents During Ramadan

The therapeutic options for management of T2DM have expanded with the introduction of new oral hypoglycemic agents (OHAs). Some of these have been used during Ramadan and have shown potential therapeutic benefit.

Metformin, the only bigaunide presently available for use, is an insulin sensitizer. Hypoglycemia has been reported to occur in 0–20% of non-fasting patients taking metformin[3]; however, severe hypoglycemia is not reported with metformin use unless given in combination with other hypoglycemic agents. Patients taking metformin alone can undertake fast safely. It is however suggested that two thirds of the total daily dose be administered immediately before the sunset meal, while other third be given before the predawn meal. Slow release formulations (XR/SR/ER) of metformin are well tolerated. These may be a better choice in fasting diabetic patients who are controlled on metformin and can be taken once daily after the sunset meal.

Thiazolidinediones, PPAR-γ agonists, are not independently associated with hypoglycemia, but can increase the hypoglycemic effects of other hypoglycemic agents. The adverse effects include weight gain, macular edema, and increased frequency of bone fractures in postmenopausal women. The controversy regarding cardiovascular safety of rosiglitazone has resulted in a more cautious approach to its use as advocated by the FDA. Pioglitazone has been found to be safe and efficacious in lowering blood glucose during Ramadan in combination with other OHAs. A randomized-controlled trial in patients already taking other OHAs did not find any increase in hypoglycemic events during Ramadan fasting with pioglitazone 30 mg once daily compared to placebo[4]; mean weight gain of 3.02 kg was observed in the pioglitazone group. Al-Arouj *et al*., writing for the ADA on recommendations for diabetic patients undertaking Ramadan fasts recommended that patients

controlled on pioglitazone alone or with other treatments, continue with their usual pioglitazone dose.[5]

Short Acting Insulin Secretagogues

The meglitinides (repaglinide and nateglinide) have short duration of action and as such are useful in patients with T2DM fasting during Ramadan. An open label, multicenter randomized study observed that repaglinide use was associated with a lower risk of hypoglycemic events compared with glibenclamide during Ramadan.[6] There were 0.03 hypoglycemic events per patient per month within this group compared to 0.05 events per patient per month in the glibenclamide group. Another study reported safety of three doses of repaglinide plus single dose insulin glargine (no hypoglycemia, no change in glycemic control or weight gain) in low-risk T2DM patients who fasted during Ramadan.[7]

Sulfonylureas (SUs) cause relatively glucose-independent stimulation of insulin secretion by closing K_{ATP} channels on β-cell membranes. For several decades, after their discovery and introduction into clinical practice, SUs were the centerpiece of the pharmacologic management of T2DM. The risk of hypoglycemia, weight gain, and concerns surrounding the cardiovascular safety of these drugs (especially the older agents like glibenclamide) together with continued introduction of newer, safer, and effective classes of antidiabetic medications some of which hold the promise (unproven) of altering the course of diabetes has led to a progressive decline in use of SUs. They, however, continue to be used in many parts of the world as first-line drugs given their less expense. Use of chlorpropamide is contraindicated during Ramadan because of possibility of prolonged hypoglycemia. Glibenclamide use was claimed to be safe during Ramadan fasting.[8] However, subsequently it has been suggested that glibenclamide may be associated with higher risk of hypoglycemia than other second generation sulfonylureas like gliclazide, glipizide, and glimepiride.[9,10] Higher numbers of hypoglycemic events have been reported to occur with glibenclamide as compared to short acting insulin secretagogue repaglinide among fasting patients during Ramadan.[6]

Several studies have shown glimepiride and gliclazide to be effective and safe during Ramadan. In a double-blind comparison of once daily gliclazide MR and glimepiride in T2DM patients (the GUIDE study) gliclazide MR was found to cause approximately 50% fewer confirmed hypoglycemic episodes in comparison with glimepiride.[9] Use of gliclazide MR 60 mg as monotherapy (evening administration) in 136 non-obese Asian men with previously well-controlled T2DM during Ramadan did not show any significant alteration in glycemic control, no weight gain and, importantly, few hypoglycemic events.[11] Similar findings were reported in a study on 122 patients (aged 48 to 60 years) from Morocco.[12]

The prospective observational study by the GLIRA study group showed that once daily evening dose of glimepiride taken at Iftar during Ramadan did not alter rates of hypoglycemia or glycemic control.[13] Another study compared repaglinide use with glimepiride or gliclazide. Fructosamine, HbA1c, and body weight did not change significantly in either group during or after Ramadan.[6] Hypoglycemia was documented only in one patient who took glimepiride during Ramadan.

The newer generation SUs like glimepiride and gliclazide MR may be used with caution given their worldwide use and relatively low cost. If the patient's glycemic control before Ramadan is stable, clinicians recommend changing the timing of once daily dose of SU from the usual morning dose to before the sunset meal; those taking twice daily SU are advised to take half their usual -evening dose with the predawn meal and the usual -morning dose with the sunset meal.

Incretin-Based Therapy

Gliptins or dipeptidyl peptidase-IV (DPP-IV) inhibitors are new oral hypoglycemic agents which act as selective inhibitors of enzyme DPP-IV 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). Gliptins are important addition to the currently available management options for patients with type 2 diabetes and are among the best tolerated drugs for the treatment of T2DM. They cause a moderate A1c reduction and are weight neutral. Many consider DPP-IV inhibitors as a substitute to sulfonylureas. They are not independently associated with hypoglycemia because they cause stimulation of insulin secretion and suppression of glucagon release in a glucose-dependent manner. As a result, this group of drugs may be particularly efficacious when hypoglycemia risk is a serious concern. In addition, due to their complementary mechanism of action, they are effective as add-on therapy to metformin, thiazolidinediones, or sulfonylureas.

Several recent studies have evaluated the safety and efficacy of this group of drugs during Ramadan fasting. In a study, Muslim diabetic patients attending primary care facilities in North West London, uncontrolled on metformin 2 gm daily, were randomized to addition of either vildagliptin

(50 mg/day) or gliclazide (160 mg bd) during Ramadan. At least one hypoglycemic event was recorded in two patients receiving vildagliptin and 16 patients receiving gliclazide.[14] Both gliclazide and vildagliptin were associated with similar reduction in HbA1c.

In another recent study from UK in Muslim diabetic patients fasting during Ramadan, no hypoglycemic event occurred in 30 patients on vildagliptin and metformin while 34 hypoglycemic events occurred in 15 of 41 patients on SU and metformin.[15] The mean between-group difference in the proportion of patients who experienced at least one hypoglycemic event 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 0.76%] post Ramadan, whereas SU had no effect on A1c. Vildagliptin caused no hypoglycemic event, was well adhered to and improved HbA1c, making it a suitable treatment option for many fasting during Ramadan.[15]

In a large open label study from Saudi Arabia, 1021 patients with T2DM (age ≥ 18 yr) who were on a stable dose of SU with or without metformin were randomized in a 1:1 ratio to either switch to Sitagliptin (100 mg) or to remain on their prestudy SU.[16] The proportion of patients who reported hypoglycemia was lower in the Sitagliptin group (6.7%) compared with the SU group (13.2%). In this study there were no reported severe events that needed medical assistance (visit to Physician or emergency room or hospitalization). The incidence of hypoglycemia with gliclazide was lower relative to other SUs and similar to that observed with Sitagliptin. Switching to a Sitagliptin-based regimen decreased the risk of hypoglycemia compared to remaining on a SU-based regimen. The evidence from these studies suggests that it may be safer to combine DPP-IV inhibitors rather than SUs with metformin in patients who are not well controlled when taking metformin alone and are planning to fast during Ramadan.

Alpha-Glucosidase Inhibitors

This group of antidiabetic agents inhibits the action of intestinal brush border enzyme α-glucosidase and retard the absorption of carbohydrates when taken with a meal. As a group, these drugs are only moderately effective and don't exert much effect on fasting glucose levels and hence are mostly used in combination with other antidiabetic agents. The risk of hypoglycemia is very low.[17] They are not associated with any systemic adverse effects but cause frequent mild to moderate GI side effects particularly flatulence. It is acceptable to continue with the prescribed doses of these drugs taken only with meals during fasting.

Conclusions

In general, oral hypoglycemic agents that act by increasing peripheral insulin sensitivity may be preferred as they carry a low risk of hypoglycemia. The newer SUs gliclazide MR and glimepiride can be safely used during Ramadan, whereas glibenclamide should be avoided because of the increased risk of hypoglycemia. DPP-IV inhibitors like Sitagliptin and Vildagliptin, which cause insulin secretion in a glucose-dependent manner, are safe and will play an important role in the management of T2DM during Ramadan fasting in future. It is not clear as yet whether the glycemic goals in patients observing fast during Ramadan should be relaxed so as to allow a safer period of fasting. The effect of short periods of intermittent hyperglycemia (as during Ramadan) on microvascular and macrovascular diabetic complications needs to be studied to address this question.

Summary of Recommended Changes to Treatment Regimen in Patients with Type 2 Diabetes Mellitus Taking Oral Hypoglycemic Agents who Fast During Ramadan[2]

Metformin 500 mg, three times daily – Change to Metformin, 1000 mg at the sunset meal, 500 mg at the predawn meal.

Glitazones, glucosidase inhibitors, or incretin-based therapies – No change needed.

If taking a long acting sulphonylurea, switch to a short acting preparation or metformin, or both; if a single daily dose is used, take this with the sunset meal.

If two or three doses are taken each day, take half the normal evening dose before dawn and the normal morning (and any midday) dose after sunset.

Emphasize the need to carry dextrose or glucose tablets at all times to treat hypoglycemia; explain the importance and legitimacy of breaking the fast in emergency situations.

Arrange for a review one week into Ramadan or earlier if concerns arise.

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