

Diabetes and Ramadan: A concise and practical update

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ABSTRACT

Despite the fact that the month of Ramadan includes 29–30 days and the duration of fasting for each day can last for between 12 and 16 h, it was estimated that a large number of individuals with diabetes do fast during Ramadan. In light of recent advancement of new pharmacological agents, drugs such as vildagliptin, sitagliptin, and liraglutide were found to be safe to use during this month of fasting. These therapeutic agents can also be used in combination with metformin. The use of sulfonylureas, in most of the recent guidelines about diabetes and Ramadan, seems not to gain much support due to the risk of hypoglycemia. In this review, we also addressed the use of insulin injection, insulin pump, and education before, during, and after Ramadan. Further research is needed to determine (i) the therapeutic benefit of new antidiabetic agents and (ii) the benefit of new technologies for the treatment of diabetes.

Keywords: Diabetes, fasting, Ramadan

Introduction

The month of Ramadan is a special occasion for all Muslims worldwide as it is the month of fasting. During fasting, Muslims abstain from all sort of oral intakes including medication. The duration of fasting starts before the beginning of dawn and ends with dusk, and this would explain the difference in hours of fasting in different parts of the world. Importantly, it was estimated that around 79% of individuals with type 2 diabetes are likely to fast.^[1] It is important to mention that the Quran has made a clear exemption for the sick, elderly, travelers, children, expectant, and breastfeeding mothers not to fast during Ramadan.^[2]

Due to the complexity of the management of diabetes during Ramadan, the understanding of the pathophysiology of fasting

with diabetes is important for the treating physician.^[3] The main concerns in fasting are hypoglycemia, hyperglycemia, dehydration, and ketoacidosis. Therefore, education about physical activity, food consumption, and medication adjustment is crucial to guard against complications. Before addressing the issues of treatment and patient education, we provide a comprehensive review of the major biochemical and physiological changes associated with fasting.

Biochemical and Physiological Changes during Fasting

Several studies have shown that fasting is associated with significant changes in the biochemical parameters among individuals with diabetes. For example, among 1301 participants with diabetes in one study, HbA1c, lipid profile, arterial blood pressure, and uric acid were significantly lower during Ramadan

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as compared to other periods of the year. One may conclude from the above that fasting may, in fact, be beneficial for the health of some individuals with diabetes.^[4]

Interestingly, no marked changes were observed in the mean glucose level, episodes of hypoglycemia, and mean glycemc excursion changes when continuous glucose monitoring among individuals with diabetes during Ramadan was applied.^[5] Furthermore, fasting in individuals with diabetes was shown to have improved leptin, adiponectin, and insulin sensitivity.^[6-9] Inflammatory markers were also shown to have diminished with plasma homocysteine, D-dimer level, C-reactive protein, interleukin-6, and fibrinogen being reduced during fasting.^[10,11] The improvement in cardiovascular and inflammatory markers may be in part attributed to decrease total calorie intake and, hence, weight reduction.^[12-14] The incidence of significant hypoglycemia and hyperglycemia in Type 2 diabetics is low as demonstrated in the study that continuously monitored blood glucose levels in Type 2-affected individuals.^[14] However, any individuals with diabetes should be educated to remain vigilant for these complications.

Ramadan is considered a month of celebration for many Muslims globally. It is with this state of ecstasy that the month carries the paradoxical risk of food excess after the hours of fasting. This is of particular importance to those individuals with fasting with diabetes.^[15] Therefore, its not surprising that excess intake of fat and carbohydrate during the night coupled with the decreased physical activity during the day were found to be associated with weight gain during Ramadan.^[16] Table 1 displays the physiological and biochemical changes associated with fasting.

Understanding the physiological and biochemical changes associated with fasting Ramadan allows a better understanding of the management approaches and application of new therapeutic agents.

Patient Education before, during, and after Ramadan

The purpose of patient education, clinical evaluation, and open reflections is, thus, to ensure patient's safety while fasting.^[31-33] It is important to emphasize that dietary counseling and education of patients are associated with a significant reduction of acute complications.^[34] For instance, the impact of individualized education before Ramadan was evaluated in individuals with Type 2 diabetes (774 individuals, from Egypt, Iran, Jordan, and Saudi Arabia). In this study, 67% received an individualized education (about nutrition, physical activity, drug adjustment, and glucose monitoring) and 33% received usual care. It was concluded that this particular study showed that individualized education improved safety during Ramadan in terms of decreasing hypoglycemic events, improved diabetes control, and prompted weight loss.^[35] Interestingly, in a small pilot study, telemonitoring was also shown to be of potential benefit in decreasing metabolic complications associated with Ramadan fasting, particularly hypoglycemia.^[36] The physician can also educate patient about that exemption from fasting is possible in case fasting will worsen the health of the individuals and this in-line with Islamic Fiqh (Islamic jurisprudence).^[37] Therefore, patient education is very important to achieve safe fasting and health-care providers are required to pass necessary information (guidelines, leaflets translated into different languages, and use of telemedicine).^[38,39] Involvement of all health practitioners may be another mean of providing safe education. For instance, pharmacists well trained about the management of diabetes during Ramadan may also contribute to patient education, especially in heavily populated or remote areas.^[40] An integrated approach addressing the management of Type 1 and Type 2 diabetes is provided in Table 2.

The International Group for Diabetes and Ramadan recommended (2015 guidelines) that Taraweeh prayers should be regarded as a physical exercise with the potential to induce dehydration and hypoglycemia.^[41] The Taraweeh prayers are long

Table 1: Summary of the biochemical and physiological changes associated with Ramadan fasting

Parameter	Impact of fasting	Reference
Glucose	Decrease in plasma glucose	[17,18]
Insulin sensitivity	Improvement of insulin sensitivity	[17,19,20]
Lipid profile	Lowered of LDL-C, total cholesterol, and triglyceride. Increased HDL-C	[21-23]
Body weight	Reduction in total body weight	[17]
Waist circumference	Decreased waist circumference	[17]
Inflammation	Lowered inflammatory markers such as CRP, IL-1, IL-6, and tumor necrosis- α	[24]
Blood pressure	Drop in blood pressure	[25]
Cardiovascular system	Incidence of ischemic heart disease, heart failure, and cerebral stroke do not increase with Ramadan fasting	[25]
Energy consumption	Decreased energy consumption	[26]
hormones	No change in estrogen, LH, FSH, and prolactin levels	[27]
Basal metabolic rate	Decreased basal metabolic rate	[26]
Other organs	No adverse effects of Ramadan fasting on the heart, lungs, hematological profile, endocrine, and neuropsychiatric functions	[27-30]

LH: Luteinizing hormone; FSH: Follicular stimulating hormone; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol; CRP: C-reactive protein; IL: Interleukin

Table 2: Summary of management of both Type 1 and 2 diabetes during Ramadan

Before Ramadan	Type 2 diabetes	Type 1 diabetes
<p>Education (monitoring of glucose, exercise, nutrition, blood pressure, lipid profile, and in case of hypoglycemia to stop fasting) - success in achieving fasting is largely depends on successful education</p> <p>On diet control, recommend small meals with regular exercise to avoid postprandial hyperglycemia (simple and complex carbohydrate in balanced meal to avoid refined sugar) preferable to try fasting before Ramadan for 2 or 3 days</p> <p>Do not recommend fasting for the following</p> <ul style="list-style-type: none"> Type 1 or Type 2 diabetes with diabetes complications or poor control Old age with illness or living alone Pregnancy or breastfeeding mother Recent history of ketoacidosis, hyperosmolar coma, severe, or recurrent hypoglycemia 	<p>Already on metformin: Use two-third of the daily dose immediately before sunset meal and the other one-third before predawn meal</p> <p>Metformin you can add vildagliptin or sitagliptin</p> <p>Pioglitazone can be used without modification of the dose (see above discussion for side effects)</p> <p>If sulfonylurea indicated, use gliclazide</p> <p>If sulfonylurea induced hypoglycemia, then switch to DPP-4 inhibitors</p> <p>Repaglinide can be used alone or with other medication to reduce postprandial hyperglycemia</p> <p>Insulin glargine can be used safely with metformin</p>	<p>Best strategy is to recommend the use of single injection of insulin glargine to be taken any time between the two meals, in addition to rapid or regular insulin according to need</p> <p>Further information can be found under the section type 1 diabetes</p>

DPP-4: Dipeptidyl peptidase-4

night prayers that last for 1–2 h and are performed during each day of the entire month of Ramadan. Therefore, individuals with diabetes are advised to drink plenty of water and to guard against hypoglycemia. Dates, a customary fruit that Muslims break their fast with, are regarded as having a low glycemic index and may result in possible improvement of glucose and lipid profile and possible reduction in cardiovascular risk factors.^[42-45] It is important that physicians should advise individuals with diabetes about the risk of developing hyperglycemia after Ramadan. Ramadan is followed by a 3-day festival known as Eid al-Fitr. This festival is usually celebrated with sweets and gifts and the potential for high calorific intake. It is, therefore, important that physicians should also emphasize the importance of resuming medications as normal and not in reduced doses.

Type 2 diabetes

The main concern with therapeutic agents during Ramadan was hypoglycemia.^[12-14] Therefore, individualized education and medication adjustment are crucial to ensure safe fasting.^[37] In the following discussion, we have included tables that provide a quick summary of medications and related studies, while in the text, we have provided the general consensus about whether to use or not to use these medications during Ramadan. Table 3 provides a list of studies about the use of sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides while Table 4 provides a list of studies about the use of incretins and glucagon-like peptide-1 (GLP-1) agonists.

General Consensus about Therapeutic Agents during Ramadan

We have included this guide consensus reached by the International Group for Diabetes and Ramadan published periodically in 2005, 2010, and 2015.^[1,16,41] We have also included recommendations from the South Asian Consensus Guidelines published in 2012.^[66] In addition, we also searched MEDLINE

for clinical trials during Ramadan, clinical reviews, and systemic reviews. For ease of reading, we have summarized the majority of these studies in the Tables 2-4 and only included general consensus in the following discussion.

Sulfonylureas

Due to the risk of hypoglycemia associated with sulfonylureas, some guidelines did not recommend them and others suggested to use them with caution during Ramadan. The only sulfonylurea associated with a minimum risk of hypoglycemia is gliclazide.

Metformin

There is general agreement in all published studies that metformin can be safely used during Ramadan; however, dose reduction is needed [Table 2].

Glitazones

Despite the low incidence of hypoglycemia with glitazones during Ramadan, their use is not widely recommended due to their side effects, for example, water retention, risk of heart failure, and weight gain.

Meglitinides

Meglitinides are safe to be used during Ramadan, and there is no risk of hypoglycemia.

Alpha-glucosidase inhibitors

Hypoglycemia is not a serious issue but is limited use due to gastrointestinal side effects. There were no randomized clinical trials available.

Dipeptidyl peptidase-4 inhibitors

There is general agreement that vildagliptin or sitagliptin as monotherapy is safe during fasting. They can be added to metformin and very low risk of hypoglycemia.

Table 3: Summary of studies about the use of sulfonylureas, biguanide, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides during the fasting month of Ramadan

Medication	Studies about the use of these medications during Ramadan
Sulfonylureas	Gliclazide MR 60 mg as monotherapy during Ramadan was associated with less hypoglycemic events and change in overall glycemic control ^[46] Gliclazide MR was significantly associated with 50% fewer confirmed hypoglycemic episodes in comparison with glimepiride ^[47] Three studies have shown glimepiride to be effective and safe during Ramadan ^[48-50] Despite the fact that Belkhadir claimed that glibenclamide (Daonil) is effective and safe for Type 2 diabetes during Ramadan, ^[51] due to high risk of hypoglycemia, it is not recommended during Ramadan Gliclazide MR was also recommended by the authors of “recommendations for management of diabetes during Ramadan” published in 2005 (chlorpropamide absolutely contraindicated during Ramadan due to risk of prolong and unpredictable hypoglycemia) ^[52]
Thiazolidinediones	Glitazone without changing the dose. ^[52] cautions needed with side effects such as heart failure and fluid retention
Metformin	Two-thirds of the dose to be taken before sunset meal and other third with predawn meal ^[52]
Meglitinides	Repaglinide three times a day plus single-dose insulin glargine is safe (no hypoglycemia, no change in glycemic control, or weight gain) for low-risk Type 2 diabetic individuals who insisted on fasting during Ramadan. ^[53] Repaglinide was associated with better glycemic control and lower frequency of hypoglycemia in comparison with glibenclamide ^[54] Glimepiride, repaglinide, and insulin glargine were tested in Type 2 diabetic individuals during Ramadan. There was no significant difference between the three therapies regarding glucose metabolism and rate of hypoglycemia ^[55]
Alpha-glucosidase inhibitors	Example is acarbose. No clinical trials during Ramadan. Very few report of hypoglycemia. Limited use due to gastrointestinal side effects, i.e., flatulence

MR: Modified release

Table 4: The recent therapeutic agents introduced for treatment of Type 2 diabetes

Medication	Studies about the use of these medications during Ramadan
The DPP-4 inhibitors, oral DPP-4 inhibitors, sitagliptin, and vildagliptin are new oral hypoglycemic agents	In systematic review, it was shown that individuals treated with either gliclazide or DPP-4 inhibitors while fasting during Ramadan have similarly low risks of experiencing symptomatic hypoglycemia ^[56] Treatment with vildagliptin was associated with fewer hypoglycemic events compared with sulfonylureas and good glycemic control ^[58,57,58] In multicenter study, to compare the use of vildagliptin and sulfonylurea with or without metformin in Indian Muslim patients with Type 2 diabetes mellitus, fasting during Ramadan. Vildagliptin-treated group showed better glycemic control and weight loss. Both medications were well tolerated ^[59] In a study from Northwest London, both gliclazide and vildagliptin were associated with similar reductions in HbA1c and a small but insignificant increase in weight. Less hypoglycemia events were recorded with vildagliptin ^[60] A multicenter, pragmatic, randomized study from clinical centers in India ($n=765$) and Malaysia ($n=1055$) showed that switching antihyperglycemic treatment to sitagliptin from a sulfonylurea reduced the risk of symptomatic hypoglycemia by 50% during Ramadan ^[61] Al Sifri <i>et al.</i> showed that switching to a sitagliptin-based regimen decreased the risk of hypoglycemia compared with a sulfonylurea-based regimen. ^[62] Several other studies showed that DPP-4 inhibitors provide a safe alternative therapeutic option during Ramadan ^[63,64]
GLP-1 mimetics exenatide and liraglutide	This study showed that liraglutide compared with sulfonylurea is well tolerated and may be an effective therapy in combination with metformin during Ramadan with more patients able to achieve target HbA1c, lose or maintain weight with no severe hypoglycemia ^[65] The South Asian Consensus Statement recommended the pre-Ramadan assessment, planning, prescription, and management and monitoring of patients who are on GLP-1 analogs, with or without other antidiabetic therapies ^[66]

GLP-1 and glucose-dependent insulinotropic polypeptide, which are incretins secreted from enteroendocrine cells postprandially in part to regulate glucose homeostasis. Dysregulation of these hormones is evident in Type 2 diabetes mellitus. In addition, four new drugs have been approved by regulatory agencies for treating Type 2 diabetes. These are exenatide, liraglutide (GLP-1 mimetics), and sitagliptin, vildagliptin (DPP-4 inhibitor).
GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase-4; HbA1c: Glycated hemoglobin

Glucagon-like peptide-1 mimetics

Due to the absence of hypoglycemia associated with the injection of exenatide and liraglutide, they can have a potential for safe use during Ramadan. In a randomized controlled trial, liraglutide in comparison to sulfonylurea is well tolerated during Ramadan and may be an effective therapy in combination with metformin in achieving glycemic control, with low risk of hypoglycemia and adequate weight loss.^[65] It is plausible to suggest that emerging

evidence supports the use of GLP-1 receptor agonists during fasting, albeit further evidence is needed.

Insulin and type 2 diabetes

The administration of long-acting insulin and mixed insulin is shown to be safe in individuals with Type 2 diabetes. For instance, premixed insulin (25% insulin lispro and 75% neutral protamine lispro) can be given with the sunset meal and half the usual

evening dose to be used with the predawn meal (suhour).^[67,68] Long-acting insulin-like glargine can be given as a single injection and this can be administered with short-acting insulin or metformin.^[69]

Type 1 diabetes

Due to the high risk of hypoglycemia, hyperglycemia, and diabetic ketoacidosis, individuals with Type 1 diabetes may find fasting challenging, especially those with poor diabetes control and comorbidities.^[11,12] Long-acting insulin use such as glargine is associated with fewer episodes of hypoglycemia, and the use of basal bolus regimen is preferred as compared with the conventional twice daily insulin regimen.^[68,69,70] However, studies have shown that NovoMix insulin has been used in Ramadan with some success. For instance, 100% of the pre-Ramadan dose of 70/30 mix insulin corresponding with the sunset meal (iftar) and 50% at a predawn meal would produce good results.^[41] Furthermore, the use of 70% of intermediate-acting insulin and 30% of short-acting insulin with two meals is also shown to be safe and episodes of serious hypoglycemia or ketoacidosis were observed.^[71,72] Further research is needed to evaluate the safety of insulin pump during fasting.^[73]

Insulin pump

Several studies have shown the potential benefit of insulin pump during the fasting month. In adolescents with Type 1 diabetes, the use of subcutaneous insulin infusion (continuous subcutaneous insulin infusion) was associated with less hypoglycemia and improvement in diabetes control.^[74] Interestingly, case series studies in adolescents and adults with Type 1 diabetes mellitus receiving insulin pump therapy during fasting showed fewer hypoglycemia episodes and adequate glycemic control.^[75] The use of highly advanced insulin pumps or artificial pancreas may provide an excellent opportunity for individuals with diabetes to fast without the risk of hypoglycemia. For instance, the new MiniMed 640G insulin pump is designed to sense hypoglycemia before it occurs and suspends insulin infusion delivery immediately. Less advanced pump such as Medtronic insulin pump, which stops insulin infusion when prespecified sensor glucose threshold is reached, has shown potential benefit. For instance, in a study of 49 patients fasted, the use of insulin pump was associated with less severe hypoglycemia and average diabetes control, no deterioration in diabetes control.^[76] In a prospective observational, single-center study, the use of insulin pump was not associated with a change in insulin administered, no major hypoglycemia event, and stable glycemic control.^[77] Due to high cost, an insulin pump is not widely used.

New Pharmacological Agents for Diabetes and Their Potential Role during Ramadan Fasting

Within the last 5 years, several pharmacological agents for the treatment of diabetes were discovered. Importantly, the main potential benefits of all these medications are a lower risk of

hypoglycemia (insulin glargine 300, inhaled insulin - Afrezza, SGLT2 inhibitors, insulin degludec, and IDegLira [insulin degludec + liraglutide]). Therefore, we recommend that clinical studies in the future may reveal which of these medications can be safely used during Ramadan fasting.

Pregnancy, Diabetes, and Fasting

Currently, there is no scientific evidence to recommend fasting for pregnant women with diabetes. The Islamic Holy texts also exempt pregnant and lactating women from fasting.

Conclusion

In recent years, numerous studies about diabetes and Ramadan fasting were published. The dipeptidyl peptidase-4 inhibitors such as sitagliptin and vildagliptin are associated with less risk of hypoglycemia without significant hyperglycemia during Ramadan. In addition, these agents can also be safely used alongside metformin. The use of sulfonylureas is not widely endorsed in the recent guidelines due to the risk of hypoglycemia. The use of liraglutide is so far appeared to be potentially safe therapy during Ramadan, but as yet there is one study about using liraglutide during Ramadan. Administration of the long-acting insulin such as glargine has shown potential benefit in selected patients with diabetes. An insulin pump can potentially enhance patients' chances to fast Ramadan without significant risks. There are still a lot of unanswered questions about the new therapeutic treatments for diabetes and Ramadan; therefore, further research is needed to evaluate the therapeutic benefit of these agents.

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Conflicts of interest

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