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Special Article

Diabetes Canada Position Statement for People With Types 1 and 2 Diabetes Who Fast During Ramadan

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Key Messages

- Many Canadian health-care providers have limited knowledge about the specifics of fasting during Ramadan.
- Providers find it difficult to counsel their patients with diabetes who intend to fast during Ramadan.
- Providers must teach patients about healthful behaviours, glucose monitoring and adjustments of antihyperglycemic medications so patients can maintain their health and safety during fasting.
- Adults with type 1 or 2 diabetes who intend to fast should receive individualized assessments before Ramadan to judge their suitability for fasting and to formulate individualized management plans.

Keywords:
diabetes
glucose monitoring
insulin
pharmacotherapy
Ramadan fasting

A B S T R A C T

Objective: Fasting from dawn to dusk during Ramadan, including abstaining from water and food, is 1 of the pillars of Islam and is observed by the majority of Muslims. Most research concerning diabetes and fasting during Ramadan originates from Middle Eastern or South Asian countries; however, differences exist in hours of work and fasting, pharmacotherapy and blood glucose monitoring between these countries and Canada.

Methods: An expert forum of 7 Canadian experts and 1 international expert collaborated to develop Canadian guidelines using the same evidence-based principles, with the exception of an independent methods review used for the Diabetes Canada clinical practice guidelines. Diabetes Canada scientific leadership and Canadian health-care providers performed independent external reviews. Religious leaders endorsed the position statement and provided letters of support. An informed patient participated in the position-statement development. Each recommendation was approved with 100% consensus of the expert forum.

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Results: Recommendations for risk stratification, education, pharmacotherapy and blood glucose monitoring for adults with type 1 and type 2 diabetes who intend to fast during Ramadan have been developed.
Conclusions: This is the first Canadian position statement on the topic of Ramadan fasting and diabetes. It was developed by an expert faculty and endorsed by Diabetes Canada, and provides guidance about pharmacotherapy and glucose monitoring for health-care providers so that they can assist Canadian Muslims living with diabetes to observe fasting during Ramadan safely.

Mots clés :
diabète
surveillance de la glycémie
insuline
pharmacothérapie
jeûne du Ramadan

R É S U M É

Objectif : Le jeûne de l'aube au crépuscule pendant le Ramadan, incluant une abstinence d'eau et de nourriture, est l'un des piliers de l'islam et est observé par la majorité des musulmans. La plupart des recherches concernant le diabète et le jeûne pendant le Ramadan proviennent des pays du Moyen-Orient ou d'Asie du Sud; Cependant, il existe des différences concernant les heures de travail et de jeûne, la pharmacothérapie et la surveillance de la glycémie entre ces pays et le Canada.
Méthodes : Un forum d'experts composé de sept experts canadiens et d'un expert international a collaboré afin d'établir des lignes directrices canadiennes en utilisant les mêmes principes que celles utilisées pour les lignes directrices de pratique clinique de Diabète Canada, fondées sur des données probantes, à l'exception d'un examen de méthodes indépendantes. La direction scientifique de Diabète Canada et les prestataires de soins canadiens ont effectué des examens externes indépendants. Les chefs religieux ont approuvé l'énoncé de principe et ont fourni des lettres de soutien. Un patient informé a participé á l'élaboration de l'énoncé de principe. Chaque recommandation a été approuvée avec 100% de consensus au sein du forum d'experts.
Résultats : Des recommandations ont été établies pour la stratification des risques, l'éducation, la pharmacothérapie et la surveillance de la glycémie chez les adultes atteints de diabète de type 1 et de type 2 qui ont l'intention de jeûner pendant le Ramadan.
Conclusions : Ceci constitue le premier énoncé de principe canadien au sujet du jeûne du Ramadan et du diabète. Il a été élaboré par un expert universitaire et approuvé par Diabète Canada et il fournit des conseils sur la pharmacothérapie et la surveillance de la glycémie aux prestataires de soins de santé afin qu'ils puissent aider les musulmans canadiens à observer le jeûne pendant le ramadan en toute sécurité.

Introduction

According to Canada's 2011 National Household Survey, there were 1,053,945 Muslims in Canada, constituting 3.2% of the population (1). The Public Health Agency of Canada estimates the prevalence of diabetes in Canada to be 3.5 million, according to 2011 data, or 9% of the total population (2). Based on these numbers, it is estimated that there are approximately 95,000 Muslims with diabetes living in Canada. However, this may be an underestimation due to the recognized higher risk for type 2 diabetes among immigrants from South Asian and Middle Eastern countries (3,4). A recent report from the Washington-based Pew Forum on Religion and Public Life suggested that the Muslim population will increase both in number and proportion to 2.7 million, or 6.6% of the Canadian population by 2030 (5). Based on this prediction, it is essential that prevention and management strategies be developed that are culturally appropriate and tailored to the Muslim population in Canada.

Fasting from dawn to dusk during Ramadan, including abstaining from water and food, is 1 of the pillars of Islam and is observed by the majority of Muslims (6). This necessitates changes in eating and sleeping habits. Traditionally, the predawn and sunset meals are different from regular meals and often include more carbohydrate-containing foods that have high glycemic indexes. In addition, individuals tend to consume larger-than-usual portions during these meals, especially at the sunset meal when they break the fast.

Each subsequent calendar year, Ramadan month starts 10 to 11 days earlier than the previous year because the Islamic calendar follows a lunar pattern and is, therefore, shorter than the Gregorian calendar. As a result, in Canada, the fasting time from dawn to dusk can vary significantly from a short day in winter to a very long day in summer. Additionally, because day length varies by latitude, the number of fasting hours can vary significantly by location in Canada; for instance, the fasting period in Toronto may be shorter than that in the same day in Edmonton. For the next 6 years, until about 2024, fasting times will be longer than 12 h for the majority of the Ramadan fasting days in most parts of Canada, with many of the fasting days being longer than 18 h. Long hours of absolute fasting during the daytime and eating during the night can increase the risk for complications, such as dehydration, hypoglycemia and hyperglycemia for individuals with diabetes. Muslims living in Muslim-majority countries have some flexibility in terms of working hours during Ramadan, but these accommodations are not typically available in Canada, adding to the challenge of observing the fast, especially for those with diabetes.

Islam offers exceptions for those who are unable to fast, including those who are traveling, sick or at risk for serious harm to health. However, fasting during Ramadan is such an integral part of the Muslim culture that many individuals ignore these allowances and choose to fast despite their medical conditions. When asked, Islamic scholars usually advise Muslims to ask their health-care providers about their ability to fast safely during Ramadan. Conversely, most health-care providers, especially those practicing in North America, have limited knowledge about the specifics of fasting during Ramadan, making it difficult for many Muslims to make informed decisions.

Most of the epidemiologic and observational research published on the topic of diabetes and fasting during Ramadan originates from Middle Eastern or South Asian countries. As mentioned, differences exist in work hours and hours of fasting during Ramadan between these countries and Canada. In addition, pharmacotherapy usage, in regard to both insulin and noninsulin antihyperglycemic agents, is known to differ according to geography (7). The availability of technology for diabetes management (e.g. continuous subcutaneous insulin infusion [insulin pump] therapy and continuous and flash glucose monitoring) is also different in Canada than in Asia and North Africa. As a result, conclusions derived from studies in these countries may not be readily generalizable to Canada.

Table 1
Risk stratification for fasting during Ramadan by people living with diabetes

Classification of risk	Risk factors
Very high risk **Must not fast**	• Poorly controlled type 1 diabetes (defined as a pre-Ramadan A1C >9%) • Severe hypoglycemia within 3 months, recurrent hypoglycemia and/or unawareness of hypoglycemia • Ketoacidosis within 3 months • Hyperosmolar hyperglycemic coma within 3 months • Acute illness • Advanced macrovascular complications, renal disease (on dialysis, stage IV or V), cognitive dysfunction or uncontrolled epilepsy • Pregnancy with diabetes or GDM treated with insulin
High risk **Should not fast**	• Type 2 diabetes with sustained poor glycemic control* • Well-controlled type 2 diabetes taking MDI or mixed insulin • Pregnancy with type 2 diabetes or GDM controlled by diet only • CKD stage 3 or stable macrovascular complications • Performing intense physical labour • Well-controlled type 1 diabetes
Moderate/low risk **Can fast, with medical advice**	• Well-controlled diabetes • Treated by lifestyle alone or with: metformin, acarbose, incretin therapies (DPP-4 inhibitors or GLP-1 RA), second-generation SU, SGLT2 inhibitors, TZD or basal insulin in otherwise healthy individuals

A1C, glycated hemoglobin levels; *CKD,* chronic kidney disease; *DPP-4,* dipeptidyl peptidase; *GDM,* gestational diabetes mellitus; *GLP-1 RA,* glucagon-like peptide-1 receptor agonist; *MDI,* multiple daily injections; *SGLT2,* sodium-glucose cotransporter-2; *SU,* sulfonylurea; *TZD,* thiazolidinedione.
Note: Reproduced with permission from Hassanein et al (8).
* The level of glycemic control is to be agreed upon between the health-care provider and the person living with diabetes.

The International Diabetes Federation (IDF) and Diabetes and Ramadan (DAR) International Alliance guidelines categorize people living with diabetes into risk groups based on various patient characteristics and the antihyperglycemic agents used (Table 1) (8). The *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* recommend, in the Nutrition Therapy chapter, that Canadians living with diabetes who fast during Ramadan should follow the IDF-DAR guidelines on dietary counselling (9).

The intent of this Canadian position statement on diabetes and Ramadan fasting is to complement the exhaustive IDF-DAR guidelines, as well as Diabetes Canada's clinical practice guidelines, by formulating evidence-based recommendations concerning glucose monitoring and pharmacotherapy for adults with diabetes in Canada who intend to fast during Ramadan. The position statement is meant to serve as a guide for Canadian health-care providers to help maintain the health and safety of their Muslim patients during Ramadan fasting. The recommendations in this position statement are based on a literature review of diabetes and Ramadan fasting, but the clinical principles could be adapted for other instances of fasting performed for religious or alternative reasons by people with diabetes.

Methods

An expert forum of 7 Canadian experts and an international topic expert (MH) collaborated to formulate, edit and review the Canadian position statement on diabetes and Ramadan fasting. The same guiding principles used in the development of the Diabetes Canada clinical practice guidelines were used to develop the position statement (10), and the chair of the 2018 Diabetes Canada clinical practice guidelines participated in the statement's development. An informed patient (a 78-year-old man with a 34-year history of diabetes who fasts yearly for Ramadan) also participated in the position statement's development so as to ensure that patient values and preferences were represented.

Clinically relevant questions were developed by the expert committee and served as the focus of a PubMed literature search. Only antihyperglycemic medications or glucose-monitoring devices with Health Canada Notice of Compliance granted by February 15, 2018, were included in the recommendations. Each recommendation was reviewed and graded by the expert committee and was approved with 100% consensus. The grading of the recommendations was based on the best available evidence, as well as the applicability to the Canadian population and followed the methods used by the 2018 Diabetes Canada clinical practice guidelines (11). However, unlike the 2018 Diabetes Canada clinical practice guidelines, the position statement did not undergo an independent methods review process to assess the accuracy of the grading of the evidence. In addition, the assigned grading was lowered if any of the following conditions existed: 1) evidence was not applicable to the Canadian population; 2) findings from relevant (and equally rigorous) studies of the topic were conflicting; and/or 3) specific subgroups of interest were not well represented in a study.

The position statement underwent independent external review for endorsement by the chair of the 2013 Diabetes Canada clinical practice guidelines, the president of Diabetes Canada, the Diabetes Canada Professional Section co-chair, a diabetes specialist, a general practitioner, 2 certified diabetes educators, a pharmacy student and a person with diabetes. A religious scholar from the Islamic Society of North America Canada endorsed the position statement and provided his letter of support.

The position statement is broken down into sections based on key topics addressed during its development.

Pre-Ramadan Diabetes Management Planning

Optimization of diabetes management pre-Ramadan is essential because glycemic control prior to Ramadan has been shown to correlate with glycemic control during the period of fasting (12). The pre-Ramadan period represents an opportunity for health-care providers to encourage their patients to make positive changes in their healthful behaviors via dietary modifications during and beyond Ramadan.

The recommended time to evaluate a patient's suitability for Ramadan fasting, to counsel on dietary modifications and to implement therapeutic changes in diabetes management is during the 1 to 3 months prior to the beginning of the fasting month. In a retrospective study, individuals with type 2 diabetes who had not received structured education were observed to have an increased rate of hypoglycemia and weight gain during Ramadan. Those who received pre-Ramadan education exhibited an approximate 50% reduction in their rate of hypoglycemia, experienced 0.7 kg of weight loss during Ramadan and had stable glycemic control (13).

Recommendations

1. For adults with type 1 or type 2 diabetes intending to fast, a pre-Ramadan individualized assessment should be performed 1 to 3 months prior to the start of fasting to reduce the risk for hypoglycemia, with maintenance of stable glycemic control (Grade C, Level 3) (13). The assessment should include:
   a. Appropriate risk stratification
   b. Review of positive and adverse experiences during previous fasting
   c. Formulation of an individualized treatment plan

d. Discussion of the importance of antihyperglycemia medication adjustment, meals, physical activity, frequency of self-monitoring of blood glucose (SMBG) and situations where it would be medically indicated to break the fast (Grade D, Consensus for all).

2. Dietary counselling should be provided based on IDF-DAR and Diabetes Canada clinical practice guidelines (Grade D, Consensus).
3. Risk stratification for people living with diabetes, including very-high-risk special populations (i.e. frail individuals, pregnant women, etc.), should be based on the published IDF-DAR guidelines (Table 1) (Grade D, Consensus).
4. For individuals who intend to fast despite being advised of their high-risk stratification, scheduled contact during Ramadan (either in clinic, virtually or over the phone) with their health-care providers or diabetes health-care team is recommended to review glucose records and make further adjustments to therapy (Grade D, Consensus).
5. People in any risk strata of the IDF-DAR guidelines should be advised to break their fast and seek immediate medical attention if they experience any documented episode of hypoglycemia or symptomatic hyperglycemia during Ramadan (Grade D, Consensus).
6. A post-Ramadan follow-up health-care visit should be considered to review any concerns with diabetes management and to help formulate a strategy for future fasting (Grade D, Consensus).

Noninsulin Pharmacotherapy for People with Type 2 Diabetes During Ramadan

Below is an alphabetical list of drug classes used to treat diabetes in Canada and a discussion of their use during Ramadan.

Alpha-glucosidase inhibitors

Although commonly used in countries in Asia, this drug class is infrequently prescribed in Canada due to its modest glycated hemoglobin (A1C)-lowering efficacy and its adverse gastrointestinal effects. Because of its low risk for resulting in hypoglycemia, this drug class is safe to continue during Ramadan if it is tolerable from a gastrointestinal standpoint and should be taken with both meals.

Biguanides

Similar to its first-line use in the treatment of type 2 diabetes, metformin maintains its primacy during Ramadan. Although it is generally considered safe for fasting, given its low risk for hypoglycemia, there are no safety studies of metformin during Ramadan. To minimize gastrointestinal intolerance, metformin should be taken ideally with the sunset and predawn meals while fasting during Ramadan. Alternatively, extended-release versions of this medication can be taken once daily with the main meal, usually the sunset meal, during Ramadan.

Dipeptidyl-4 inhibitors

Over the past 10 years, the use of this drug class has grown due to its ability to lower blood glucose levels while including a low risk for hypoglycemia and good tolerability. Multiple studies comparing these agents to sulfonylureas have suggested a significant reduction in symptomatic hypoglycemia during Ramadan in favour of dipeptidyl-4 (DPP-4) inhibitors (14–18). For people who eat a light predawn meal during the fasting month and for those who prefer to take their medications only with their sunset meals, switching to a once-daily, extended-release, fixed-dose combination of metformin with a DPP-4 inhibitor taken at the sunset meal may be preferred during Ramadan.

Glucagon-like peptide-1 receptor agonists

In addition to potent A1C reduction and low risk for hypoglycemia, an additional benefit of glucagon-like peptide (GLP)-1 receptor agonists relevant to the fasting period includes increased satiety along with a beneficial impact on weight. Studies conducted during Ramadan showed that liraglutide leads to significant improvement in glycemic control and reduction in symptomatic hypoglycemia and weight compared to sulfonylureas (19,20). Because of the potential adverse effect of nausea and abdominal discomfort, this drug class should not be started during the 4 weeks prior to Ramadan but can be continued during the fasting month if it had been started previously and is tolerated well. Shorter-acting GLP-1 receptor agonists (exenatide and lixisenatide) should be taken before meals (especially prior to the sunset meal during Ramadan), while longer-acting agents can be taken at any time.

Insulin secretagogues

Insulin secretagogues have been associated with a 20% increased risk for hypoglycemia during Ramadan (21). However, this risk is not seen uniformly throughout the class; both gliclazide and repaglinide show relatively lower risk for hypoglycemia during Ramadan (14,15,21,22). Because of the hypoglycemia risk, secretagogues should be adjusted prior to Ramadan, preferably by switching to another class of antihyperglycemic agent that does not include increased risk for hypoglycemia. If insulin secretagogues are continued, counselling about hypoglycemia and risk-reduction strategies, including reduced dosages, discontinuing glyburide in favour of gliclazide or a shorter-acting secretagogue taken only with the postsunset meal, are strongly recommended. If glyburide must be continued during this month, the morning predawn meal dose should be held or reduced by at least 50% to reduce the risk for hypoglycemia.

Sodium-glucose cotransporter-2 inhibitors

Because of the osmotic diuresis and natriuresis associated with this class of antihyperglycemics, a concern regarding the risk of volume depletion exists during Ramadan, especially during the longer summer fasting periods in Canada. Studies conducted during Ramadan have compared this drug class to sulfonylureas, and they showed significantly lower risks for hypoglycemia and no increase in diabetic ketoacidosis, albeit with a slightly increased risk for volume-depletion symptoms (23,24). Because of the risk for dehydration, these medications should not be started during the 4 weeks prior to Ramadan. Health-care providers should consider, on an individual basis, the pros and cons of either reducing or holding the dosage of sodium-glucose cotransporter-2 (SGLT2) inhibitors temporarily during the month of fasting. A temporary hold may be considered, especially for individuals at high risk for volume depletion, such as age older than 75 years, estimated glomerular filtration rate lower than 60 mL/min/1.73 m^2 and those taking loop diuretics. However, caution should be used when reducing or holding this drug class in individuals with histories of established clinical cardiovascular disease because it has the potential to result in heart-failure exacerbation or an interruption of the cardioprotective benefit of these agents. If such high-risk individuals become symptomatic with either orthostasis or heart-failure symptoms during Ramadan, they should automatically be restratified as being at very high risk and discouraged from future fasting.

Thiazolidinediones

A study comparing pioglitazone to other oral antihyperglycemic agents during Ramadan did not show a significant risk for hypoglycemia (25). Individuals who are currently taking this medication can continue taking it during Ramadan. Because the maximum glucose-lowering effect of this class takes approximately 1 month, this timeline should be considered prior to switching or initiating thiazolidinediones during Ramadan.

General Pharmacotherapy Advice Before Ramadan

People living with type 2 diabetes, who are taking metformin, GLP-1 receptor agonists, insulin secretagogues or SGLT2 inhibitors prior to initiating Ramadan fasting should be educated about the symptoms of vomiting, diarrhea and orthostasis, with instructions to break their fast and seek immediate medical attention should any of these symptoms develop.

Recommendations

See Table 2.

1. Agents that have a low risk of causing hypoglycemia or orthostasis (metformin, DPP-4 inhibitors, alpha-glucosidase inhibitors and thiazolidinediones) can be used safely during Ramadan (Grade B, Level 2 [14,15] for sitagliptin; Grade B, Level 2 [25] for pioglitazone; Grade D, Consensus for all others).
2. When feasible, insulin secretagogues should be switched to antihyperglycemic agents with lower risk for hypoglycemia for the duration of Ramadan so as to reduce the risk for hypoglycemia (Grade B, Level 2 [14,15] for sitagliptin; Grade B, Level 2 [19,20] for liraglutide; Grade B, Level 2 [23] for canagliflozin; Grade B, Level 2 [24] for dapagliflozin; Grade D, Consensus for others), especially for individuals with higher risks for hypoglycemia (Grade D, Consensus). If it is not feasible to switch to a different class, insulin secretagogues with lower risks for hypoglycemia (gliclazide, repaglinide) should be used to reduce risks for hypoglycemia (Grade C, Level 2 [14,15] for gliclazide; Grade C, Level 2 [22] for repaglinide) along with concomitant dosage reduction of 25% to 50% (Grade D, Consensus). Repaglinide dosage should be adjusted according to alterations in meal times and sizes during Ramadan (Grade D, Consensus). If glyburide is continued during fasting, the morning dose should be held or reduced by ≥50%, depending on the carbohydrate content of the predawn meal (Grade D, Consensus).
3. GLP-1 receptor agonists can be continued during Ramadan to maintain glycemic control with low rates of hypoglycemia (Grade C, Level 2 [19,20] for liraglutide; Grade D, Consensus for others) but should not be started within 4 weeks prior to Ramadan because of possible adverse gastrointestinal effects (Grade D, Consensus). If adverse gastrointestinal effects occur during Ramadan, dosage reduction or temporary discontinuation of this class should be considered (Grade D, Consensus).
4. SGLT2 inhibitors can be continued during Ramadan to maintain glycemic control in cases of low rates of hypoglycemia (Grade C, Level 2 [23] for canagliflozin; Grade C, Level 2 [24] for dapagliflozin; Grade D, Consensus for empaglifozin). Dosage reduction or a temporary hold of SGLT2 inhibitor medication should be considered for people at high risk for volume depletion (age >75 years, estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or taking loop diuretics) (Grade D, Consensus). For people with clinical cardiovascular disease, SGLT2 inhibitors should not be held during Ramadan due to their role in reducing major cardiovascular events and hospitalizations due to heart failure (Grade D, Consensus).
5. People living with type 2 diabetes who develop vomiting, diarrhea or orthostasis during Ramadan should break their fast immediately, hold certain antihyperglycemic medications (metformin, secretagogues, GLP-1 receptor agonists, SGLT2 inhibitors), continue blood glucose monitoring and seek immediate medical attention (Grade D, Consensus).

Insulin Management of Type 2 Diabetes During Ramadan

There is limited literature about the use of commonly used insulin regimens during Ramadan. Most studies (either observational or randomized trials) have been small, but 2 observational studies found insulin glargine to be safe during Ramadan, showing no significant increases in hypoglycemia compared to nonfasting individuals or when compared to those taking oral antihyperglycemic agents (26,27). A multinational study reported an increased rate of hypoglycemic events in 349 patients treated with insulin glargine and repaglinide once daily with the sunset meal during Ramadan compared to before Ramadan (28). An open-label study randomized 49 fasting subjects to glimepiride, repaglinide or insulin glargine and compared them to 16 nonfasting subjects with type 2 diabetes. This study found no difference in the risk for hypoglycemia between the fasting and nonfasting groups (27).

A small, randomized, open-label crossover study compared insulin lispro to regular human insulin, both taken at predawn and sunset meals, in combination with twice-daily neutral protamine Hagedorn (NPH) insulin as basal insulin. The insulin lispro group showed lower 1-h and 2-h postsunset meal blood glucose values compared to the regular human insulin group. Although the number of subjects with hypoglycemic episodes was similar in both arms, the frequency of hypoglycemia was higher with regular insulin compared to insulin lispro (2.6±0.2 vs. 1.3±0.1 episodes per person every 14 days; $p<0.002$) (29).

Insulin lispro Mix 25 was compared to human insulin 30/70 in an open-label randomized crossover study of 151 subjects. The evening premeal fasting and the 2-h postprandial excursion after the sunset meal were significantly lower with insulin lispro Mix 25 compared to insulin 30/70. There was no difference in hypoglycemia between the 2 groups (30). Another observational study switching the evening dose of human insulin 30/70 twice daily to lispro Mix 50 in one half of the participants 2 weeks before Ramadan found no significant reduction in hypoglycemia (31).

A recent open-label treat-to-target trial randomized 263 subjects from 5 different countries to twice-daily insulin degludec-aspart combination (not available in Canada) or biphasic insulin aspart 30. The degludec-aspart combination had significantly lower rates of overall and nocturnal hypoglycemia, with similar A1C efficacy (32). In this trial, the insulin dosage adjustment pre-Ramadan was in tandem with the IDF-DAR recommendations (8). Another open-label controlled multicentre cluster randomized trial comparing insulin detemir (40% total daily dosage) given at sunrise and biphasic insulin aspart (60% total daily dosage) given at the evening meal to standard care. The intervention group was noninferior to the control group in terms of the mean 4-point SMBG levels during fasting; however, the intervention group was associated with a lower rate of adverse events, including hypoglycemia and syncope (33).

In conclusion, despite the limited data available regarding the optimal insulin regimen or type for patients with type 2 diabetes during Ramadan, results from small studies suggest that it may be safe to fast on insulin therapy as long as the treatment is individualized and modified. Individuals treated with premixed or intermediate-acting NPH insulin may be at higher risk for hypoglycemia and insulin stacking when the duration of the fast exceeds 15 h and the time difference between the predawn and sunset meals is shorter than 8 h.

Table 2
Noninsulin and insulin pharmacotherapy for type 2 diabetes: Recommendations for changes and adjustments 1 to 3 months prior to Ramadan

Medications considered safe during Ramadan		
Drug class	Dosage	Recommendation
Biguanides		
Metformin	500–850 to 1,000 mg BID	No change
Metformin XR	500 to 2,000 mg OD	No change
DPP-4 inhibitors		
Sitagliptin	25–50 to 100 mg OD	No change
Saxagliptin	2.5 to 5 mg OD	No change
Linagliptin	5 mg OD	No change
DPP-4 inhibitor/metformin combination		
Sitagliptin/metformin	50/500, 850 or 1,000 mg BID	No change
Sitagliptin/metformin XR	50/500, 50/1,000 or 100/1,000 mg OD	No change
Linagliptin/metformin	2.5/500, 850 or 1,000 mg BID	No change
Saxagliptin/metformin	2.5/500, 850 or 1,000 mg BID	No change
Alpha-glucosidase inhibitors		
Acarbose	25–50 to 100 mg TID	No change
Thiazolidinediones		
Pioglitazone	15–30 to 45 mg OD	No change
Medications safe to continue but not to start		
Drug class	Dosage	Recommendation
SGLT2 inhibitors		
Canagliflozin Dapagliflozin Empagliflozin	100–300 mg OD 5–10 mg OD 10–25 mg OD	1. Reduce dose or hold temporarily prior to fasting for those with high risk for dehydration (>75 years of age, eGFR <60 mL/min/1.73 m^2, loop diuretic) 2. Do not hold dose for those with clinical cardiovascular disease 3. Do not initiate within 4 weeks prior to or during Ramadan 4. Hold for vomiting, diarrhea or orthostasis
SGLT2 inhibitor/metformin combination		
Canagliflozin/metformin Dapagliflozin/metformin Empagliflozin/metformin	50 or 150/500, 850 or 1,000 mg BID 5/850 or 1,000 mg BID 5 or 12.5/500, 850 or 1,000 mg BID	1. Reduce dose or hold temporarily prior to fasting for those with high risk for dehydration (>75 years of age, eGFR <60 mL/min/1.73 m^2, loop diuretic) 2. Do not hold dose for those with clinical cardiovascular disease 3. Do not initiate within 4 weeks prior to or during Ramadan 4. Hold for vomiting, diarrhea or orthostasis
GLP-1 receptor agonists		
Liraglutide Exenatide Exenatide extended release Dulaglutide Lixisenatide Semaglutide	0.6–1.2 to 1.8 mg OD 0.6–1.2 to 1.8 mg OD 2 mg qweekly 0.75–1.5 mg qweekly 10–20 mg OD 0.25–0.5 to 1 mg qweekly	1. No change if tolerating prior to Ramadan 2. Do not initiate within 4 weeks prior to or during Ramadan 3. Reduce dose or hold for nausea, vomiting, diarrhea or orthostasis 4. Exenatide should be taken before 2 meals 5. Lixisenatide should be taken before sunset meal 6. Longer-acting agents can be taken any time
Medications that may need to be adjusted/changed due to risk for hypoglycemia		
Secretagogue	Dosage	Recommendation
Glimepiride Glyburide Gliclazide MR Repaglinide	1–2–3 to 4 mg OD 2.5–5 to 10 mg BID 30–60 to 120 mg OD 0.5–1–2 to 4 mg AC meals	1. Consider switching to an alternative drug class with lower risk for hypoglycemia 2. If continuing, consider switching to a safer agent within a class with lower risk for hypoglycemia and reducing dose by 25% to 50% 3. Repaglinide may be safest in class; adjust according to alteration of meal times and sizes during Ramadan
Insulin adjustment and change recommendations for type 2 diabetes		
Insulin type		Recommendation
Basal		
Degludec, detemir, glargine U100, glargine U300		• Preferred options; consider reducing dose by 15% to 30%
Neutral protamine Hagedorn (NPH)		• Consider switching to longer acting basal analogs or reduce dose by 25% to 50%
Short-acting		
Aspart/faster aspart, glulisine, lispro		• Preferred options. Take usual evening meal dose at sunset meal, reduce predawn meal dose by 25% to 50%, omit lunchtime dose
Human regular insulin		• Consider switching from human regular insulin to rapid-acting insulin analogs
Premixed		
Biphasic insulin aspart, human insulin mix 30, lispro mix 25, lispro mix 50		• Consider switching to an alternative regimen (basal insulinoral agents, basal insulin GLP-1 receptor agonist, basal insulin plus 1 mealtime bolus insulin, or basal-bolus insulin taken with each meal), depending on patient- and agent-level characteristics, when feasible • If continuing, reduce predawn meal dose by 25% to 50% and take usual evening meal dose at sunset meal

BID, twice daily; *DPP-4*, dipeptidyl peptidase; *eGFR*, estimated glomerular filtration rate; *GLP-1*, glucagon-like peptide-1; *OD*, once daily; *SGLT2*, sodium-glucose cotransporter-2; *TID*, three times daily.

Recommendations

1. For adults with type 2 diabetes needing insulin initiation just prior to or during Ramadan, a basal, long-acting analog insulin (detemir, glargine) or an ultralong analog insulin (degludec, glargine U300) may be preferred over intermediate-acting basal or premixed insulin options during the fasting month to reduce the risk for hypoglycemia (Grade D, Consensus).
2. For individuals already on a regimen containing intermediate-acting insulins (NPH, premixed):
   a. Consider switching to a long-acting or ultralong insulin basal analog 1 to 3 months prior to Ramadan, when feasible, so as to lower the risk for hypoglycemia (Grade D, Consensus)
   b. U500 formulation of human regular insulin should be treated like intermediate-acting insulin, and consideration should be given to switching to an alternative insulin regimen pre-Ramadan (Grade D, Consensus)
   c. When switching from premixed or self-mixed insulin, the choice of regimen options (basal insulin-oral antihyperglycemic agents, basal insulin-GLP-1 receptor agonists, basal insulin-plus 1 mealtime bolus insulin or basal-bolus insulin given with each meal) should be individualized (Grade D, Consensus)
   d. If a switch is not feasible, the dose of NPH or premixed insulin taken with the predawn meal should be reduced by 25% to 50%, depending on carbohydrate content, timing of last insulin dose and risk for hypoglycemia (Grade D, Consensus).
3. For individuals already taking a regimen containing long-acting basal insulin analogs (degludec, detemir, glargine, glargine U300), a dosage reduction of 15% to 30% should be considered on fasting days to reduce the risk for hypoglycemia (Grade D, Consensus).
4. For individuals already taking a regimen containing bolus insulin:
   a. A rapid-acting insulin analog (aspart, faster-acting aspart, glulisine, lispro) is preferred over human regular insulin so as to lower the risk for hypoglycemia and postprandial hyperglycemia (Grade C, Level 2 [29,30] for lispro; Grade D, Consensus for aspart, faster-acting aspart, glulisine)
   b. Patients should be advised to take their normal bolus dose with their sunset meal, omit their lunchtime bolus dose and lower their predawn meal dose by 5% to 50%, depending on carbohydrate intake and glucose readings (Grade D, Consensus).
5. For individuals managed by any insulin regimen, less intensive glycemic targets during Ramadan, aiming for fasting and premeal SMBGs of 5.5 to 7.5 mmol/L, are preferred so as to reduce the risk for hypoglycemia (Grade D, Consensus). Insulin dosage adjustment to achieve these conservative targets should be individualized, taking into consideration insulin sensitivity and total daily insulin dosage as well as the duration of fast (Grade D, Consensus).
6. Individuals taking a complex insulin regimen, especially those with increased risk for hypoglycemia, should be evaluated by a diabetes-management team pre-Ramadan (Grade D, Consensus).

Management of Type 1 Diabetes During Ramadan

Fasting poses unique challenges for individuals with type 1 diabetes because of the severity of the risks involved. Extreme excursions in blood glucose levels can lead to life-threatening consequences, such as severe hypoglycemia, dehydration or diabetic ketoacidosis. Because of this, the IDF-DAR guidelines categorize any individual with type 1 diabetes as being at high risk or very high risk (8). Despite being considered at high risk, many individuals with type 1 diabetes do fast. The large population-based Epidemiology of Diabetes and Ramadan study, conducted in 12,243 people with diabetes from 13 Muslim-majority countries, reported that 42.8% of individuals with type 1 diabetes fasted for at least 15 days during Ramadan (34). However, there was a 3-fold increase in severe hyperglycemia with and without ketoacidosis and a 4.7-fold increase in severe hypoglycemia in those with type 1 diabetes. Small observational studies, however, suggest that children, adolescents and adults with type 1 diabetes who are otherwise healthy and have stable glycemic control may fast safely with regular self-monitoring and under professional guidance with close supervision (35). Criteria for stability of glucose control include absence of serious complications and no episodes of severe hypoglycemia or ketoacidosis within 3 months prior to Ramadan. Individuals with type 1 diabetes who have poor control, do not comply with blood glucose monitoring or have hypoglycemia unawareness should be actively discouraged from fasting.

Limited studies have investigated the safety and efficacy of various insulin regimens for individuals with type 1 diabetes who fast during Ramadan. Insulin lispro was superior to regular human insulin for the prevention of hypoglycemia when used in combination with an intermediate-acting insulin taken twice daily (36). Insulin pump therapy has not been shown to be superior to basal-bolus injection therapy in reducing rates of hypoglycemia during fasting, but it is associated with less glucose variability (37). Using the low-glucose suspend feature on certain insulin pumps reduced the rates of hypoglycemia without excessive severe hyperglycemia, but this technology, together with continuous glucose monitoring (CGM), may not be available routinely (38). It is important to note that none of the insulin-pump studies that took place during Ramadan were randomized.

Dosing of bolus insulin should be individualized according to unique eating patterns during Ramadan. Titration based on carbohydrate counting or estimation should be encouraged during fasting. Reducing the dosage of basal insulin is recommended in general, especially during daytime fasting hours when on an insulin pump. One study investigated self-reduction of basal insulin on pump therapy or basal-bolus insulin by individuals living with type 1 diabetes, but this strategy did not decrease the risk for hypoglycemia (39). Several studies investigated a basal insulin dosage reduction between 5% and 25%; however, hypoglycemia rates remained high (40–42). Especially considering the prolonged fasting duration in Canadian summers, a conservative, individualized initial reduction of 20% to 40% in basal insulin injections (or daytime insulin with pumps) is recommended, with weekly reassessments, ideally based on uploaded CGM or SMBG data.

Recommendations

1. For people with type 1 diabetes who intend to fast, a medical assessment should be performed 1 to 3 months prior to Ramadan to evaluate individual risks for fasting and to optimize insulin management (Grade D, Consensus).
2. People with poorly controlled type 1 diabetes (i.e. pre-Ramadan A1C levels >9.0%, infrequent blood glucose monitoring and those with hypoglycemia unawareness) should be advised to not fast (Grade D, Consensus).
3. For those using regular human insulin as their bolus insulin, switching to a rapid-acting insulin analog (aspart, faster-acting aspart, glulisine, lispro) should be considered so as to reduce the rates of hypoglycemia (Grade C, Level 2 [36] for lispro; Grade D, Consensus for aspart, faster-acting aspart, glulisine) 1 to 3 months prior to Ramadan.

4. For those using basal-bolus injection therapy, a basal analog insulin (detemir, glargine) is preferred over intermediate-acting insulin during Ramadan (Grade D, Consensus). Alternatively, a once-daily ultra-long-acting basal insulin (degludec, glargine U300) may be used to further reduce the risk for hypoglycemia and minimize the chance of missed insulin doses or periods of inadequate background insulin on board during prolonged fasting periods (Grade D, Consensus).
5. Insulin-to-carbohydrate ratios and insulin-sensitivity factors should remain unchanged during fasting if stable and well controlled (Grade D, Consensus).
6. All basal insulin doses and daytime basal doses when on insulin-pump therapy should be reduced by a minimum of 20% for fasting days to reduce the risk for hypoglycemia (Grade D, Consensus) and reassessed weekly for further adjustments (Grade D, Consensus).
7. People with type 1 diabetes should monitor blood ketones when SMBG readings are elevated (>14.0 mmol/L) to screen for diabetic ketoacidosis. Those with blood ketones >0.6 mmol/L should break their fasts, take a supplemental dose of rapid-acting insulin for correction of blood ketones and reevaluate their ability to fast safely during Ramadan (Grade D, Consensus).

Monitoring Glycemic Control While Fasting During Ramadan

Self-monitoring of blood glucose

SMBG forms the cornerstone of the management of diabetes, both during and outside of fasting. Although there is a misconception that pricking the skin for monitoring glycemic control invalidates the fast, religious authorities agree that this is not the case (43). Another commonly held myth that makes people minimize SMBG checks is that they may have to break their fast on finding out about their hypoglycemic episodes if they were to check frequently. In fact, frequent SMBG may reduce the frequency and severity of hypoglycemic episodes so that fasting can be performed safely during Ramadan.

Types 1 and 2 diabetes treated with insulin. For insulin-treated subjects, SMBG ≥3 times daily has been associated with improved glycemic control outside of fasting in both types of diabetes (44,45). Fasting during Ramadan is associated with an increased risk for severe hypoglycemic episodes in individuals with both types of diabetes, while hyperglycemic episodes are increased, particularly in those with type 1 diabetes (34). Evidence that employing SMBG improves glycemic control during Ramadan is derived principally from observational studies that examined it as a part of the effectiveness of diabetes education programs, making it difficult to determine whether the effects observed were the result of frequent SMBG or other aspects of the program. In a small cohort of 21 subjects with both type 1 and 2 diabetes using the basal-bolus insulin regimen, a diabetes-education program including SMBG ≥5 times per day was associated with a reduction in hypoglycemic episodes during Ramadan (46). Another prospective study, which assessed twice-daily SMBG among subjects with type 1 or type 2 diabetes (67% taking insulin) showed a reduction in hypoglycemic episodes during Ramadan (47). Although limited by study methodology, these reports provide the only available evidence associating frequent SMBG with a reduction in hypoglycemic episodes in individuals with diabetes who were fasting during Ramadan. However, as mentioned above, insulin dosage adjustment to optimize care and to prevent and detect hypoglycemia indicates the need for regular SMBG. This is of particular concern before the main meal (usually the sunset meal). Indeed, monitoring for postprandial SMBG excursions may help many individuals to adjust their food intake and/or their insulin dosages during Ramadan.

Type 2 diabetes treated with noninsulin regimens. Similar methodologic limitations exist in studies examining the effect of SMBG in diabetes treated with noninsulin medications during Ramadan. In a prospective study, participants in an education program that included SMBG twice daily experienced a decrease in body mass index, A1C levels and severe hypoglycemic episodes during Ramadan (13). Similarly, weight loss and a decrease in the number of hypoglycemic episodes was observed in a retrospective study in which participants in a diabetes education program were advised to test glucose when symptomatic while fasting (48). Neither study, however, listed the daily SMBG frequency in the control groups. Additionally, sulfonylurea use was common among participants in these studies, questioning the generalizability of these findings to current nonsulfonylurea, noninsulin regimens commonly used in Canada.

Continuous and flash glucose monitoring. CGM and flash glucose monitoring (FGM) by individuals with either type 1 or type 2 diabetes and FGM by those with type 1 diabetes have not identified a worsening of glycemic control during Ramadan (49–51). To our knowledge, no study to date has compared the utility of CGM or FGM vs. SMBG in improving glycemic control when fasting during Ramadan. Further studies are needed to assess the utility of CGM or FGM in individuals with diabetes who fast during Ramadan, particularly among those using complex insulin regimens.

Recommendations

1. For individuals fasting during Ramadan who use insulin:
   a. Education on the frequency of SMBG testing during fasting should be provided to improve A1C levels and reduce rates of hypoglycemia (Grade C, Level 3 [13,48]). SMBG should be undertaken at least 5 times per day for people living with type 1 diabetes (Grade D, Consensus) and 2 to 5 times per day for those living with type 2 diabetes (Grade D, Consensus), in addition to periods of symptomatic hyper/hypoglycemia (Grade D, Consensus)
   b. In the short term, real-time CGM or FGM during fasting to adjust insulin doses and prevent hypoglycemia risk may be considered for people living with type 1 or type 2 diabetes who are taking complex insulin regimens, defined as basal plus at least 1 additional administration of bolus insulin (Grade D, Consensus)
   c. For individuals with diabetes who do not require insulin, SMBG should be individualized according to the type of therapy, the risks for hypoglycemia or hyperglycemia, the levels of glycemic control and the durations of fast (Grade D, Consensus).

Conclusions

This is the first Canadian position statement on the topic of Ramadan fasting and diabetes. It was developed by an expert faculty in collaboration with Diabetes Canada, and it provides guidance on pharmacotherapy and glucose monitoring for health-care providers so that they can assist Canadian Muslims living with diabetes to fast safely during Ramadan. The best available evidence was used to formulate recommendations using a standard grading system. The literature search revealed significant knowledge gaps, which highlights the need for further research in this field, including more studies performed in the Canadian population.

Overall, this Canadian position statement for Ramadan fasting and diabetes highlights the need for further education for health-care providers and patients about the risks associated with fasting

(hypoglycemia, hyperglycemia, dehydration, diabetic ketoacidosis), their prevention and management, as well as the importance of healthful eating during Ramadan. Sustained education and dissemination of the recommendations included in this position statement may assist people living with diabetes to manage their diabetes safely during Ramadan fasting.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at https://www.canadianjournalofdiabetes.com.

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