

Recommendations for Management of Diabetes During Ramadan

Update 2010

MONIRA AL-AROUJ, MD¹
SAMIR ASSAAD-KHALIL, MD, PHD²
JOHN BUSE, MD, PHD³
IBTIHAL FAHDIL, MD, PHD⁴
MOHAMED FAHMY, MD, PHD⁵
SHERIF HAFEZ, MD, FACP⁶
MOHAMED HASSANEIN, FRCP⁷

MAHMOUD ASHRAF IBRAHIM, MD⁸
DAVID KENDALL, MD⁹
SUHAIL KISHAWI, MD¹⁰
ABDULRAZZAQ AL-MADANI, MD¹¹
ABDULLAH BEN NAKHI, MD¹
KHALED TAYEB, MD¹²
ABRAHAM THOMAS, MD¹³

Since our last publication about diabetes and fasting during Ramadan (1), we have received many inquiries and comments concerning important issues that were not discussed in the previous document, including the voluntary 1- to 2-day fasts per week that many Muslims practice throughout the year, as well as the effect of prolonged fasting (more than 18 h a day) in regions far from the equator during Ramadan when it occurs in summer—a phenomenon expected to affect millions worldwide for the next 10–15 years. Since 2005, there have been substantial additions to the literature, including two studies examining the effect of structured education and support for safe fasting, both of which had promising results (2,3). In addition, new medications, such as the incretin-based therapies, have been introduced with less risk for hypoglycemia.

According to a 2009 demographic study, Islam has 1.57 billion adherents, making up 23% of the world population of 6.8 billion, and is growing by ~3% per year (4). Fasting during Ramadan, a holy month of Islam, is a duty for all healthy

adult Muslims. The high global prevalence of type 2 diabetes—6.6% among adults age 20–79 years (5)—coupled with the results of the population-based Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study, which demonstrated among 12,243 people with diabetes from 13 Islamic countries that ~43% of patients with type 1 diabetes and ~79% of patients with type 2 diabetes fast during Ramadan (6), lead to the estimate that worldwide more than 50 million people with diabetes fast during Ramadan.

Ramadan is a lunar-based month, and its duration varies between 29 and 30 days. Muslims who fast during Ramadan must abstain from eating, drinking, use of oral medications, and smoking from pre-dawn to after sunset; however, there are no restrictions on food or fluid intake between sunset and dawn. Most people consume two meals per day during this month, one after sunset and the other before dawn.

Fasting is not meant to create excessive hardship on the Muslim individual according to religious tenets. Neverthe-

less, many patients with diabetes insist on fasting during Ramadan, thereby creating a medical challenge for themselves and their health care providers. It is increasingly important that medical professionals be aware of potential risks associated with fasting during Ramadan and with approaches to mitigate those risks. These issues are rapidly becoming global issues, not only in Indonesia, Pakistan, and the Middle East, but also in North America, Europe, and Oceania.

Although recommendations for management of diabetes in patients who elect to fast during Ramadan were proposed in 1995 at a conference in Casablanca (7), our previous document was prompted by the EPIDIAR study (6). The purpose of this review is to evaluate new data that has emerged since the publication of the 2005 article and to refine our recommendations.

In this revised document, we continue to avoid use of the terms “indications” or “contraindications” for fasting because fasting is a spiritual issue for which patients make their own decision after receiving appropriate advice from religious teachings and from health care providers. However, we emphasize that fasting, especially among patients with type 1 diabetes with poor glycemic control, is associated with multiple risks.

SUMMARY OF MAJOR CHANGES AND UPDATES — The current report:

- Addresses the voluntary 1- to 2-day fasts per week that many Muslims practice throughout the year
- Discusses the effect of prolonged fasting (more than 18 h a day) in regions far from the equator during Ramadan when it occurs in summer (a phenomenon expected to affect millions of people world-wide for the next 10–15 years)
- Reviews additional and novel literature, including studies examining the effect of structured education and support for safe fasting
- Provides additional information including the clinical use of new medica-

From the ¹Dasman Diabetes Institute, Dasman, Kuwait; the ²Department of Internal Medicine, Unit of Diabetes & Metabolism, Alexandria Faculty of Medicine, Alexandria, Egypt; the ³Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina; the ⁴Eastern Mediterranean Office of the World Health Organization, Cairo, Egypt; the ⁵Department of Internal Medicine and Endocrinology, Ain Shams University, Cairo, Egypt; the ⁶Department of Internal Medicine and Diabetes, Cairo University, Cairo, Egypt; ⁷Consultant Diabetes and Endocrinology, North Wales, U.K.; the ⁸EDC, Center for Diabetes Education, McDonough, Georgia; the ⁹American Diabetes Association, Alexandria, Virginia; the ¹⁰Ministry of Health, Palestinian National Authority, Shifa Hospital, Gaza, Palestine; ¹¹Dubai Hospital, Dubai, United Arab Emirates; ¹²Al-Nour Hospital, Mekkah, Saudi Arabia; and the ¹³Division of Endocrinology, Diabetes, and Bone and Mineral Disorders, Department of Medicine, Henry Ford Hospital, Detroit, Michigan.

Corresponding author: Mahmoud Ibrahim, mahmoud@arab-diabetes.com.

The document and specific recommendations were developed in collaboration with members of the American Diabetes Association (ADA). This report represents the collective analysis, evaluation, and opinion of the authors at the time of publication and does not represent the official position of ADA.

DOI: 10.2337/dc10-0896

© 2010 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

tions with an emphasis on those with lesser risk for hypoglycemia, such as incretin-based therapies

- Addresses safety information and the use and limitations of existing medications such as thiazolidinediones
- Addresses the growing global scope of the challenge of diabetes and fasting during Ramadan—more than 50 million people with diabetes will fast during Ramadan in 2010

PATHOPHYSIOLOGY OF FASTING

Insulin secretion, which promotes the storage of glucose in liver and muscle as glycogen, is stimulated by feeding in healthy individuals. During fasting, circulating glucose levels tend to fall, leading to decreased secretion of insulin. Concurrently, levels of glucagon and catecholamines rise, stimulating the breakdown of glycogen, and at the same time gluconeogenesis is augmented (8). As fasting becomes protracted for more than several hours, glycogen stores become depleted, and the low levels of circulating insulin allow increased fatty acid release from adipocytes. Oxidation of fatty acids generates ketones that can be used as fuel by skeletal and cardiac muscle, liver, kidney, and adipose tissue, thus sparing glucose for continued utilization by brain and erythrocytes.

The transition from the fed state through brief fasting and into prolonged starvation is mediated by a series of complex metabolic, hormonal, and gluco-regulatory mechanisms. Felig (9) conveniently divided the transition from a fed to a fasted state into three stages:

- 1) the postabsorptive phase, 6–24 h after beginning fasting
- 2) the gluconeogenic phase, from 2–10 days of fasting
- 3) the protein conservation phase, beyond 10 days of fasting.

Although most religious fasts seldom exceed 24 h, the variability of the duration of every phase may lead to different physiological responses to fasting. This variability may explain the feasibility of prolonged fast even in subjects with type 1 diabetes in some studies (11). After an overnight fast, the average rate of glucose utilization by a healthy human is ~7 g per hour. By extrapolation, the 70–80 g of glycogen present in the liver can provide glucose to the brain and peripheral tissues for about 12 h (10).

In individuals without diabetes, the processes described above are regulated by a delicate balance between circulating levels of insulin and counterregulatory hormones that help maintain glucose concentrations in the physiological range. In patients with diabetes, however, glucose homeostasis is perturbed by the underlying pathophysiology and often by pharmacological agents designed to enhance or supplement insulin secretion. In patients with type 1 diabetes, glucagon secretion may fail to increase appropriately in response to hypoglycemia. Epinephrine secretion is also defective in some patients with type 1 diabetes because of a combination of autonomic neuropathy and defects associated with recurrent hypoglycemia (8). In patients with severe insulin deficiency, a prolonged fast in the absence of adequate insulin can lead to excessive glycogen breakdown and increased gluconeogenesis and ketogenesis, leading to hyperglycemia and ketoacidosis. Patients with type 2 diabetes may suffer similar perturbations in response to a prolonged fast; however, ketoacidosis is uncommon, and the severity of hyperglycemia depends on the extent of insulin resistance and/or deficiency.

In a recent study, normal volunteers were subjected to intermittent 20-h fasts every 2nd day for 15 days while maintaining body weight. Plasma free fatty acid and β -hydroxybutyrate concentrations increased after 20 h of fasting, confirming that the subjects were fasting. Insulin-mediated whole-body glucose rates increased and insulin-induced inhibition of lipolysis in adipose tissue was more prominent after than before the intervention. After the 20-h fasting periods, plasma adiponectin was increased compared with the basal levels before and after the intervention. This experiment was the first to show in humans that intermittent fasting increases insulin-mediated glucose uptake rates, compatible with the thrifty gene concept (12). Limited human data suggests higher HDL cholesterol and lower triacylglycerol concentrations but no effect on blood pressure from fasting. In terms of cancer risk, there is no human evidence to date of the effects of fasting. However, animal studies found decreases in lymphoma incidence, longer survival after tumor inoculation, and lower rates of proliferation of several cell types (13).

Table 1—Major risks associated with fasting in patients with diabetes

Hypoglycemia
Hyperglycemia
Diabetic ketoacidosis
Dehydration and thrombosis

RISKS ASSOCIATED WITH FASTING IN PATIENTS WITH DIABETES

— Fasting during Ramadan has been uniformly discouraged by the medical profession for patients with diabetes. In keeping with this, a large epidemiological study conducted in 13 Islamic countries on 12,243 diabetic individuals who fasted during Ramadan showed a high rate of acute complications (6). However, a few studies on this topic using relatively small groups of patients suggest that complication rates may not be significantly increased (14–18). Some of the major potential complications associated with fasting in patients with diabetes are outlined in Table 1.

Hypoglycemia

Decreased food intake is a well-known risk factor for the development of hypoglycemia (19). It has been estimated that hypoglycemia accounts for 2–4% of mortality in patients with type 1 diabetes (20). There are no reliable estimates concerning the contribution of hypoglycemia to mortality in type 2 diabetes; however, it is felt that hypoglycemia is an infrequent cause of death in this group of patients. Rates of hypoglycemia are several-fold lower in patients with type 2 compared with type 1 diabetes (6), and rates are even lower in patients with type 2 diabetes treated with oral agents (21).

The effect of fasting during Ramadan on rates of hypoglycemia in patients with diabetes is not known with certainty. The largest dataset is the recent EPIDIAR study (6), which showed that fasting during Ramadan increased the risk of severe hypoglycemia (defined as hospitalization due to hypoglycemia) some 4.7-fold in patients with type 1 diabetes (from 3 to 14 events \cdot 100 people⁻¹ \cdot month⁻¹) and 7.5-fold in patients with type 2 diabetes (from 0.4 to 3 events \cdot 100 people⁻¹ \cdot month⁻¹). The incidence of severe hypoglycemia was probably underestimated in this study because events requiring assistance from a third party without the need for hospitalization were not included. Although the average A1C in these patients at the beginning of Ramadan was not given, it is unlikely that the patients in this

study had good glycemic control. Severe hypoglycemia was more frequent in patients in whom the dosage of oral hypoglycemic agents or insulin were changed and in those who reported a significant change in their lifestyle (6).

Hyperglycemia

Long-term morbidity and mortality studies in people with diabetes, such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), demonstrated the link among hyperglycemia, microvascular complications, and possibly macrovascular complications (19,22). However, there is no information linking repeated yearly episodes of short-term hyperglycemia (e.g., 4-week duration) and diabetes-related complications. Control of glycemia in patients with diabetes who fasted during Ramadan has been reported to deteriorate, improve, or show no change (21–25). The extensive EPIDIAR study showed a fivefold increase in the incidence of severe hyperglycemia (requiring hospitalization) during Ramadan in patients with type 2 diabetes (from 1 to 5 events \cdot 100 people⁻¹ \cdot month⁻¹) and an approximate threefold increase in the incidence of severe hyperglycemia with or without ketoacidosis in patients with type 1 diabetes (from 5 to 17 events \cdot 100 people⁻¹ \cdot month⁻¹) (6). Hyperglycemia may have been due to excessive reduction in dosages of medications to prevent hypoglycemia. Patients who reported an increase in food and/or sugar intake had significantly higher rates of severe hyperglycemia (6).

Diabetic ketoacidosis

Patients with diabetes, especially those with type 1 diabetes, who fast during Ramadan, are at increased risk for development of diabetic ketoacidosis, particularly if their diabetes is poorly controlled before Ramadan (6). In addition, the risk for diabetic ketoacidosis may be further increased due to excessive reduction of insulin dosages based on the assumption that food intake is reduced during the month.

Dehydration and thrombosis

Limitation of fluid intake during the fast, especially if prolonged, is a cause of dehydration. The dehydration may become severe as a result of excessive perspiration in hot and humid climates and among individuals who perform hard physical labor. In addition, hyperglycemia produces an

osmotic diuresis, further contributing to volume and electrolyte depletion. Orthostatic hypotension may develop, especially in patients with preexisting autonomic neuropathy. Syncope, falls, injuries, and bone fractures may result from hypovolemia and the associated hypotension. In addition, contraction of the intravascular space can further exacerbate the hypercoagulable state that is well demonstrated in diabetes (23). Increased blood viscosity secondary to dehydration may enhance the risk of thrombosis and stroke (24). A report from Saudi Arabia suggested an increased incidence of retinal vein occlusion in patients who fasted during Ramadan (25). However, hospitalizations due to coronary events or stroke were not increased during Ramadan (26). There are no data concerning the effect of fasting on mortality in patients with or without diabetes.

MANAGEMENT— It is worth re-emphasizing that fasting for patients with diabetes represents an important personal decision that should be made in light of guidelines for religious exemptions and after careful consideration of the associated risks in consultation with health care providers. Most often, the medical recommendation will be to not undertake fasting. However, patients who insist on fasting need to be aware of the associated risks of the fasting experience and techniques to decrease this risk. Patients may be at higher or lower risk for fasting-related complications depending on the number and extent of their risk factors. Conditions associated with “very high,” “high,” “moderate,” and “low” risk for adverse events in patients with type 1 or type 2 diabetes who decide to fast during Ramadan are listed in Table 2.

General considerations

Several important issues deserve special attention.

Individualization. Perhaps the most crucial issue is the realization that care must be highly individualized and that the management plan will differ for each specific patient.

Frequent monitoring of glycemia. It is essential that patients have the means to monitor their blood glucose levels multiple times daily. This is especially critical in patients with type 1 diabetes and in patients with type 2 diabetes who require insulin.

Nutrition. During Ramadan there is a major change in the dietary pattern com-

Table 2—Categories of risk in patients with type 1 or type 2 diabetes who fast during Ramadan

Very high risk	Severe hypoglycemia within the 3 months prior to Ramadan
	A history of recurrent hypoglycemia
	Hypoglycemia unawareness
	Sustained poor glycemic control
	Ketoacidosis within the 3 months prior to Ramadan
	Type 1 diabetes
	Acute illness
	Hyperosmolar hyperglycemic coma within the previous 3 months
	Performing intense physical labor
	Pregnancy
	Chronic dialysis
High risk	Moderate hyperglycemia (average blood glucose 150–300 mg/dl or A1C 7.5–9.0%)
	Renal insufficiency
	Advanced macrovascular complications
	Living alone and treated with insulin or sulfonylureas
	Patients with comorbid conditions that present additional risk factors
	Old age with ill health
	Treatment with drugs that may affect mentation
Moderate risk	Well-controlled diabetes treated with short-acting insulin secretagogues
Low risk	Well-controlled diabetes treated with lifestyle therapy, metformin, acarbose, thiazolidinediones, and/or incretin-based therapies in otherwise healthy patients

Note: This classification is based largely on expert opinion and not on scientific data derived from clinical studies.

pared with other times of the year. Most health problems are likely to arise from inappropriate diet or as a consequence of over-eating and insufficient sleep. Therefore, the diet during Ramadan for people with diabetes should not differ significantly from a healthy and balanced diet. The nutritional advice should be tailored to their special needs and medical problems. It should aim at maintaining a constant body mass. In most studies, 50–60% of individuals who fast maintain their body weight during the month, while 20–25% either gain or lose weight (6). The common practice of ingesting large amounts of foods rich in carbohydrates and fats, especially at the sunset

meal, should be avoided. Because of the delay in digestion and absorption, ingestion of foods containing “complex” carbohydrates (slow digesting foods) may be advisable at the predawn meal, which should be eaten as late as possible before the start of the daily fast. It is also recommended that fluid intake be increased during nonfasting hours.

Exercise. Normal levels of physical activity may be maintained. However, excessive physical activity may lead to a higher risk of hypoglycemia and should be avoided, particularly during the few hours before the sunset meal. Quite commonly, multiple prayers are performed after the sunset meal; this generally involves repeated cycles of rising, kneeling, and bowing and should be considered a part of the daily exercise program. In some patients with poorly controlled type 1 diabetes, exercise may lead to severe hyperglycemia.

Breaking the fast. All patients should understand that they must always and immediately end their fast if hypoglycemia (blood glucose of <60 mg/dl [3.3 mmol/l]) occurs because their blood glucose may drop further if they delay treatment. The fast should also be broken if blood glucose reaches <70 mg/dl (3.9 mmol/l) in the first few hours after the start of the fast, especially if insulin, sulfonylurea drugs, or meglitinide are taken at predawn. Finally, the fast should be broken if blood glucose exceeds 300 mg/dl (16.7 mmol/l). Patients should avoid fasting on “sick days.”

Pre-Ramadan medical assessment

All patients with diabetes who wish to fast during Ramadan should prepare by undergoing a medical assessment and engaging in a structured education program to undertake the fast as safely as possible. This assessment should take place 1–2 months before Ramadan. Specific attention should be devoted to patients’ overall well-being and to the control of their glycemia, blood pressure, and lipids. Appropriate blood studies should be ordered and evaluated. Specific medical advice must be provided to individual patients concerning the potential risks they must accept if they decide to fast. During this assessment, necessary changes in diet or medication regimen should be made so that the patient initiates fasting while on a stable and effective program. This assessment should also extend to those who do not wish to fast because they often are exposed to the risk of hypo- and hyper-

glycemia during Ramadan as a reflection of social habits encountered during the month.

Ramadan-focused structured diabetes education

The role of structured education for patients is well established in the management of diabetes. This should be extended to Ramadan-focused diabetes education. Many Muslims with diabetes are very passionate about fasting during Ramadan. This passion is a golden opportunity to empower people with diabetes for better management of their diabetes, not only during Ramadan but also throughout the year. However, many health care professionals find that they are unable to give the appropriate medical advice due to lack of knowledge about the optimum management of diabetes while fasting. Indeed, often people with diabetes feel that there is lack of harmony between the medical and the religious advice they receive. Hence, a Ramadan-focused diabetes educational program should ideally include three components:

- 1) An awareness campaign aimed at people with diabetes, health care professionals, the religious and community leaders as well as the general public
- 2) Ramadan-focused structured education for health care professionals
- 3) Ramadan-focused structured education for people with diabetes.

Raising the general awareness of Ramadan and diabetes should strengthen the harmony between medical and religious advice. This is of particular importance in non-Muslim countries where poor communication and understanding between these communities is commonplace. Greater understanding regarding the religious context and perspective regarding Ramadan and the act of fasting, as well as the potential risks and the medical options to achieve a safer outcome for those who wish to fast, is critical for all parties.

Health care professionals should be trained to deliver a structured patient education program that includes a better understanding of fasting and diabetes, individual risk quantification, and options to achieve safer fasting. This includes 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 hyper-

glycemia. The educational program should include advice on the timing and intensity of physical activity during fasting. Certainly, it is important that use of diabetes-related medications and their potential risk during fasting are also discussed.

A well-trained health care professional should be able to deliver all these components to people with diabetes either individually or in a group session at diabetes centers, primary health care centers, local mosques, and/or community centers. The ability to deliver this educational program in a simple, structured method and in the patients’ own language is a distinct advantage, especially in multilingual communities. Certainly, many of the components of the program will help empower people with diabetes to take better care of themselves throughout the year.

An example of such an educational program, which involves increasing awareness and training for health care professionals and the local community about diabetes and Ramadan through a structured education program, was conducted in 2007 in the U.K. for a group of 111 people with type 2 diabetes (2). Though the group excluded people treated with insulin, secretagogues were used in over 90% of the people. Individualized medication dose adjustments were suggested to all patients. At the end of Ramadan, when compared with a control group comprising those who did not participate in the Ramadan-focused diabetes education, those who received such education exhibited a nearly 50% reduction in hypoglycemic event rates despite fasting, whereas those in the control group had experienced a fourfold increase in the rate of hypoglycemic events from baseline during fasting. It is important to note that this occurred while glycemic control was maintained at the same level for 12 months (2). Furthermore, the group that received structured education lost a small amount of weight compared to weight gain in the control group (27).

Management of patients with type 1 diabetes

Fasting at Ramadan carries a very high risk for people with type 1 diabetes. This risk is particularly exacerbated in poorly controlled patients and those with limited access to medical care, hypoglycemic unawareness, unstable glycemic control, or recurrent hospitalizations. In addition, the risk is also very high in patients who

are unwilling or unable to monitor their blood glucose levels several times daily. It is currently recommended that treatment regimens aimed at intensive glycemia management be used in patients with diabetes. The DCCT and its follow up, the Epidemiology for Diabetes Interventions and Complications (EDIC) study, demonstrated that intensive glycemia management is protective against microvascular and perhaps macrovascular complications and that the benefits are long lasting (19,28). Glycemic control at near-normal levels requires use of multiple daily insulin injections (three or more) or use of continuous subcutaneous insulin infusion through pump therapy. Close monitoring and frequent insulin dose adjustments in this setting are essential to achieve optimal glycemic control and avoid hypo- or hyperglycemia in patients with type 1 diabetes.

Some patients with type 1 diabetes prefer to fast at Ramadan, and most of them change their insulin regimens immediately before, during, and a few days after this month. However, very few studies have documented the safety and/or efficacy of different insulin regimens in type 1 diabetic patients who fast during the month of Ramadan. The current understanding is that the basal-bolus regimen is the preferred protocol of management. It is thought to be safer, with fewer episodes of hyper- and hypoglycemia. A frequently used option is once- or twice-daily injections of intermediate or long-acting insulin along with premeal rapid-acting insulin. It is unlikely that other regimens, including one or two injections of intermediate-, long-acting, or premixed insulin, would provide adequate insulin therapy. A recent small study with insulin glargine suggests the relative safety and efficacy of this agent in 15 relatively well-controlled patients with type 1 diabetes who fasted for 18 h and experienced a minimal decline in mean plasma glucose from 125 to 93 mg/dl with only two episodes of mild hypoglycemia (29). Another study in patients with type 1 diabetes using insulin glulisine, lispro, or aspart instead of regular insulin in combination with intermediate-acting insulin injected twice a day led to improvement in postprandial glycemia and was associated with fewer hypoglycemic events (30). Clinical studies with other types of insulin in multiple daily injection regimens during fasting are limited.

Continuous subcutaneous insulin infusion (pump) management is an ap-

pealing alternative strategy, but at a substantially greater expense. Compared with those who did not fast during Ramadan, patients with type 1 diabetes on insulin pump therapy who fasted showed a slight improvement in A1C (3).

Management of patients with type 2 diabetes

Diet-controlled patients. In patients with type 2 diabetes who are well controlled with lifestyle therapy alone, the risk associated with fasting is quite low. However, there is still a potential risk for occurrence of postprandial hyperglycemia after the predawn and sunset meals if patients overindulge in eating. Distributing calories over two to three smaller meals during the nonfasting interval may help prevent excessive postprandial hyperglycemia. Physical activity may be modified in its intensity and timing, e.g., ~2 h after the sunset meal.

Patients treated with oral agents. The choice of oral agents should be individualized. In general, agents that act by increasing insulin sensitivity are associated with a significantly lower risk of hypoglycemia than compounds that act by increasing insulin secretion.

Metformin. Patients treated with metformin alone may safely fast because the possibility of severe hypoglycemia is minimal. However, perhaps the timing of the doses should be modified to provide two-thirds of the total daily dose with the sunset meal and the other third before the predawn meal.

Glitazones. The thiazolidinedione or glitazone agents (pioglitazone and rosiglitazone) are not independently associated with hypoglycemia, though they can amplify the hypoglycemic effects of sulfonylureas, glinides, and insulin. However, they are associated with weight gain and anecdotally can be associated with increased appetite. The longstanding concerns regarding cardiovascular safety, caused by the increased frequency of heart failure, continue despite greater understanding that the mechanism of this adverse effect seems to be related to renal tubular sodium and water reabsorption and not to an intrinsic affect on cardiac contractility. More recently, apprehension has emerged regarding reports of increased frequency of macular edema and of bone fractures, particularly in postmenopausal women. The recent controversy regarding the cardiovascular safety of rosiglitazone seems to have been largely mitigated by the Rosiglitazone

Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study, which failed to demonstrate either harm or benefit. Nevertheless, most perceive a relative advantage of pioglitazone compared with rosiglitazone vis-à-vis lipid effects. A practical issue of significant importance with respect to the utility of glitazones in periods of fasting such as Ramadan is that these agents require 2–4 weeks to exert substantial antihyperglycemic effects. Therefore, these agents cannot be quickly substituted for agents associated with hypoglycemia during periods of fasting (31).

Sulfonylureas. It has been suggested that this group of drugs is unsuitable for use during fasting because of the inherent risk of hypoglycemia. However, severe or fatal hypoglycemia is a relatively rare complication of sulfonylurea use. Nevertheless, their use should be individualized with caution. Use of chlorpropamide is relatively contraindicated during Ramadan because of the possibility of prolonged and unpredictable hypoglycemia. Similarly, it has been suggested that glyburide or glibenclamide may be associated with a higher risk of hypoglycemia than other second-generation sulfonylureas, specifically gliclazide, glimepiride, and glipizide (32,33). Finally, it should be noted that the sulfonylureas glyburide (glibenclamide) and gliclazide MR have played a central role in the long-term outcome studies UKPDS and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), both of which demonstrated microvascular benefits and at least trends toward improvements in cardiovascular disease without evidence of excess mortality (34). Additional studies on the use of sulfonylureas in patients who fast during Ramadan are needed before strong recommendations on their utility can be made. Nevertheless, because of their worldwide use and relatively low cost, these agents may be used in Ramadan, though with caution.

Short-acting insulin secretagogues. Members of this group (repaglinide and nateglinide) are useful because of their short duration of action. They could be taken twice daily before the sunset and predawn meals. One study in patients with type 2 diabetes who fasted showed that use of repaglinide was associated with less hypoglycemia compared with glibenclamide (35). Nateglinide has the shortest duration of action and therefore

the lowest risk of severe fasting hypoglycemia among the secretagogues.

Incretin-based therapy. Therapies that affect the incretin system include glucagon-like peptide-1 receptor agonists (GLP-1ras) exenatide and liraglutide and dipeptidylpeptidase-4 inhibitors (DPP-4is) alogliptin, saxagliptin, sitagliptin, and vildagliptin. These classes of agents are not independently associated with hypoglycemia, though they can increase the hypoglycemic effects of sulfonylureas, glinides, and insulin. Exenatide in particular can be dosed before meals to minimize appetite and promote weight loss. With its short half-life of 2 h, it is not associated with a substantial effect on fasting glucose. Liraglutide is dosed once a day, independent of meals, and is more effective in controlling fasting glycemia. Both require titration to effective doses over a period of 2–4 weeks and are associated with mild to moderate nausea in almost half of those exposed on at least one occasion, particularly as therapy is initiated. DPP-4is are among the best tolerated drugs for the treatment of diabetes. They are moderately less effective in A1C lowering than GLP-1ras and, importantly vis-à-vis treatment during Ramadan, do not require titration. Many have touted their potential role as a substitute for sulfonylureas. However, there are no specific studies of these agents during periods of fasting with respect to either tolerability or efficacy (36).

α -Glucosidase inhibitors. Acarbose, miglitol, and voglibose slow the absorption of carbohydrates when taken with the first bite of a meal. Because they are not associated with an independent risk of hypoglycemia, particularly in the fasting state, they may be particularly useful during Ramadan. However, they are only modestly effective and exert little or no effect on fasting glucose, and therefore are usually used in combination with other agents to control fasting glucose. α -Glucosidase inhibitors are associated with frequent mild to moderate gastrointestinal effects, particularly flatulence. Using modest doses and slowly initiating therapy are reported to minimize the frequency of these adverse effects (37).

Patients treated with insulin. Problems facing patients with type 2 diabetes who administer insulin are similar to those with type 1 diabetes, except that the incidence of hypoglycemia is less. Again, the aim is to maintain necessary levels of basal insulin to prevent fasting hyperglycemia. An effective strategy would be ju-

dicious use of intermediate- or long-acting insulin preparations plus a short-acting insulin administered before meals. Although hypoglycemia tends to be less frequent, it is still a risk, especially in patients who have required insulin therapy for a number of years or in whom insulin deficiency predominates in the pathophysiology. Very elderly patients with type 2 diabetes may be at especially high risk.

Using one injection of a long-acting or intermediate-acting insulin can provide adequate coverage in some patients as long as the dosage is appropriately individualized; however, most patients will require rapid- or short-acting insulin administered in combination with the basal insulin at meals, particularly at the evening meal, which typically contains a larger caloric load. There is some evidence suggesting that use of a rapid-acting insulin analog instead of regular human insulin before meals in patients with type 2 diabetes who fast during Ramadan is associated with less hypoglycemia and smaller postprandial glucose excursions (38,39). In a recent study, the use of premixed lispro with neutral protamine lispro in a 50:50 ratio for the evening meal and regular human insulin with NPH in a 30:70 ratio at the early morning meal during Ramadan compared with regular human insulin at 30:70 twice daily was associated with moderate improvement in glycemic control and hypoglycemia (40).

Insulin pumps. An insulin pump provides continuous insulin delivery over 24 h with basal infusion rates programmed and individualized for each patient. Patients self-administer boluses of insulin with meals or at times of hyperglycemia, often with mathematical support from the pump. The reliance on exclusively rapid-acting or short-acting insulin allows for flexibility over an extremely wide range of insulin doses with great precision. However, frequent glucose monitoring is required because failure of the pump or the infusion site can result in severe deterioration in control over a few hours. Theoretically, the combined risks of hypoglycemia from prolonged daytime fasting and hyperglycemia from excessive nighttime eating can be better managed by an insulin pump-based regimen than by multiple insulin dose-injection therapy. Hypoglycemia can be aborted, reduced, prevented, and even more readily treated in pump-treated patients by timely downward adjustments or even

stopping insulin delivery from the pump. Such an advantage is not available to those treated with a conventional insulin injection in which insulin continues to be released from the site of injection throughout its predetermined duration of action. Any excess insulin action can only be counteracted by intake of carbohydrates.

Fasting at Ramadan may be successfully accomplished in people with type 1 diabetes if they are fully educated and facile with the use of the insulin pump and are otherwise metabolically stable and free from any acute illnesses. Prior to Ramadan, they should receive adequate training and education, particularly with respect to self-management and insulin dose adjustment. They should adjust their infusion rates carefully according to results of frequent home blood glucose monitoring. Most will need to reduce their basal infusion rate while increasing the bolus doses to cover the predawn and sunset meals.

Diabetic medication adjustment during Ramadan

Illustrative examples and recommendations for adjusting therapy during Ramadan in patients with type 2 diabetes are shown in Table 3.

Pregnancy and fasting during Ramadan

Pregnancy is a state of increased insulin resistance and insulin secretion and of reduced hepatic insulin extraction. Fasting glucose concentrations are lower and postprandial glucose and insulin levels are substantially higher in healthy pregnant women than in healthy women who are not pregnant. Elevated blood glucose and A1C levels in pregnancy are associated with increased risk for major congenital malformations. Fasting during pregnancy would be expected to carry a high risk of morbidity and mortality to the fetus and mother, although controversy exists (41). While pregnant Muslim women are exempt from fasting during Ramadan, some with known diabetes (type 1, type 2, or gestational) insist on fasting. These women constitute a high-risk group, and their management requires intensive care (42).

In general, women with pregestational or gestational diabetes are at very high risk and may be strongly advised not to fast during Ramadan. However, if they insist on fasting, special attention should be given to their care. Pre-Ramadan eval-

Table 3—Recommended changes to treatment regimen in patients with type 2 diabetes who fast during Ramadan

Before Ramadan	During Ramadan
Patients on diet and exercise control	Consider modifying the time and intensity of physical activity; ensure adequate fluid intake
Patients on oral hypoglycemic agents	Ensure adequate fluid intake
Biguanide, metformin 500 mg, three times daily	Metformin, 1,000 mg at the sunset meal, 500 mg at the predawn meal
TZDs, AGIs, or incretin-based therapies	No change needed
Sulfonylureas once a day	Dose should be given before the sunset meal; adjust the dose based on the glycemic control and the risk of hypoglycemia
Sulfonylureas twice a day	Use half the usual morning dose at the predawn meal and the usual dose at sunset meal
Patients on insulin	Ensure adequate fluid intake
Premixed or intermediate-acting insulin twice daily	Consider changing to long-acting or intermediate insulin in the evening and short or rapid-acting insulin with meals; take usual dose at sunset meal and half usual dose at predawn meal

AGI, α -glucosidase inhibitor; TZD, thiazolidinedione. Note: The recommendations given in this table are for illustrative purposes and are largely based on expert clinical opinion and not on scientific data derived from clinical studies. The recommendations must be adjusted for each specific patient. Adapted from Akbani et al. (43).

uation of their medical condition is essential. This includes preconception care with emphasis on achieving near-normal blood glucose and A1C values, counseling about maternal and fetal complications associated with poor glycemic control, and education focused on self-management skills. Ideally, patients should be managed in high-risk clinics staffed by an obstetrician, diabetologists, a nutritionist, and diabetes nurse educators. The management of pregnant patients during Ramadan is based on an appropriate diet and intensive insulin therapy. The issues discussed above concerning the management of type 1 and type 2 diabetes also apply to this group, with the exception that more frequent monitoring and insulin dose adjustment is necessary.

Management of hypertension and dyslipidemia

Dehydration, volume depletion, and a tendency toward hypotension may occur with fasting during Ramadan, especially if the fast is prolonged and is associated with excessive perspiration. Hence, the dosage and/or the type of antihypertensive medications may need to be adjusted to prevent hypotension. Diuretics may not be appropriate during Ramadan for some patients. It is a common practice that the intake of foods rich in carbohy-

drates and saturated fats is increased during Ramadan. Appropriate counseling should be given to avoid this practice, and agents that were previously prescribed for the management of elevated cholesterol and triglycerides should be continued.

CONCLUSIONS— Fasting during Ramadan for patients with diabetes carries a risk of an assortment of complications. In general, patients with type 1 diabetes are at very high risk of life-threatening complications. Patients with type 1 diabetes who have a history of recurrent hypoglycemia or hypoglycemia unawareness or who are poorly controlled are at very high risk for developing severe hypoglycemia. On the other hand, an excessive reduction in the insulin dosage in these patients (to prevent hypoglycemia) may place them at risk for hyperglycemia and diabetic ketoacidosis. Hypo- and hyperglycemia may also occur in patients with type 2 diabetes, but is generally less frequent and has less severe consequences than in patients with type 1 diabetes. A patient's decision to fast should be made after ample discussion with a health care provider concerning the risks involved. Patients who insist on fasting should undergo pre-Ramadan assessment and receive appropriate education and instructions related to physical activity, meal planning, glu-

cose monitoring, and dosage and timing of medications.

Newer pharmacological agents have lesser hypoglycemic potential and may have specific advantages during Ramadan. Similarly, insulin pump therapy may provide greater safety in the Ramadan setting. There are a few studies of these newer techniques in the Ramadan setting with encouraging results, but in general this challenging therapeutic situation has not been adequately addressed in clinical trials.

Acknowledgments— The Egyptian Diabetes Center, with support from Les Laboratoires Servier, made this work possible.

J.B.'s institution has received funds from multiple pharmaceutical and device companies for his services as an investigator and consultant, he currently has grants pending, and his travel accommodation expenses have been covered by the American Diabetes Association. A.T. is on the speaker's bureau for Novo Nordisk and Takeda and has received research grants from Roche, Eli Lilly and Company, and Amylin Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

The authors are thankful for all of the comments received regarding their previous report, each of which were considered during the preparation of this update.

References

1. Al-Arouj M, Bouguerra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, Ismail-Beigi F, El-Kebbi I, Khatib O, Kishawi S, Al-Madani A, Mishal AA, Al-Maskari M, Nakhi AB, Al-Rubean K. Recommendations for management of diabetes during Ramadan. *Diabetes Care* 2005;28:2305–2311
2. Bravis V, Hui E, Salih S, Mehar S, Hassanein M, Devendra D. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with type 2 diabetes who fast during Ramadan. *Diabetic Medicine* 2010;27:327–331
3. Benbarka MM, Khalil AB, Beshyah SA, Marjei S, Awad SA. Insulin pump therapy in Moslem patients with type 1 diabetes during Ramadan fasting: an observational report. *Diabetes Technol Ther* 2010;12:287–290
4. Miller T, Ed. Mapping the Global Muslim Population: A Report on the Size and Distribution of the World's Muslim Population, [Internet] c2009. Washington, DC, Pew Research Center. Available from <http://pewforum.org/newassets/images/reports/Muslimpopulation/Muslimpopulation.pdf>. Accessed 8 October 2009
5. International Diabetes Federation. *Diabetes Atlas 2009*. 4th ed. Brussels, International Diabetes Federation, 2009

6. Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C, Jabbar A, EPIDIAR study group. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004;27:2306–2311
7. International Meeting on Diabetes and Ramadan Recommendations. *Edition of the Hassan II Foundation for Scientific and Medical Research on Ramadan*. Casablanca, Morocco, FRSMR, 1995
8. Royer PE, Davis SN, Shamooh H. Hypoglycemia in diabetes (Review). *Diabetes Care* 2003;26:1902–1912
9. Felig P. Starvation. In *Endocrinology*. DeGroot LJ, Ed. New York, Grune & Stratton, 1979, p. 1927–1940
10. Cahill GF Jr. Starvation in man. *N Engl J Med* 1970;282:668–675
11. Reiter J, Wexler ID, Shehadeh N, Tzur A, Zangen D. Type 1 diabetes and prolonged fasting. *Diabet Med*, 2007;24:436–439
12. Halberg N, Henriksen M, Söderhamn N, Stallknecht B, Ploug T, Schjerling P, Dela F. Effect of intermittent fasting and refeeding on insulin action in healthy men. *J Appl Physiol* 2005;99:2128–2136
13. Varady KA, Hellerstein MK. Alternate-day fasting and chronic disease prevention: a review of human and animal trials. *Am J Clin Nutr* 2007;86:7–13
14. Uysal AR, Erdoğan MF, Sahin G, Kamel N, Erdoğan G. Clinical and metabolic effects of fasting in 41 type 2 diabetic patients during Ramadan (Letter). *Diabetes Care* 1998;21:2033–2034
15. Laajam MA. Ramadan fasting and non-insulin-dependent diabetes: effect on metabolic control. *East Afr Med J* 1990; 67:732–736
16. Mafauzy M, Mohammed WB, Anum MY, Zulkifli A, Ruhani AH. A study of the fasting diabetic patient during the month of Ramadan. *Med J Malaysia* 1990;45: 14–17
17. Belkhadir J, el Ghomari H, Klöcker N, Mikou A, Nasciri M, Sabri M. Muslims with non-insulin dependent diabetes fasting during Ramadan: treatment with glibenclamide. *BMJ* 1993;307:292–295
18. Katibi IA, Akande AA, Bojuwoye BJ, Okesina AB. Blood sugar control among fasting Muslims with type 2 diabetes mellitus in Ilorin. *Niger J Med* 2001;10:132–134
19. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–986
20. Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, Smith AW, Hill RD, Bingley PJ, Patterson CC, Qiao Z, Keen H. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med* 1999;16:466–471
21. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes. *Arch Int Med* 2001;161:1653–1659
22. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352: 837–853
23. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570–2581
24. Akhan G, Kutluhan S, Koyuncuoglu HR. Is there any change in stroke incidence during Ramadan? *Acta Neurol Scandin* 2000;101:259–261
25. Alghadyan AA. Retinal vein occlusion in Saudi Arabia: possible role of dehydration. *Ann Ophthalmol* 1993;25:394–398
26. Temizhan A, Dönderici O, Ouz D, Demirbas B. Is there any effect of Ramadan fasting on acute coronary heart disease events? *Int J Cardiol* 1999;70:149–153
27. Hassanein M, Bravis V, Hui E, Devendra D. Ramadan-focused education and awareness in type 2 diabetes. *Diabetologia* 2009;52: 367–368
28. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290: 2159–2167
29. Mucha GT, Merkel S, Thomas W, Bantle JP. Fasting and insulin glargine in individuals with type 1 diabetes. *Diabetes Care* 2004;27:1209–1210
30. Kadiri A, Al-Nakhi A, El-Ghazali S, Jabbar A, Al Arouj M, Akram J, Wyatt J, Assem A, Ristic S. Treatment of type 1 diabetes with insulin lispro during Ramadan. *Diabet Metab* 2001;27:482–486
31. Retnakaran R, Zinman B. Thiazolidinediones and clinical outcomes in type 2 diabetes. *Lancet* 2009;373:2088–2090
32. Scherthaner G, Grimaldi A, Di Mario U, Drzewoski J, Kempler P, Kvapil M, Novials A, Rotliers R, Rutten GE, Shaw KM. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest* 2004;34:535–542
33. Rendell M. The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs* 2004;64:1339–1358
34. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
35. Mafauzy M. Repaglinide versus glibenclamide treatment of type 2 diabetes during Ramadan fasting. *Diabetes Res Clin Pract* 2002;58:45–53
36. Drucker DJ, Sherman SI, Gorelick FS, Bergenstal RM, Sherwin RS, Buse JB. Incretin-based therapies for the treatment of type 2 diabetes: evaluation of the risks and benefits. *Diabetes Care* 2010;33:428–433
37. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005:CD003639
38. Mattoo V, Milicevic Z, Malone JK, Schwarzenhofer M, Ekangaki A, Levitt LK, Liong LH, Rais N, Tounsi H, Ramadan Study Group. A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; 59:137–143
39. Akram J, De Verga V. Insulin lispro (Lys(B28), Pro(B29) in the treatment of diabetes during the fasting month of Ramadan. Ramadan Study Group. *Diabet Med* 1999;16:861–866
40. Hui E, Bravis V, Salih S, Hassanein M, Devendra D. Comparison of Humalog Mix 50 with human insulin Mix 30 in type 2 diabetes patients during Ramadan. *Int J Clin Pract*. 10 March 2010 [Epub ahead of print]
41. Malhotra A, Scott PH, Scott J, Gee H, Wharton BA. Metabolic changes in Asian Muslim pregnant mothers observing the Ramadan fast in Britain. *Br J Nutr* 1989; 61:663–672
42. Azizi F. Research in Islamic fasting and health. *Ann Saudi Med* 2002;22:186–191
43. Akbani MF, Saleem M, Gadit WU, Ahmed M, Basit A, Malik RA. Fasting and feasting safely during Ramadan in the diabetic patient. *Pract Diab Int* 2005;22:100–104