A Review of Ramadan Fasting and Diabetes Mellitus: Controversies regarding the Effects of Ramadan Fasting on Diabetic Patients

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ABSTRACT

Although several studies have investigated the effects of Ramadan fasting on diabetic patients, the exact impacts on diabetes control have not been well elucidated yet. There are neither precise quantitative criteria nor clear guidelines regarding Ramadan fasting for diabetic patients. This review aimed to discuss the results of previous studies. The neglected points in performed studies should be considered in the design and interpretation of future research related to Ramadan fasting in diabetic patients. A thorough research was carried out on the internet, using the following keywords: "Ramadan", "Ramadan fasting", "Islamic fasting", "fasting in Ramadan", and "fasting", in combination with words such as "diabetes mellitus", "hyperglycemia", "hypoglycemia", and "diabetic ketoacidosis". Databases including PubMed, Google Scholar, and some regional databases were searched in order to find related articles (cross-sectional, descriptive-analytical, cohort, clinical trial, and review studies), published during 1957-2013. The obtained data showed that Ramadan fasting could be non-risky for partially controlled diabetic patients. However, the safety of Ramadan fasting for diabetic patients with different blood glucose levels and complications is not yet determined. Many deficiencies and limitations are observed in the related studies such as the heterogeneity of participants including differences in lifestyle and circadian rhythm changes. Therefore, well controlled studies need to be performed to evaluate factors affecting blood glucose level during Ramadan fasting.

Keywords: Diabetes mellitus Hyperglycemia Hypoglycemia Ramadan fasting

Introduction

Several studies have investigated the effects of Ramadan fasting on variations in blood glucose level. However, there is still a great deal of controversy regarding the risks of fasting, necessary changes in medication use, and appropriate dietary intake in diabetic patients. In this paper, we attempted to disclose the effects of Ramadan fasting on various aspects of diabetes and discuss the possible contributing factors.

Materials and Methods

A thorough research was carried out on the internet, using the following keywords: "Ramadan", "Ramadan fasting", "Islamic fasting", "fasting in Ramadan", and "fasting", in combination with words such as "diabetes mellitus", "hyperglycemia", "hypoglycemia", and "diabetic ketoacidosis". Databases including PubMed, Google Scholar, and some regional databases were searched in order to find related articles (e.g., cross-sectional, descriptive-analytical, cohort, clinical trial, and review articles), published during 1957-2013.

Variations of dietary intake in diabetic patients during Ramadan

The key to the management of diabetes mellitus is an appropriate and balanced diet; therefore, any dietary variations can affect disease control. Ramadan fasting is associated with unavoidable changes in dietary patterns and food intake. In some studies, reduced calorie intake of about 300 kcal per day has been reported in type 2 diabetic patients (1, 2).

In a study conducted in Algeria on 276 obese
diabetic patients, a significant decrement of 335 kcal in daily energy intake was observed (3). This study revealed that the frequency of food intake decreased during Ramadan. Overall, 77%, 14%, and a low proportion of total daily energy came from Iftar (evening meal), Sahar (pre-dawn meal), and dinner (usually consumed a few hours after Iftar), respectively. On the other hand, in other months of the year, the highest amount of caloric intake was during lunch (>35%) and dinner (30%) (3). Also, calories from carbohydrates and dietary fibers decreased and levels of protein, saturated fat, trans fatty acids, and cholesterol increased during this month (3).

Inconsistent with the previous study, low calorie and fat intake, as well as increased carbohydrate intake, has been reported in other articles (4). In a population-based study, physical activity level, food intake, sleep duration, and fluid intake did not change in more than 50% of the subjects. Moreover, the amount of food intake did not change in 51% and 56% of type 1 and type 2 diabetic patients, respectively. However, an increase in food intake was reported in 20% and 18% of patients, and a decrease in 23% and 30% of type 1 and type 2 diabetic patients, respectively (5).

**Anthropometric changes in diabetic patients during Ramadan**

In articles investigating the effects of Ramadan fasting on diabetic patients, no changes (5-14), decrease (1, 3, 5, 15-17), or even increase in body weight (18) have been reported. In a previous study, a significant reduction in body weight (up to 3 kg) was observed in obese individuals; however, these patients gained weight gradually after the end of Ramadan. Also, no significant changes of waist circumference or waist-to-hip ratio were observed (3).

Furthermore, a mean of 0.8 kg/m² decrease in body mass index (BMI) was reported by reducing caloric intake by 300 Kcal/day. The weight loss induced by Ramadan fasting in diabetic patients was associated with reduced energy intake and meal frequency (2). In some studies, body weight and BMI remained unchanged (5, 13, 19), while others reported an increase in body weight, although the weight gain was insignificant (20). In these studies, weight gain was associated with reduced physical activity and increased fat, sugar, and total energy intake (20).

Moreover, a study showed that basal metabolism decreases during Ramadan (19). Since the decrease in basal metabolism reduces the need for energy in the body, weight gain may still occur even by keeping the energy intake unchanged. Most diabetic patients reduce their physical activity due to the fear of hypoglycemia during Ramadan (11, 21). Reduced physical activity not only does not inhibit weight loss as an effect of Ramadan fasting, but also leads to weight gain.

**Variations of glycemia in diabetic patients during Ramadan**

Fasting in healthy subjects may contribute to an increase in insulin action, which leads to increased glucose uptake by tissues (22). Animal studies have shown that hunger can lead to a 7-fold increase in insulin sensitivity (23) and may reduce the incidence of diabetes (24). In some studies, a slight reduction (25-28) or variation (29) in blood glucose was reported.

Typically, in the month of Ramadan, fasting blood glucose level slightly decreases in the first few days, although it returns to the pre-Ramadan level in the second decade of this month (30). However, in a study, an average of 20-25% reduction in salivary glucose was observed in the first 10 days, followed by a decline in the next 10 days and an increase on day 29. This increment within the last 10 days of Ramadan was not similar to the normal level of salivary glucose in other months of the year (31).

Some studies have shown that fasting has no adverse effects on serum glucose in diabetic patients (1, 6-8, 11-13, 32-38). Ramadan fasting induces a significant decrease in fasting blood glucose (1-3, 15, 28, 34, 39-44), glycated hemoglobin (HbA1c) (3, 15, 28, 40-42, 45), and serum fructosamine, without producing beta-butyrates (2). The reduction in serum fructosamine may be due to decreased energy intake (1, 2). In fact, fructosamine level determines the blood glucose level over the past 2-3 weeks and can be a better indicator of the effects of fasting, compared to HbA1c (46).

In a previous article, blood glucose measurements before Iftar and Sahar and 2 hours after these meals showed no changes within the 1st, 2nd, 3rd, and 4th weeks of fasting.
However, after the end of Ramadan, glucose concentration gradually increased (2); this increment was accompanied by an increase in food intake. In fact, one of the causes of fructosamine increase after the end of Ramadan may be an increase in carbohydrate intake on Eid al-Fitr (Feast of Breaking the Fast) and the following days (20).

Variations in blood glucose level could be related to the type of consumed foods, compliance with medications, and individual differences in the regulation of energy metabolism (47). The conflicts between the obtained results could be due to differences in the dietary patterns of different subjects (47). Also, blood glucose level during Ramadan fasting was higher in diabetic patients, referring to medical centers. During Ramadan, the number of patients referring to medical centers was lower than other months of the year, which could be one of the causes of hyperglycemia in fasting individuals.

The acute complications of Ramadan fasting in diabetic patients

Hyperglycemia and diabetic ketoacidosis

Hyperglycemia is one of the potential complications associated with fasting. This condition could be caused by a reduction in drug dosage, increased food intake especially carbohydrate, and decreased physical activity (5). If glycemic control is poor, the production of ketone bodies will be accelerated due to lower liver glycogen levels. Therefore, in some studies, fasting has also led to diabetic ketoacidosis (5, 48).

Diabetic patients (especially type 1 diabetic patients) are at a potential risk of diabetic ketoacidosis if their blood glucose is poorly controlled before Ramadan (5). In those with relatively proper control of blood glucose, ketone bodies do not increase during Ramadan fasting (47). However, a significant change in the incidence of hyperglycemia in type 2 diabetic patients has been reported.

In a study, hospitalization due to hyperglycemia in patients with type 1 and type 2 diabetes mellitus was respectively 3 and 5 times more than the pre-Ramadan period; drug dose reduction was noted as the main reason for this increment (5). Generally, hyperglycemia may be caused by an adverse reaction to dose reduction, which aimed to prevent hypoglycemia. In a previous study, patients with increased food intake experienced higher frequencies of severe hyperglycemia (5).

Hypoglycemia

Reduced calorie intake during Ramadan fasting may contribute to hypoglycemia. The majority of diabetic patients do not consult their physicians to adjust their medication doses in Ramadan (5); this may be one of the causes of hypoglycemia (5, 13, 45, 49, 50). However, in some studies, no increased incidence of hypoglycemia has been reported (1, 6, 9, 11, 33, 34, 41, 51-53). Also, in type 1 diabetic patients, due to a decrease in glucagon and epinephrine responses to hypoglycemia, the risk of hypoglycemia increased during Ramadan (54).

Symptoms of hypoglycemia may be present at different blood glucose levels. In some patients, symptoms of hypoglycemia have been reported in a glucose concentration of 60-80 mg/dl, while in some cases, these symptoms have been even recorded at concentrations higher than 80 mg/dl. However, this difference was influenced by the compliance of individuals with low blood glucose and also the degree of their metabolic control (2).

According to a previous study, variation in the incidence of hypoglycemia in type 2 diabetes was significant, and the frequency of hypoglycemia and hyperglycemia increased, compared to a year before Ramadan (5). However, the increased incidence of severe hypoglycemia and hyperglycemia in patients with type 2 diabetes was statistically significant; in fact, the increased risk of hypoglycemia was related to a change in subjects’ medication dosage and physical activity (5).

In the mentioned study, fasting increased the risk of severe hypoglycemia (defined as hospitalization due to hypoglycemia) 4.7 times in type 1 diabetic patients and about 7.5 times in individuals with type 2 diabetes. The lower estimated incidence of hypoglycemia may be probably due to excluding non-hospitalized patients.

In the aforementioned study, the prevalence of severe hypoglycemia was higher in patients with changes in hypoglycemic agents or insulin level and those with major changes in their lifestyle (5). Factors that may increase the risk of hypoglycemia during Ramadan included
geographical location (e.g., Indonesia, Malaysia, and Saudi Arabia), body weight <70 kg, waist circumference < 90 cm, insulin therapy, and prior history of hypoglycemia before Ramadan (22). A 4-fold increase in the incidence of hypoglycemia in diabetic patients, who had not been trained about fasting, was observed, whereas individuals, who had participated in educational programs, showed lower weight loss and reduced incidence of hypoglycemia (16).

Dehydration and thrombosis
Restriction of fluid intake during prolonged fasting can lead to dehydration. Hot climates, severe physical activities, and conditions leading to excessive sweating intensify dehydration. Hyperglycemia can cause osmotic diuresis and imbalance in electrolyte and blood volume. Moreover, in patients, who are already suffering from autonomic neuropathy, orthostatic hypotension may occur. Cardiac arrest, falls, injuries, and bone fractures may occur due to the effects of dehydration and low blood pressure. Also, dehydration can enhance blood clotting in patients with diabetes (55), and increased blood viscosity due to dehydration may increase the risk of thrombosis (56, 57).

Oral medications
Sulfonylureas
Those receiving multiple sulfonylureas often face problems during Ramadan fasting. Theoretically, use of long-acting sulfonylureas with afternoon and Iftar meals better controls blood glucose (58, 59). In a study, receiving 60 mg of gliclazide (modified-release type) at Iftar led to a decrease in fasting blood glucose. Therefore, this medication could be used during Ramadan without disrupting the blood glucose level in diabetic patients (60).

In another investigation, patients receiving glibenclamide at Sahar and Iftar experienced increased blood glucose and weight gain; in addition, hypoglycemia occurred in 4% of these participants (33). Ramadan fasting in patients under glimepiride monotherapy (receiving the same typical dosage at Iftar) led to a 0.3% reduction in HbA1c; however, 5% of patients experienced hypoglycemia (41). In fact, glyburide (glibenclamide) might be more significantly associated with the risk of hypoglycemia, compared to the second generation of sulfonylureas, particularly gliclazide, glimepiride, and glipizide (58, 61).

Biguanides (Metformin)
In a study conducted on patients with well-controlled type 2 diabetes, fasting and postprandial blood glucose levels decreased during Ramadan fasting, while serum insulin level increased; however, all the changes were within the normal range (39). In fact, medications, inducing sensitivity to insulin, are associated with a lower risk of hypoglycemia during fasting, compared to drugs elevating insulin secretion (62). Therefore, the risk of acute hypoglycemia is lower in patients receiving only metformin.

Thiazolidinediones and α-glucosidase inhibitors
An important issue concerning the use of glitazones during Ramadan fasting is that it takes 2-4 weeks until these medications affect the blood glucose. Thus, it is not possible to quickly replace these medications with other glucose-lowering agents (63). Patients using α-glucosidase inhibitors or thiazolidinediones such as glitazone are at a lower risk, and according to specialists’ advice, their medication dosage does not need to be altered (54).

Meglitinides (repaglinide)
According to a previous study, serum fructosamine level decreased more significantly in patients using repaglinide, compared to those taking glibenclamide in Ramadan (17, 33). There was no significant difference in terms of glycemia between patients receiving single-dose glimepiride along with gliclazide and those taking repaglinide twice a day. Nevertheless, hypoglycemia was reported in patients receiving repaglinide (6). It seems that repaglinide is an appropriate choice for diabetic patients using sulfonylureas (6, 17, 33, 41).

As a previous study indicated, Ramadan fasting does not result in any changes in fasting or postprandial blood glucose, HbA1c, or serum fructosamine in three groups taking glimepiride at sunset (maximum dosage of 8 mg), repaglinide at dawn and sunset (maximum dose of 4 mg during each meal), and insulin glargine at 22 p.m. On the other hand, 2-h postprandial blood glucose was higher in non-fasting
patients, compared to fasting individuals; however, the effects of all 3 prescriptions were similar (20), and the risk of hypoglycemia did not change in these patients. It should be mentioned that the type and dosage of evaluated medications had been modified six months prior to the study (20).

**Dipeptidyl peptidase-4 (DPP-4) inhibitor**

In a study on type 2 diabetic patients with HbA1c higher than 8.5%, adding 50 mg of vildagliptin (twice a day) to the normal treatment with metformin improved hyperglycemia, without increasing the risk of hypoglycemia; however, this effect was not observed by adding 160 mg of glimepiride (twice a day) to the normal treatment (64).

Vildagliptin prevents the rapid degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoceptive peptide, elevates the plasma concentration of the active forms of these hormones, and increases the sensitivity of pancreatic cells to glucose (65). Vildagliptin together with metformin, sulfonylureas, and thiazolidinediones reduces the incidence of hypoglycemia (66, 67); therefore, vildagliptin may be a better agent than sulphonylurea (68, 69).

**GLP-1 receptor agonists**

Compared to sulphonylurea, liraglutide (GLP-1 receptor agonist) may be more effective in combination with metformin in managing glycemia and severe hypoglycaemia (70).

**Insulin therapy**

**Type 1 diabetes**

Some type 1 diabetic patients opt to fast during Ramadan, and most of these patients change their insulin dosage immediately before, during, and some days after Ramadan. However, few studies have been conducted on the safety or efficacy of different insulin regimens in fasting patients with type 1 diabetes. In a study conducted on 15 patients receiving insulin glargine and rapid-acting insulin, all subjects, even those with some degrees of neuropathy, retinopathy, and nephropathy, tolerated fasting without facing any problems, and their mean daily blood glucose decreased during Ramadan (71).

In a study, glycosylated hemoglobin slightly improved in patients with type 1 diabetes using insulin pump, and there was a 5-50% reduction in insulin need in 50% of cases (52). In addition, insulin lispro, aspart, or lispro mix 25 could control blood glucose through lowering the frequency of hypoglycemia (72). It seems that if patients are given the necessary instructions about adjusting their insulin dosage [e.g., using analog insulin instead of neutral protamine hagedorn (NPH) and regular insulin and avoiding fasting in case of blood glucose drop], fasting would have fewer untoward effects on type 1 diabetic patients (73).

**Type 2 diabetes**

In a previous study, use of insulin glargine, together with glimepiride at sunset, led to a decrease in fasting blood glucose and HbA1c. However, the incidence of hypoglycemia increased, particularly in patients with low body weight and waist circumference. Blood glucose level > 120 mg/dl had a protective effect against hypoglycemia (45). Insulin lispro, aspart, and lispro mix 25 were associated with a lower incidence of hypoglycemia. Furthermore, using rapid-acting insulin analogs instead of regular insulin before meals resulted in a lower incidence of hypoglycemia and reduced the elevation of postprandial blood glucose (74, 75).

Combination of insulin lispro and Neutral Protamine Lispro (NPL) with a 50:50 ratio during Iftar and regular insulin along with NPH with a 30:70 ratio at Sahar led to the improvement of blood glucose and lowered the incidence of hypoglycemia; however, regular insulin and NPH with a ratio of 30:70 (used twice a day) did not have the same effects (76).

Evidence shows that hypoglycemia and hyperglycemia are preventable by training patients, holding educational programs (16, 77), adjusting medication dosages, modifying patients’ lifestyle, self-monitoring of blood glucose, and novel therapeutic strategies (5, 16, 72, 78-83). Also, acute complications of fasting can be mitigated through the medical evaluation of patients before Ramadan and patient follow-up during and after this month (16).

Currently, no information is available regarding the effect of fasting on the mortality rate of diabetic patients and the interactive effect of fasting on chronic complications of diabetes. Based on the available data, it is hardly possible to demonstrate the innocuousness of
Changes and variations in dietary carbohydrate also lead to contradictory results. For instance, increasing carbohydrate intake at each meal without adjusting oral medication or insulin dosage would lead to increased blood glucose. Also, patient’s reaction to insulin injection may vary in different hours of the day (103, 104). Differences between individuals in consuming foods with a wide range of glycemic indices also affect postprandial blood glucose (105). Moreover, the increase in glycemic load (especially during Iftar) for overcoming low blood glucose (induced by fasting) can increase postprandial blood glucose and disrupt glycemic control.

In most diabetic patients, consumption of high glycemic-index foods (e.g., dates) increases, especially during Iftar (106). Weight loss in overweight or obese people decreases insulin resistance and consequently lowers blood glucose concentration (107, 108). Studies have shown that reduced daily calorie intake may decrease the blood glucose level, even if it does not result in significant weight loss (109). Therefore, a slight increase in blood glucose level, without significant changes in body weight, can lead to a change in blood glucose, which is often overlooked in the interpretation of the results.

Typically, patients are advised to increase the number of their daily meals and consume about 3-5 carbohydrate servings at each meal and 1-2 servings during snacks (109). If fasting diabetic patients take only two main meals during the day, they might receive their carbohydrate snacks as two main meals, especially during Iftar; this would lead to a rise in postprandial blood glucose.

A factor influencing the number of meals in Ramadan fasting may be the season in which Ramadan falls. Since time interval between sunset and bedtime reduces in summer, the number of daily meals during the day, the number of meals and time interval between breaking the fast and late-night snack decreases; this reduced time interval may affect glycemic control (110). Conversely, the time interval between sunset and bedtime increases in winter, and therefore, there is more free time to consume snacks. The effect of these factors on glycemic control has not been analyzed in studies conducted in different seasons.

Additionally, some people tend to eat a light meal at Iftar, followed by a large meal like...
dinner (which can vary among individuals) (87, 111). Thus, individual differences in meal frequency contribute to the inconsistency of the results.

An appropriate liquid intake is essential for maintaining body water, normal osmolality of body liquids, and excretion of excess glucose. In Ramadan fasting, liquid consumption is restricted to the time interval between Iftar and Sahar, and partial dehydration occurs during Ramadan fasting (112). Dehydration may increase serum glucose concentration (113). Thus, differences in liquid consumption, the season of Ramadan, ambient temperature, and lifestyle could lead to contradictory results in different studies.

Furthermore, in most studies, changes in physical activity and their effects on blood glucose level have been ignored in the interpretation of the results. Even though a decrease in physical activity has been reported in Ramadan (89, 114), it may not be true in all cases.

Conclusion

As the results indicated, fasting could be non-risky in patients with partially controlled diabetes and type 2 diabetic individuals, using oral glucose-lowering agents. Based on the obtained findings and considering several confounding factors, which were ignored in the analysis of the results, we cannot determine the exact effect of Ramadan fasting on metabolic control; also, we cannot assure the safety of fasting for different patients. Presently, there are neither precise quantitative criteria (covering medication, diet, and physical activity) nor clear guidelines regarding Ramadan fasting for diabetic patients. Therefore, well controlled studies should be conducted by considering all the factors affecting blood glucose in this period. However, based on clinical experience, the following points need to be considered:

1. All diabetic patients, who decide to fast, should be evaluated 2-3 months before Ramadan by a physician regarding the safety and complications of fasting and be informed about the necessary changes and required trainings.

2. Currently, Ramadan fasting is allowed in stable type 2 diabetic patients (normal or overweight), who are educable and use oral glucose-lowering agents.

3. Patients at high risk of fasting complications include insulin-treated patients, uncontrolled diabetic patients, breastfeeding mothers, patients experiencing unawareness hypoglycemia, gestation, the elderly, hypoglycemic individuals, patients affected by disease complications, non-educable patients, and those living alone.

4. It is necessary to educate patients with regard to symptoms of hypoglycemia, hyperglycemia, and loss of body water. Patients should be also trained about the measures, which need to be taken in these circumstances.

5. In addition to drugs, adjusting the dietary intake and physical activity (regarding its duration and intensity) should be considered.

6. Experts forbid fasting in patients with fasting blood sugar: < 70 or > 200 mg/dl. Fasting should be stopped in case the blood glucose level exceeds 250-300 or drops to < 60-70 mg/dl.

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