

Review Article

Diabetes and Ramadan

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Fasting during Ramadan, in the holy month of Islam, is an obligatory duty for healthy adult Muslims. People who fast during Ramadan must abstain from eating, drinking, smoking and need to stop their medications from daybreak to sunset. Depending on the geographical settings and season, the duration of the daily fast may range from 12 to 20 hours. Diabetic patients who fasten in Ramadan may have some risks. Hypoglycemia, hyperglycemia, diabetic ketoacidosis, dehydration and venous thrombosis are possible risks for fasting patients in diabetes. Physicians responsibility is to assess the patients and verify the high, intermediate and low risk groups. Likewise; physicians also need to identify the patients who can fasten during Ramadan, educate them and arrange their treatment. Following the observational studies and guidelines this review summarizes the management of a diabetic patient who wants to fasten during.

Keywords: Ramadan; Diabetes mellitus; Fasting**Abbreviations**

FOXO-1: Forkhead Box Protein O1; AMP: Adenosine Monophosphate; Sir-2, Sirt-1: Sirtulin Related Genes; IL-6: Interleukin 6; TNF: Tumor Necrosis Factor; CRP: C-Reactive Protein; HDL: High density Lipoprotein; LDL: Low Density Lipoprotein; GFR: Glomerule Filtration Rate; HOMA-IR: Homeostatic Model Assessment Insulin Resistance; SGLT-2: The Sodium/Glucose Cotransporter 2; GLP-1: Glucagon-Like Peptide-1; DPP-4: Dipeptidyl Peptidase-4; NPH: Neutral Protamine Hagedorn

Introduction

Muslims fast during Ramadan. It is one of the five pillars of Islam. Epidemiologic studies show that many of the diabetic patients want to fasten in the ramadan. Ramadan fasting for diabetics is associated with some risks. These are hypoglycemia, hyperglycemia, dehydration and increased risk of thrombosis. Physicians need to identify the diabetic patients who are eligible to fasten and also arrange their medication. This review summarizes the management of diabetic patients who want to fasten in ramadan through the guidelines and observational studies on this topic.

The first section addresses hunger physiology, determining the effects of short term intermittent hunger on healthy people and diabetic patients also discussing the possible risks. Second section describes the management of diabetic patients who want to fasten during Ramadan.

The effect of fasting on healthy people and on diabetic patients

Energy metabolism in humans: Energy utilization in humans takes places in two phases. First phase; known as the postprandial (absorbative) phase covers the period between oral intake of food until it is totally absorbed from the gastrointestinal channel. It starts with intake of food and lasts approximately 4 hours. During this phase food is absorbed from the gastrointestinal channel and nutrients are utilized and stored. Also in this phase; carbohydrates are used

acutely or stored in the liver in form of glucogen (glucogenesis), fatty acids are stored in the adipose tissue (lipogenesis) and aminoacids are transferred to the cells for protein synthesis. Insulin is primarily responsible for this phase. As this phase expires; the second phase known as the postabsorptive period or the fasting period starts. Stored fuel is used to supply critical energy threshold. Stored glucogen is used at the first 6-24 hours (glucogenolysis). Fatty acid oxidation and ketogenesis is started (lipolysis). Then; gluconeogenesis occur in the liver also supplying the glucose levels for brain from aminoacids, lactate and glycerol (2-10 days). Insulinopenia, glucagonemia, sympatoadrenal discharge and in advanced stages cortisol are responsible for these effects. In advanced stages (12 hours-3weeks) stored fat is exhausted and energy is only supplied by gluconeogenesis from protein (starvation) [1].

The effect of short term or intermittent fasting on human physiology: Experimental studies show that during short term repeating fasting, hypothalamic neuropeptide Y levels decrease, insulin resistance of peripheral muscles decreases, insulin levels released from pancreas go down, insulin sensitivity in the adipose tissue increases, leptin levels decrease, adiponektin levels increase, plasma insulin like growth factor-1 levels decrease, cardiac parasympatic tonus increases, heart rate and blood pressure decreases, FOXO-1 levels decrease, AMP kinase levels increase and stress resistance of the cells increases [2]. In addition; in the cardiovascular system, infarct area gets smaller and in the postinfarct period cell apoptosis and myocardial fibrosis decrease, p53 and p38 apoptotic gen expression on the cell level decrease and with Sir2, Sirt 1 gen expression increases, cell death slows down, and with decreases in levels of IL-6, TNF and CRP, inflammatory processes breaks down, and lipid profile improves with decreased tryglicerid levels and increased high density lipid profiles [3].

Metabolic effects of Ramadan fasting: Fasting during Ramadan is an obligatory duty for healthy adult Muslims. People who fast during Ramadan must abstain from eating, drinking, smoking and stop taking medications-if any from daybreak to sunset. Depending

on the geographical settings and season, the duration of the daily fasting may range from 12 to 20 hours. Normally, people take three main meals daily. During Ramadan the number reduces to two, one large meal at sunset (iftar) and one light meal before dawn (suhur). The metaanalysis of 21 studies containing 531 male and 299 female subjects during Ramadan reveals an intermediate decrease in males body weight, mean body fat and body mass index which was not seen in females. Unlike females, males generally continue daily activity during ramadan and this was thought to be the reason for this difference. No waist and hip circumference changes were noted for both genders. Body weight loss for males were highest at the third week of ramadan but after ramadan returned to preramadan levels [4]. In males; a decrease in total cholesterol and tryglicerid levels was noted, besides HDLcholesterol increase in females and specific LDL cholesterol decrease for both genders was found. Ramadan fasting does not have a specific effect on renal functions of healthy population but on 31 patients with chronic renal failure a progress in GFR and a reduction in urinary sodium and protein release is noted [5]. On the other hand; another study on 15 chronic renal patients not under dialysis has shown an increase in renal tubular damage without a change in glomerular filtration rate [6]. A study which has assessed the glucose metabolism during Ramadan fasting on healthy people has demonstrated a specific reduction on fastening blood glucose and on insulin resistance measured with HOMA-IR compared to preramadan period, also with a recovery on beta cell functions calculated with HOMA-beta at the fourth week of Ramadan [7]. However; in diabetic patients; increased glucogenolysis secondary to absolute insulin deficiency and hyperglycemia and risk of ketoacidosis due to glucogenolysis and ketogenesis, already present insulin resistance, the disruptive effects of current medications on insulin and counter insulin mechanisms and impairment in insulin resistance and increased gluconeogenesis secondary to loss of diurnal rhythm of cortisol altogether may inhibit the anticipated positive effects of Ramadan fasting and prepare ground for acute diabetic complications.

Possible risks for fastening patients in diabetes: EPIDIAR study conducted in 13 Islamic nations on 12914 diabetic patients has revealed that 43% of type 1 diabetic patients and 79% of type II diabetic patients have been fastening in Ramadan, which means about 55 million diabetics on earth have been fastening each year [8]. According to the data of this study, risk of hypoglycemia has increased 4.7 fold and 7.5 fold for type 1 and type 2 diabetics respectively. Decreased caloric intake, long hours of fasting (16-20 hours in summer), lack of glucogen storage due to insulin deficiency and resistance, the continuous effects of insulin and secretogogs, and patients concerns of disturbing their fast with self glucose monitoring are main factors which increase the risk of hypoglycemia. Indeed the READ study which addresses Ramadan education for diabetic patients has revealed a 4 fold increase in hypoglycemia for the uneducated group [9]. Also according to EPIDIAR data, hyperglycemia risk with or without ketoacidosis that requires hospitalization has increased 5 fold and 3 fold for fastening type I and type II diabetic patients respectively. The reasons for hyperglycemia are: increased calorie and simple carbohydrate intake, the effects of counterinsulin hormones, insulin deficiency, increased glucogenolysis, ketogenesis and gluconeogenesis, patients improper use of medications, and lack of self glucose monitoring. Another problem encountered in fastening diabetics is increased risk

of dehydration. Insufficient fluid intake, liquid loss with perspiration especially in summer, osmotic diuresis secondary to hyperglycemia and side effects of medications (SGLT-2 inhibitors-osmotic diuresis, GLP-1 agonists-vomiting, metformin-diarrhea) are possible reasons for dehydration [10]. Finally hypercoagulability states, triggered by hyperglycemia and hypovolemia may induce risk of thrombosis and stroke, acute coronary events, cerebral venous and sinus thrombosis and retinal vein occlusion [11,12].

Management of diabetic patients who want to fasten in Ramadan

Actual guidelines that contain data on observational and randomised studies and expert opinions regarding to diabetic patients who wish to fasten during Ramadan have been prepared [13-15]. According to these guidelines patients who wish to fasten during Ramadan must be taken under assessment at least a few months in advance. The preliminary assessment consists of duration of diabetes, medications, comorbid conditions, diabetic vascular complications, hypo- hyperglycemic events, history of ketoacidosis and hypoglycemic coma, previous fasting history, life conditions, and assessment of self glucose monitoring. Blood pressure, body mass index must be taken and systemic and neuropathic examination must be made. HbA1c, blood glucose profile, renal functions, eye examination, urinary albumin creatinin rate, an electrocardiogram (further cardiac tests if necessary) must be assessed. A risk classification for a patient is obtained through this data which is divided into four groups.

- **Low risk patients:** Those; who are under control with diet only and those who have good metabolic control with no complications with any one of the following or with a combination of the following drugs; metformin, DPP-4 inhibitors, acarbose, thiazolidinediones, GLP-1 agonists and SGLT-2 inhibitors.
- **Medium risk patients:** Patients with no complication and those in low risk group with HbA1c levels between 7.5%-8.5% and those who have HbA1c less than 7.5% with sulphonylureas, meglitinide or insulin therapy.
- **High risk patients:** Those who have a HbA1c between 8.5-10% or those whose fastening plasma glucose is between 150-300 mg/dl, those who have specific microvascular (retinopathy, nephropathy, neuropathy) or macrovascular complications, those who live alone and use insulin or secretagogues, those over 75 years of age, and those who have comorbid conditions like dementia, congestive heart failure, malignity, uncontrolled hypertension and stroke are in this group.
- **Very high risk patients:** Type 1 diabetics, pregnant diabetics, those who have HbA1c > 10% or fastening blood sugar > 300 mg/dl, those who experienced hypoglycemia attack or repeating hypoglycemic attacks in 3 months, those who have history of diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic coma and also those who have comorbidities like hypoglycemia unawareness, dialysis, advanced heart failure are in this group

American Diabetes Association (ADA) has suggested in 2005 Ramadan guidelines that the diabetic patients not fasten due to possible risks fastening may bring out [16]. As a result high risk patients should not be permitted to fasten during Ramadan and very high risk patients should definitely be prohibited to do so. Low risk

patients may fasten without any change in medication after receiving supervision and medium risk patients must be told about risks of fasting but for those who insist on must be monitored closely [13].

Patient education: After preliminary assessment and determination of risk groups patients who are allowed to fasten must be given education on the issue. Patient education starts with explaining the risks of fasting and ways to overcome them. Diet, exercise, self glucose monitoring, prevention and correction of hypoglycemia, when to break fast and patient visit frequency must be involved. An important study shows that patient education decreases hypoglycemia 4 fold and also that; mean HbA1C levels are more stable [17]. Another study has shown that 23-30.1% of patients who are not given education do not break fast even if they have a hypoglycemic attack [18].

Diet education must consist of advisory on consuming simple carbohydrates during iftar and complex carbohydrates during suhur, preference for a low glycemic index (35-55) diet, increasing the amount of fibers in the diet and decreasing saturated fats [19,20]. Ma-Pi 2 diet which suggests consumption of low sugar, and is rich in complex carbohydrates and dietary fiber containing cereal and vegetables and fermented products, poor in unrefined salt, fat and animal proteins should be advised to those patients according to American Diabetes Association and European Nutrition Suggestions [19,21].

During period of satiety it must be emphasized that light to moderate exercise is safe and beneficial. Tarawih prayer established at night during Ramadan is a good example for light exercise. Even so; the possible risk of hypoglycemia during this period must be underlined [22]. Heavy exercise is not suggested to patients under insulin or secretagogues. Patients must be advised to refrain from exercise at final hours of fasting.

Prior to Ramadan patients must be ensured that home glucose monitoring during fasting hours does not break fasting [23]. A survey on diabetics fasting in Ramadan has displayed that 67 % of patients believed that finger lancing for self glucose monitoring broke fasting [24]. Hypo and hyperglycemic symptoms must be well defined to patients and in the presence of such symptoms self glucose monitoring is needed for alterations in medication. Those who use insulin or secretagogues must obtain routine glucose measurements before and after iftar and suhur and at mid day [22].

Patient education must cover prevention from hypoglycemia as well as signs and symptoms. Home glucose assessment must be thought to patients, means of treatment must be reviewed one month before Ramadan, necessary changes must be fulfilled, suhur skipping and heavy physical activity during hunger must be strictly banned, time of hypoglycemia must be recorded and when to break fasting must be made clear [19]. A capillary blood glucose <70 mg/dl during any time of fasting or <70 mg/dl at the beginning of fasting for insulin or secretagogue users and random capillary glucose >300 mg/dl calls for fasting break [13].

Patients visits must start two months before Ramadan and risk determination must be made in this first visit, treatment and drug dose regulations must be made, patient education must be planned,

visit frequency must be determined, hypo-hyperglycemic situations and solutions, dose regulations for insulin and secretagogue users, after Ramadan warnings and return to pre-Ramadan issues must be considered [20].

Treatment management: It is stated that most patients change the drugs or their frequency during Ramadan without their physicians approval or even stop it completely [25]. Therefore; in order to prevent hypo-hyperglycemic attacks and increase patient adherence to medication; some changes of treatment; suitable for Ramadan can be arranged.

Metformin: It is known that this group of drugs have hypoglycemia risk up to 21% even in satiety [26]. Metformin therapy is accepted to be safe for fasting patients in general. It can be taken during iftar and suhur without dose change [13]. Another idea is to take 2/3 of the total dose in iftar and 1/3 in suhur. Those who use long release pills need to take the medication as a single dose at iftar [19]. Gastrointestinal irritation and dehydration secondary to diarrhea caused by metformin may be of concern during Ramadan.

Acarbose: Although there is no data on effectivity and reliability of acarbose during Ramadan, a real life analysis shows that acarbose taken with meals have low hypoglycemia risk (%0.03) [27]. Therefore it can be taken with meals without changing the dose [19].

Thiazolidinediones: Although their effectivity and reliability are not studied; due to their low risk of hypoglycemic events thiazolidinediones are assumed to be safe for Ramadan fasting. Their potential to cause weight gain is a disadvantage. As mean duration for maximal antihyperglycemic effect can be as long as 10-12 weeks, initiating the drug just before Ramadan is not advised [10]. They can be used in iftar or suhur without changing the dose.

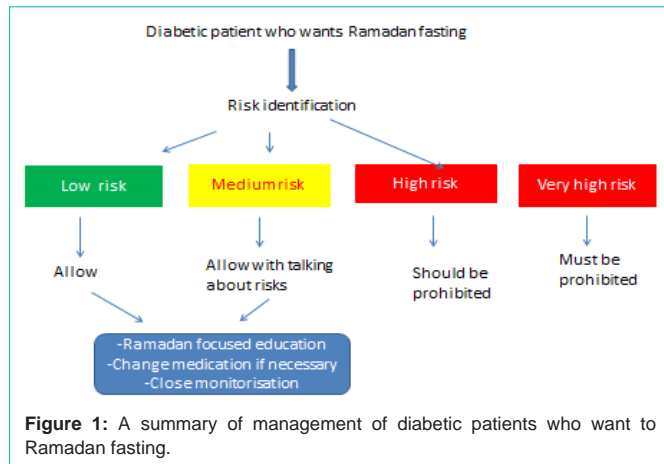
Sulphonylureas and meglitinides: Sulphonylureas are insulin secretagogues and also well known to induce hypoglycemia risk. However; there are conflicting data on sulphonylurea use during Ramadan. The GLIRA study which is an extensive, prospective and an observational study including 332 patients from six countries has determined that the hypoglycemia risk and glycemic effect of glimepride is similar if used before iftar compared to pre-Ramadan [28]. Another study conducted on 136 patients taking Gliclazide MR 60 mg showed that moving the dose to iftar does not induce hypoglycemia risk [29]. Besides; an observational study including 1378 patients from 5 countries in which a sulphonylurea either as monotherapy or with metformin has reported at least one hypoglycemic event in 19.7 % of cases [30]. Risk of hypoglycemic attacks with glibenclamide, glimepride and gliclazide are 25.6%, 16.8 % and 14% respectively. The risk of symptomatic hypoglycemia was found to be significantly higher in another study in which 1066 patients were randomized into sitagliptin and sulphonylurea groups in Ramadan. This risk was higher in glibenclamide than glimepride and gliclazide, similarly with the previous study (respectively 19.7%, 12.4% and 6.6%) [31]. As a result sulphonylurea use in Ramadan is associated with increased risk of hypoglycemia, and special patient groups (eg. elder patients, patients who have experienced hypoglycemia with sulphonylureas, and those who use high risk hypoglycemic drugs such as glibenclamide) may benefit from drug alteration. Those with medium risk, using glibenclamide may benefit from replacement with gliclazide. Those

who have HbA1c levels below 7.5% before Ramadan are suggested to reduce drug dose [13]. The suggested medication algorithm for single dose long acting sulphonylurea users is to take the morning dose at iftar, and for two dose users is to carry the morning dose to iftar and adding half of the evening dose at suhur [32]. The common sense for these drugs is to avoid them as much as possible due to risk of hypoglycemia [19]. Short acting insulin secretagogues; meglitinides seem to be advantageous over long acting sulphonylureas in terms of hypoglycemia during Ramadan. One study has compared the efficacy and reliability of glargine, glimepride and repaglinide and showed no significant difference between them [33]. However; two different studies have reported less hypoglycemic events with repaglinide when compared to glibenclamide users [34,35]. Still; an observational study of authors of this review has shown that preprandial repaglinide with insulin glargine does not increase risk of hypoglycemia in Ramadan [36]. Although they don't carry hypoglycemia risk as much as sulphonylureas; meglitinides should be taken before iftar and suhur due to their potential hypoglycemic effects.

Incretin based therapies: DPP-4 inhibitors are among oral antidiabetics preferred at Ramadan for their low hypoglycemic potential and a satisfying number of studies for efficacy and safety on patients fasting during Ramadan. In a multicentric, observational cohort study (VECTOR) vildagliptin or gliclazide was added to metformin and low HbA1c levels and less hypoglycemic events were recorded for the vildagliptin group. Patient adherence was found to be better for vildagliptin (vildagliptin dose skip %0.2, gliclazide dose skip %7.6, $p=0.0204$) [37]. Another Ramadan study where another DPP-4 inhibitor sitagliptin was compared to sulphonylureas; better patient adherence and less hypoglycemic events were observed in the sitagliptin group [31]. Another study in 10 countries containing more than 1300 patients (VIRTUE) has revealed that vildagliptin caused less hypoglycemia in fasting diabetics (5.9% vs 19.8%; OR (95CI%)=0.23 (0.16;0.34) and $P<0.001$), supplied better glycemic control (HbA1c change -0.24 % vs 0.02%) and better weight control (-0.76 kg vs -0.13 kg) compared to sulphonylureas [38]. A recent study (STEADFAST) has randomized 557 well controlled patients from 16 countries who received metformin and any sulphonylurea before Ramadan, to vildagliptin and gliclazide groups during Ramadan. Less hypoglycemic events were observed in the Vildagliptin group (3% vs 7%) but no significant difference was determined in terms of glycemic control, patient adherence and weight change [39]. Finally a meta-analysis including 16 randomized controlled studies and 13 observational studies has revealed that DPP-4 inhibitors reduce the risk of hypoglycemia to 1.5 fold when compared to the sum of sulphonylurea, meglitinide and basal insulin therapies [40]. As a result DPP-4 inhibitors are safe during Ramadan. No dose change is necessary and they can be taken before iftar or suhur. There are a limited number of studies regarding to efficacy and safety of treatments with GLP-1 analogues during Ramadan. The READ study which observed the effect of Ramadan education on hypoglycemia has concluded that metformin and exenatide combination caused much less hypoglycemia than metformin and gliclazide [9]. A study on 99 obese patients who want to fasten during Ramadan compared metformin plus liraglutide with metformin plus sulphonylureas. More patients were preserved at the desired HbA1c levels (<7%) with liraglutide, though serious hypoglycemia was not seen in both

groups, statistically greater number of recorded hypoglycemic events was seen at the sulphonylurea group. Significant weight loss and drop in diastolic blood pressure was seen in the liraglutide group [41]. As a result GLP-1 analogues seem to be effective and safe for patients who want to fast during Ramadan compared to sulphonylureas. However emesis and vomiting related dehydration as potential side effects of this drugs may make a problem.

Insulin: Especially elder patients who use insulin are under greater risk of hypoglycemia compared to metformin during Ramadan [10]. There are limited number of studies on type 2 diabetics patients fasting during Ramadan and expert opinions are first at hand. A multicentric, prospective, observational study has revealed that glargine combined with metformin did not cause more hypoglycemic events compared to glimepride and repaglinide [33]. The safety of insulin glargine combined with repaglinide during Ramadan has been shown in our study too [36]. However in another study patients not previously using insulin ($n=100$) and those already under insulin ($n=249$) were given glargine insulin and glimepride for Ramadan fasting and higher frequency of hypoglycemic events were seen [42]. A Ramadan study which compared premeal regular insulin plus insulin glargine or NPH insulin for basal insulin in type 1 diabetic patients has revealed that insulin glargine provided better glycemic control [43]. A heterogeneous group of patients with standard diabetes treatment ($n=118$) was compared with a group ($n=127$) taking bifazinc insulin aspart (novomix 70) at iftar and insulin Detemir at suhur. Sixty percent of total insulin dosage was given at iftar and 40% at suhur and glycemic effect was found to be similar to the conventional management with less hypoglycemic event rate [44]. According to South Asian Consensus guideline; dose of analogue insulin for basal insulinization can be given unchanged and NPH dose halved during suhur [45]. It is also stated to 20% decrease in glargine insulin increases safety [20]. A study which compared short acting analogue insulin to regular human insulin has revealed better postprandial glucose levels and low rate of hypoglycemic events with insulin lispro [46]. A study conducted on fasting patients taking basal insulin and analogue bolus insulin at iftar and suhur revealed that a 10-20% decrease in basal insulin makes the management safer and more effective than a premix insulin regimen [47]. There are studies that investigate the efficacy and safety of mixed insulins used during Ramadan. One has compared 25% insulin lispro and 75% neutral lispro protamine (humalog mix 25) to 30% regular human insulin and 70% isofan (humulin m 70/30) to find humalog mix 25 provide better prandial glycaemic values, better mean daily glycaemic values, better tolerability but same weight gain and hypoglycemic events [48]. Another study has replaced mixed insulin during iftar with insulin lispro 50% and neutral lispro protamine 50% and at suhur with insulin lispro 25% and neutral lispro protamine 75% reducing doses 30% and has ended up with better glycemic control and less hypoglycemia compared to conventional analogue mix insulin treatment [49]. Treatment advise with premix analogue mixed insulins is given as taking the morning dose unchanged at iftar and half of the evening dose at suhur [13]. For treatment with premix insulins the daily doses are suggested to be increased by 20% if the measurements of blood glucose levels, before iftar and suhur are > 300 mg/dl, by 10% if >180mg/dl, not changed if between 100-180 mg/dl and reduced by 10% if between 70-100 mg/dl [14].



Conclusion

Studies have proved that if not directed properly diabetic patients may fast during Ramadan and disturb their blood glucose control and be vulnerable to consequent risks. Physicians responsibility in such conditions is to assess the patients; and for high risk groups is to prohibit fastening, for medium and low risks groups is to arrange the treatment and follow the patients. It is important to properly educate the patients to fasten in Ramadan and arrange their medications to minimize risks. The simple algorithm for physicians is given in Figure 1. During Ramadan; patients must be in close contact with their physician, diabetes nurse and dietitian. Also patients must be directed to physician control by health care organizations and religious institutions.

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