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An Overview about Fasting and Diabetes in Ramadan

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Abstract: Background: All adult and teenage Muslims must fast throughout the holy month of Ramadan in accordance with one of Islam's five pillars. Muslims often eat two meals each day during the fasting month: suhur (before dawn) and iftar (after nightfall). It is critical for medical professionals to educate diabetic patients on safe fasting practices because individuals with diabetes may experience challenges when fasting. Muslim people with diabetes can fast during Ramadan with the right information, preparation, and adjustments to their medications, despite the fact that prolonged stringent fasting increases the risk of hypoglycemia and diabetic ketoacidosis. Up until May 2023, this review's literature search was carried out utilizing PubMed and Google Scholar. Only articles written in English were considered. Current methods for controlling blood sugar levels during Ramadan involve a mix of dietary advice for patients, frequent glucose monitoring, medication, and insulin treatment. Patients' demands should be taken into account while adjusting insulin therapy during fasting, and regular assessments of finger prick blood sugar levels should be performed. Breaking the fast is necessary in case specific symptoms like low or high blood sugar, dehydration, or acute illness manifest, or if blood glucose levels rise to more than 300 mg/dL or fall below 70 mg/dL values. Medications like tirzepatide, which is a dual agonist of gastric-inhibitory peptide and glucagonlike-peptide 1 receptors, and new insulin formulations like pegylated insulin have demonstrated promise in controlling blood sugar levels throughout Ramadan. In addition to insulin-dependent drugs, individuals with type 2 diabetes are also benefiting from the added cardiovascular effects of sodium-glucose-cotransporter-2 inhibitors, such as the FDA-approved ertugliflozin..

Keywords: Fasting, Type 2 diabetes

Introduction

One of Islam's five pillars and an obligation for all healthy Muslim adults and adolescents is fasting throughout the month of Ramadan. The majority of Muslims only eat two meals a day, suhur (before dawn) and iftar (after dusk) when fasting. Even though, they are free from this requirement, pregnant women and sick people frequently fast[1]. Recent global data suggests that over 148 million muslims are diabetics, and despite the exemption to fast, 116 million of them choose to fast. Furthermore, with lack of food intake for a longer period

of time, the most commonly reported symptom is hypoglycemia. A study done on a semi-structured focus group of 53 participants with type 2 diabetes mellitus, who fasted during Ramadan, showed that 43% of them reported having hypoglycemia, and 13% of the total participants reported having a fear of developing hypoglycemia while fasting[2]. This demonstrates that, despite the fact that people with diabetes mellitus and the elderly are excluded from fasting, the urge to fast still outweighs health considerations[3].

As a general rule, during a fast, one is not permitted to consume any food or drink, including through gastrostomy tubes, or take any medications through any mucosal route, including the mouth, nose, or rectum[3]. A person's glycemic control, weight, and lipid profile may alter as a result of changes in diet, physical activity, and sleep patterns, which may necessitate adjusting insulin doses and timing as well as oral hypoglycemic medications[4]. It is crucial that medical staff educate Muslim patients about safe fasting to minimize the difficulties that diabetic persons can have when fasting[2]. Therefore, to expand upon the subject of diabetic patients fasting during the month of Ramadan, we write this review regarding the implications in diabetic patients when fasting during Ramadan, its pathophysiology, treatment regimen, and the complications associated with this.

Ramadan is the ninth month of the Islamic calendar and is widely regarded as the most important month by Muslims with significant historical and religious implications. Some reasons for its significance include it being the month Muslims believe the Holy Quran was revealed to the Prophet Muhammad (peace be upon him), and Muslims were commanded to observe fast, abstaining from all sustenance, from sunrise till sunset[5].

While there is widespread awareness regarding the practice of fasting by Muslims during Ramadan, it is not the only purpose. Muslims from around the globe also believe that this is the month where prayer, recitation of the Quran, and community-serving charitable contributions should be given the utmost importance[6]. Muslims refrain from daily norm social practices as well as participation in entertainment-seeking behavior. In Muslim-majority countries, work hours are also altered and reduced[7].

The actual practice of fasting is only one of the fundamental pillars of Ramadan. In its totality, the month is supposed to harmoniously bring together a community of Muslims together in practice where they can learn how to abstain from daily comforts and pleasures in order to better appreciate their lives, experience a glimpse of the hardships of less fortunate people around the world and to practice their faith repetitively so that certain practices can carry over to the rest of the year[8].

Pathophysiology of diabetes and insulin resistance

The pathophysiology of the disease has been well-explained in previous literatures. However, the relationship between diabetes in fasting in healthy individuals and diabetics will be expanded upon further.

Beta-cells of the pancreas are responsible for the production of insulin, which is synthesized from pre-insulin. While maturing, pre-insulin goes through several conformational processes in the endoplasmic reticulum (ER) to change to pro-insulin. Proinsulin is then transported from the ER to the Golgi apparatus, where it enters immature secretory vesicles and is broken into C-peptide and insulin. After the maturation process, the insulin is stored in granules and is released under the trigger of high glucose levels. Some other components can also trigger the release of insulin, including amino acids, fatty acids, and hormones[9-11].

Physiology of Fasting in Healthy Individuals

During the first few hours of fasting, glucose levels fall, inhibiting insulin secretion. When glucose levels fall below the physiologically normal range of 65-70 mg/dL, two counterregulatory hormones, epinephrine, and glucagon, are activated and released. This causes glucagon to initiate hepatic glycogenolysis and epinephrine

to seek to keep glucose levels within the normal physiological range[3,9]. As fasting progresses, the levels of these two hormones keep increasing, eventually causing the formation of glucose via a combination of two mechanisms, i.e., previously activated glycogenolysis and newly-activated gluconeogenesis, which forms de novo glucose with the help of amino-acids residues and glycerol. After the depletion of hepatic glycogen levels, which can take anywhere from 12 to 36 h, ketone bodies are produced by mobilizing fatty acids from adipose tissue. These ketone bodies are used as a source of fuel for vital organ functions, while glucose is saved for the brain and erythrocytes[3,9,12-14].

These free fatty acids undergo beta-oxidation in the liver, producing ketones such as beta-hydroxybutyrate (-OHB) and acetoacetate, which are used to generate energy by the brain, muscles, and other tissues. The usage of ketones aids in the preservation of lean muscle mass, the improvement of body composition, the optimization of physiological function, and the slowing of aging and disease processes[3,12,13,15,16].

Physiology of Fasting in Diabetic Individuals

The physiology of fasting in diabetics varies with the type of diabetes. For those with type-2 diabetes, insulin resistance is the primary process. However, with increasing severity, the beta-cells can get exhausted and have a similar picture to type-1 diabetes mellitus. During the early stages of type 2 diabetes, adopting a fasting or extremely low-calorie diet, or practicing controlled fasting with slight weight loss, can lead to positive outcomes for the underlying pathophysiological factors of insulin resistance and adiposity, ultimately resulting in the normalization of blood sugar levels. In essence, this can reverse the T2 diabetes phenotype[3,9,12].

Nonetheless, in the absence of exogenous insulin, there is a theoretical possibility of significant hyperglycemia and clinically relevant ketogenesis in individuals with advanced type 2 diabetes, particularly those with type 1 diabetes, where insulin deficiency is absolute. Furthermore, the risk of severe hypoglycemia may emerge as a result of defective hypoglycemic counterregulatory responses, an inability to diminish circulating insulin of exogenous origin, and decreased adrenal and sympathetic neural tone. When patients have poor diabetes control, as seen by persistent hyperglycemia, the threshold for the release of counterregulatory hormones rises, in contrast to patients who have recurrent hypoglycemia, such as those who maintain stringent diabetic control. [3,12,17,18].

A study done by Lessan and colleagues on 56 diabetic patients (50 type 2 diabetics and six types 1 diabetics) showed that in periods of Ramadan and non-Ramadan, there was a statistically significant difference in mean glucose levels during the period of 24 h[19]. Diabetes and insulin regimens during Ramadan Since Islam constitutes one of the major global religions, it is probable that a healthcare provider will come across an Islamic patient during their practice. It is important for a physician to develop cultural sensitivity towards such patients, especially during the holy month of Ramadan[20]. It is a concern that strict fasting for prolonged periods could put the patient at risk for episodes of hypoglycemia and diabetic ketoacidosis. However, with adequate knowledge, a cautious approach, and medication adjustment as described below, Islamic patients with diabetes should be able to fast during Ramadan. The current regimens used to control blood sugar levels in patients during Ramadan involve a multicentric approach[21]. Intermittent fasting, which is only gaining popularity in recent times, includes abstinence from the consumption of any calories for more than twelve hours, followed by food consumption for a brief period of time in repeated cycles[22]. Ramadan is a type of intermittent fasting where people fast during the day and break their fast at night. Two major meals are consumed during this time: The iftar, when the fast is broken before sunset after a long day of fast, and the suhur, when a calorie-dense meal is consumed before sunrise just before starting the day-long fast[21]. Intermittent fasting is found to improve insulin resistance by reducing the intake of calories, which has been shown to halt the progression of chronic diseases such as diabetes by downstream endocrine signaling[22]. Although, it is recommended that patients with diabetes who wish to undergo fasting for Ramadan should plan

at least two-three months prior so that their body gets enough time to get acclimatized to the new dietary schedule[23]. It is generally recommended that patients with diabetes stop their oral sulfonylurea medications during Ramadan or use them with extreme caution due to the risk of hypoglycemia[1,24]. Insulin therapy can be continued during fasting if titrated well according to the patients' requirements. Patients' baseline glycaemic control must be taken into consideration with regular assessment of finger prick blood sugar levels[23]. Basal insulin such as neutral protamine hagedorn and glargine are taken once or twice a day and provide coverage over long hours. Bolus insulin can be short-or rapid-acting, providing mealtime coverage[25]. If a patient is on once-a-day basal insulin, they should take it with the Iftar meal with a slight reduction in the dose based on the patients' baseline sugar levels. If a patient is on twice-a-day basal insulin, they must take the usual dose along with their iftar meal but reduce the second dose taken with the suhur meal depending on the glycaemic control[21]. For patients on rapid-acting insulin, it is important to continue the same dose with their Iftar meal and take the second mealtime dose with their Suhur meal, titrating the dosage to a lower level[26]. Pre-mixed insulin regimens correspond more closely to the physiologic secretion of insulin in our body, such as insulin lispro 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro) and biphasic insulin aspart 70/30 (70/30; 70% insulin aspart protamine suspension and 30% insulin aspart). These suspensions suit patients who need both basal and mealtime insulin dosages[27]. It is recommended during Ramadan that the patient take their usual morning dose with their Iftar meal and reduce the dosage of evening insulin along with their suhur meal. It is always important to keep a constant check on the patients' blood sugar levels to prevent hypoglycemia. Patients should also ensure adequate hydration and should be educated about breaking the fast if they feel unwell[28].

Complications of diabetes due to lack of food intake Many Muslim patients may avoid going to the doctor before Ramadan out of concern that they might be told not to fast. Therefore, this prompts them to change their course of treatment without consulting a doctor[3]. Hypoglycemia, hyperglycemia, diabetic ketoacidosis, dehydration, and thrombosis are complications brought on by such changes[29]. Patients with type 1 diabetes had a 4.7-fold increased risk of hypoglycemia, compared to a 7.5-fold rise in type 2 diabetes patients. This number is frequently under-reported, though, because mild to moderate hyperglycemia typically does not necessitate medical attention. Numerous hours of fasting and failure to alter medicine dosages may be contributing factors[29]. According to the epidemiology of diabetes and Ramadan 1422/2001 study, patients with type 2 diabetes saw a five-fold increase in the chance of developing severe hyperglycemia during Ramadan, while those with type 1 diabetes experienced a three-fold increase in the risk of experiencing severe hyperglycemia with or without ketoacidosis. However, if a person has high blood sugar levels before Ramadan, their chance of developing diabetic ketoacidosis increases during fasting[21]. Additionally, a report from Saudi Arabia indicated that individuals who fasted throughout Ramadan had a higher risk of retinal vascular occlusion. Dehydration results from the persons' inability to drink fluids while fasting. In hot, humid areas and in those who engage in strenuous physical activity on a daily basis, the severity worsens. The patient becomes hypercoagulable as a result of the intravascular space contracting due to an increase in clotting factors, a decrease in endogenous anticoagulants, and impaired fibrinolysis. One of the factors that raise the risk of thrombosis is an increase in blood viscosity[21]. Risk factors for hypoglycemic episodes during Ramadan Fasting during Ramadan is associated with increased variability in glucose levels and has been associated with an increased risk for both hyperglycemia as well as hypoglycemia in diabetic patients[1,30]. A previous incidence of hypoglycemia during non-fasting months also significantly increases the risk of encountering another hypoglycemic episode during fasting, as the Multi-country retrospective observational study of the management and outcomes of patients with diabetes during Ramadan study demonstrated[31]. Other studies conducted across multiple geographies have demonstrated similar findings[32,33]. One study also showed a > 4-fold increase in severe hypoglycemic episodes requiring hospitalization in diabetic patients during Ramadan[34]. The use of sulfonylureas and insulin is associated with a greater risk of hypoglycemic episodes[33] as compared to glucagon-like-peptide-1 receptor agonists and 2nd generation sulfonylureas[35,36]. Hypoglycemia risk can also be elevated in regions with longer fasting durations, hot and arid atmospheres, and culturally distinct dietary practices[37]. Management of diabetic patients with

hypoglycemic episodes during fasting The management of hypoglycemia during Ramadan focuses on two aspects of treatment. Firstly, pre-Ramadan preparation and treatment of diabetes to ensure strong long-term glucose control, and secondly, signs and symptoms awareness in patients in order to recognize when to break the fast, if necessary, as well as maintaining regular monitoring of blood glucose. Nutritional patient education: Three months before Ramadan and the intended date of fasting initiation, pre-treatment education, and counseling should be initiated with the help of a multidisciplinary team. Dosages of all drugs should be stabilized, and a two-time regimen should be devised (pre and post-fast). If receiving insulin, self-titration should be practiced and taught. Additional considerations for co-morbid diseases such as chronic kidney disease should also be noted, and dietary and drug practices should be modified accordingly[37]. Prespecified, individualized macronutrient and energy requirement prescriptions: Prespecified, individualized macronutrient and energy requirement prescriptions in attunement with the medications being administered should be devised and recommended to the patients. Duration and total daily energy expenditure should be considered. Adequate, measured macronutrient intake (carbohydrate \leq 130 grams/d) has been known to reduce the rate of hypoglycemic episodes. Other recommendations include daily dietary cholesterol $<$ 300 milligrams/d and the division of meals into four unequally distributed meals with the highest carbohydrate load pre- and post-iftar immediately[38]. Regular blood glucose monitoring: Patients need to be encouraged to self-monitor glucose up to two times a day if at moderate risk of hypoglycemic episodes. However, if elevated risk is observed, a 7-point time scale monitoring method is recommended daily[39]. Medications: It is recommended to switch to glucagon-like peptide-1 (GLP-1) agonists from sulfonylureas, adjust doses, and consider the value of sodium-glucose-cotransporter-2 (SGLT2) inhibitors. Insulin delivered twice daily based on self-titrated and self-blood glucose monitoring is recommended[30]. Recognizing signs of severity: Certain signs of self-monitoring or the presence of certain symptoms have been associated with worsening hypoglycemic episodes associated with severe morbidity. For these indications, it is recommended that the fast should be immediately broken. These factors have been listed as the following[1]: (1) Blood glucose $>$ 300 mg/dL; (2) blood glucose $<$ 70 mg/dL; and (3) symptoms of hypoglycemia, hyperglycemia, dehydration, or acute illness. What's new in the treatment of diabetes: Recently, there have been some new insulin formulations that have been approved for the treatment of diabetes. Pegylated insulin moieties containing polyethylene glycol attached to the basic insulin structure have become more common because they ensure a slow and steady absorption of insulin from the injected site. Externally providing heat to the subcutaneously injected site has also been shown to increase the absorption of insulin[40]. Apart from modifications in insulin structures and function, there has been an increasing rise in incretin-based treatments for patients with diabetes[41]. Incretins are hormones that stimulate insulin secretion after the consumption of a meal in correspondence with the rising glucose levels. The glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are the two most common incretins[42]. A new concept of "twincretin" is also coming up, such as the drug tirzepatide which is a dual agonist of both GIP and GLP-1 receptors, thus increasing the efficacy of insulin release[43]. Semaglutide, a GLP-1 agonist, is gaining popularity not only for its treatment in diabetes mellitus but also because it has been shown to cause weight loss in obese patients, which is also a risk factor for developing insulin resistance and diabetes[44]. There has also been a rise in the usage of non-insulin-dependent medications such as SGLT2 inhibitors. These drugs prevent the renal reabsorption of glucose, thus enhancing its excretion and lowering blood sugar levels. The most recent SGLT inhibitor approved by the Food and Drug Administration is ertugliflozin, which has been found to have additional cardiovascular benefits in patients with type 2 diabetes (2017)[45,46]. Apart from its beneficial effects of increasing insulin release, as described above, GIP also causes fat deposition in the adipocytes, thus contributing to insulin resistance[41]. There are upcoming studies being done to see if GIP antagonists might have beneficial effects in reversing this insulin resistance and possibly metabolic syndrome. There are certain drugs with unknown mechanisms, such as dopamine receptor agonist bromocriptine that seem to be beneficial in the treatment of diabetes. It is found to reduce patients' fasting and postprandial blood glucose levels without having any effect on the release of insulin in the body[47]. With the wide array of medications available for patients with diabetes, it is important

for a physician to keep themselves updated with the most recent and upcoming treatment modalities.

Strategies for Controlling Diabetes during Ramadan

Pre-Ramadan medical evaluation: Before embarking on fasting during Ramadan, it is essential for diabetic individuals to undergo an assessment one to two months prior to the commencement of the holy month. This evaluation serves the purpose of gauging the patients' diabetes management, as well as identifying any acute and chronic diabetes-related complications and other coexisting medical conditions. The assessment is crucial in determining the level of risk the patient might face during Ramadan fasting, which is classified as very high, high, or moderate/low according to the International Diabetes Federation's criteria. Based on this risk categorization, patients should be appropriately advised regarding the feasibility of observing the fast. Raising the patients' understanding of the potential risks associated with fasting during Ramadan can significantly decrease the likelihood of complications. Proper education regarding dietary habits, physical activity, dosage of medications and recognition of warning signs is crucial[48,49].

Diet and Exercise It is imperative to encourage all diabetic patients to have the pre-dawn meal on fasting days. Ideally, a diet inclusive of slow energy-releasing complex carbohydrates for the predawn meal and simple carbohydrates for sunset meal. While diabetic patients can engage in their regular physical activities, including moderate exercise, they should be cautious about excessive physical exertion, especially in the evening, to prevent hypoglycemia. Some patients may choose not to monitor their blood glucose during fasting, fearing that finger pricking for blood sugar testing breaks the fast. Therefore, it is important to clarify to patients that this belief is a misconception and monitoring blood glucose levels is essential for their well-being[49-51].

Adjusting diabetes medications: Various diabetic medications have been described in the literature and clinical practice. Medications such as metformin, dipeptidyl peptidase 4 -inhibitors (sitagliptin), thiazolidinediones, short-acting insulin secretagogues can be used during fasting in diabetic individuals. However, medications like sulfonyl carry a higher risk of hypoglycemia, and SGLT2 inhibitors with their increased risk of dehydration as well as the urinary tract infections should typically be avoided in fasting diabetic individuals[52].

Insulins: Ramadan fasting poses an increased risk of hypoglycemia for individuals undergoing insulin treatment. To mitigate this risk while fasting, those using premixed insulin can consider switching to a multiple-dose regimen comprising a basal insulin and short-acting insulin administered before meals. The short-acting insulin dose should be adjusted according to the expected carbohydrate intake for each meal. However, this risk can also be mitigated with the use of an insulin pump during Ramadan[30,36].

Monitoring of blood glucose while fasting: Frequent monitoring of blood glucose during fasting is critical and as mentioned earlier, pricking your finger while fasting does not break the fast[51]. Additionally, in case of any hypoglycemic symptoms, the fast can be broken and it is acceptable under the laws of Islam. Management of complications in diabetic patients remains the same during Ramadan as it does usual.

CONCLUSION Muslims consider Ramadan, the ninth month of the Islamic calendar, to be the most significant month historically and religiously. During this month, the majority of Muslims only eat two meals a day, suhur (before dawn) and iftar (after dusk), after fasting for around 30 d. It is important for medical staff to educate Muslim patients on safe fasting practices, particularly for those with diabetes who may face difficulties. Current strategies for managing blood sugar levels during Ramadan involve a multidisciplinary approach, including nutritional education, regular blood glucose monitoring, medications, and insulin therapy. Insulin therapy can be continued during fasting if properly adjusted to the patients' needs. Patients on once-a-day basal insulin should take it with the Iftar meal, with a slight reduction in the dose based on their baseline sugar levels. Patients on twice-a-day basal insulin should take the usual dose with their iftar meal but reduce the second dose taken with the suhur meal based on their glycaemic control. Newer insulin formulations, such as pegylated insulin moieties, and drugs like tirzepatide, a dual agonist of both GLP-1 and GIP, have been introduced. Additionally, newer medications like SGLT2 inhibitors, including ertugliflozin, have shown many benefits, including additional cardiovascular benefits for patients with type 2 diabetes. Encourage diabetic patients to have a pre-dawn meal on fasting days with slow energy-releasing complex carbohydrates. For the sunset meal, opt for simple carbohydrates. Moderate exercise is allowed, but caution is advised against excessive physical exertion in the evening to

prevent hypoglycemia. Clarify that monitoring blood glucose during fasting is essential for their well-being, as finger pricking does not break the fast

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