Section A -Research paper

Ramadan Fasting in Type 1 Diabetes Mellitus

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Abstract:

The pandemic of diabetes mellitus is no longer contagious. Type 1 diabetes has become much more common, and recent years have seen increases in rates in many nations, including Muslim nations. As the number of individuals observing Ramadan rises, medical personnel will need to learn about the customs and assist people in maintaining their health throughout the fasting month. The custom of fasting from sunrise to sunset for a full month is a fundamental aspect of Ramadan. Despite being a religious practice, this has a big impact on how diabetics are managed. Individuals diagnosed with diabetes are typically thought to be at an increased risk of fasting. According to current international recommendations, people with diabetes and other comorbidities are risk-stratified into several categories, and this categorization is used to choose whether or not to fast. Although the effects of Ramadan fasting on high-risk patients have been the subject of numerous research, nothing is known regarding the safety of Ramadan fasting in these patients at this time. This post will go over the customs surrounding the month of Ramadan and provide advice on how diabetics can safely observe the fast.

Keywords: Ramadan, Fasting, Type 1 Diabetes Mellitus.

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Introduction:

It is estimated that 460 million individuals worldwide have diabetes in 2019, and by 2045, there will be 700 million people with the disease-a minimum of 51% growth. On the other side, it is anticipated that by 2045, the number of diabetic patients would have increased by at least twice in the Islamic World, where a significant section of the population fasts. As a result, it is crucial that relevant research and recommendations on Ramadan fasting and diabetes be updated often **[1].**

Patients with diabetes mellitus (DM) are more susceptible to developing a variety of potential fasting-related problems,

including dehydration, hypoglycemia, hyperglycemia, and diabetic ketoacidosis (DKA), since diabetes is a metabolic disease that affects numerous organs. But it shouldn't be disregarded that, for some DM patients, fasting can be very helpful—as long as they faithfully follow the evidence-based recommendation and the counsel of their religious doctors. **[1].**

Diabetes usually carries significant complications, including the possibility of hypo- and hyperglycemia. Many people opt to fast despite all of these risks, including those for whom fasting is forbidden by religion. For example, it has been shown that fasting during Ramadan increases the risk of severe hypoglycemia and diabetic ketoacidosis (DKA) in people with type 1 diabetes. Still, a lot of the disease's sufferers decide to fast once a year. Therefore, in order to reduce the risks and enable this group of patients with diabetes to fast in a somewhat safer way, it is essential that safe Ramadan fasting instructions for patients with various forms of diabetes be devised.**[2].**

Management of Patients with type 1 diabetes:

In order to reduce the danger of hypoglycemia during the Ramadan fast, careful blood sugar monitoring, together with the appropriate use of specific insulin kinds and regimens, can be life-saving. Recent worldwide research of T1DM patients who opted to fast revealed that most of the participants had hypoglycemic episodes of varying lengths and severity. **[3].**

In this sense, it is important to recognize the significant advantages that the newest diabetes-control technology can offer. It has been shown that, as compared to conventional insulin injection regimens, continuous subcutaneous insulin infusion (CSII) devices can significantly lower the risk of hypoglycemia in people with type 1 diabetes. Furthermore, the introduction of the low-glucose suspend (LGS) function to insulin pumps in recent years has shown to be very helpful in lowering hypoglycemia episodes and assisting type 1 diabetic patients who fast to carry out the ritual in a safer way **[4].**

If a person with type 1 diabetes decides to fast, they should ideally use a continuous glucose monitoring (CGM) device to check their blood glucose levels on a frequent basis. Credible evidence has been presented by the results of a recent study, which shows that real-time continuous glucose monitoring (CGM) significantly improves several adverse outcomes associated with diabetes, such as a lower HbA1c, less fluctuations in blood sugar, a lower risk of hypoglycemia, and a longer Time in Range (TIR)—defined as the amount of time spent in the target range of plasma glucose, which is between 70 and 180 mg/dL. It should be noted, nonetheless, that in kids and teenagers with type 1 diabetes, the efficacy of continuous glucose monitoring (CGM) relies on patient compliance and the amount of time the sensor is used during fasting hours **[5].**

In addition to enhancing glycemic control, it has been shown that using cutting-

edge diabetes control technologies during Ramadan Fasting can greatly benefit hypoglycemia and glycemic excursion prediction. Studies have demonstrated the benefits of various cutting-edge technology, including as flash glucose monitoring (FGM) systems, for T1DM patients who are fasting **[6].**

Patients with type 1 diabetes should be advised of the serious effects associated with consuming food and beverages that are customarily heavy in fat and carbohydrates during Ramadan in some Islamic countries. Furthermore, moderate and continuous water and beverage consumption throughout non-fasting hours should be encouraged rather than excessive amounts of liquid consumption before dawn **[7].**

When it comes to managing insulin therapy for patients with type 1 diabetes who observe the Ramadan fast, a number of guidelines suggest that pre-prandial bolus insulin is preferable to insulin given during or following Sahar and Iftar. They also advise that the foundation for appropriate insulin dosage adjustments should be regular self-monitoring of blood sugar (SMBG), or better yet, continuous glucose monitoring (CGM). Given that this strategy is linked to a decreased risk of hypoglycemia, especially in children and adolescents, it is recommended by multiple studies that the administration of a long-acting insulin analog in combination with a premeal dose of a rapid-acting insulin analogue be promoted **[1].**

The safety and effectiveness of first-generation basal insulin analogs (e.g., glargine) in persons with managed type 1 diabetes who are fasting have been reported in the majority of observational studies. However, a few studies have shown that this regimen may cause a notable drop in plasma glucose concentrations with a propensity for hypoglycemia, which typically happens around the conclusion of the fasting hours. Some publications have recommended lowering the basal insulin dose during Ramadan in order to lessen this risk. While some authors have suggested a reduction of up to 40%, the majority of authors have suggested a 20% reduction and early nighttime administration of the pre-Ramadan basal dose **[8].**

Ideally, basal insulin should be given earlier in the day. This is crucial to minimize the amount of active insulin that the body's tissues and organs are exposed to in the last hours of fasting. Numerous studies that have employed continuous glucose monitoring devices have validated this approach, with the majority showing that over 70% of hypoglycemia incidents occur within the final six hours of fasting **[9].**

However, opinions differ over the exact insulin dosage adjustments that must be made during Ramadan in order to achieve optimal glycemic control while minimizing the risk of hyperglycemia. In this context, **[10]** have suggested administering pre-Iftar and pre-dawn doses of rapid acting insulin, respectively, equivalent to the pre-Ramadan lunch and pre-dawn doses, respectively. The exact timing of the medications is also still up for debate. According to one study, giving a rapid-acting insulin bolus dose 20

minutes before a meal produces noticeably better postprandial glucose control than giving the insulin bolus right before or right after meals. When eating meals that are heavy in fat and protein, as is typically the case during Iftar, this time becomes even more crucial **[11].**

It has been demonstrated that using long lasting insulin analogs is better to using intermediate acting insulins, especially in children and adolescents, as the latter cause blood glucose levels to steadily drop in the final hours of fasting before the iftar meal. It is noteworthy to emphasize that insulin pumps have demonstrated remarkable efficacy in the management of individuals with type 1 diabetes who observe the Ramadan fast **[1].**

Compared to the traditional regimen of many insulin injections, adjustments to an insulin pump can significantly reduce the risks of both hyperglycemia from an excessive iftar meal and hypoglycemia from protracted midday hunger. For those with diabetes, the option to reduce or even stop the basal insulin infusion rate with insulin pumps can make fasting safer and reduce the chance of hypoglycemia episodes during the fasting period **[7].**

Effect of Ramadan Fasting on Microvascular Complications:

End-stage renal disease (ESRD) is mostly caused by diabetic kidney disease, which affects twenty to forty percent of those with diabetes. The simplest way to screen for kidney damage (albuminuria) is to evaluate the urinary albumin-to-creatinine ratio (UACR), which can be obtained from a random spot urine sample. On the other hand, there are no standards or established procedures, and there is little information available **[12].**

The effects of the Ramadan fast on renal physiology are not limited to scholarly research or the concerns of Arab countries. With the increasing number of Muslims relocating to Western countries, globalized physicians face challenges like as treating Muslim patients with chronic kidney disease (CKD) who wish to observe Ramadan by fasting. On the other hand, there are no standards or established procedures, and there is little information available **[12]**.

According to a prior study by Abushady et al. [12], fifty percent of the patients showed a significant decrease in eGFR after Ramadan fasting (96.3±21.5 vs 89.7±22.7 ml/min/1.73 m2p=0.002), and serum creatinine, blood urea nitrogen (BUN), and urine albumincreatinine ratio (ACR) all significantly increased after the Ramadan fast (p value = 0.003, 0.012, and 0.003 respectively). With a mean difference of 0.063 mg/dl, 1.125 mg/dl, and 7.197 mg/dl, respectively, in a maintained glycemic control. The dehydration-causing restriction on fluid intake during the fast, especially if it is prolonged, accounts for these findings. Excessive perspiration can make dehydration worse in hot, muggy weather and in people who exercise vigorously.

Marbut et al. [13] In a research of thirty normal, healthy male doctors aging between 26 and 30 years, blood urea levels increased non-significantly approaching the

end of Ramadan from October 26, 2003, to November 24, 2003. The maximum temperature ranged from 10 to 15ºC, with an average fast duration of roughly 12 hours.

Emami-Naini et al. [14] indicated a non-significant increase in BUN after Ramadan, underscoring the importance of adequate hydration for diabetic individuals preparing to fast.

Additionally, Kamar et al. [15] reported that after Ramadan fasting, the albumin creatinine ratio significantly increased from 98.41±160.49 to 141.49±228.62 in a study involving 74 diabetic patients (whose ages ranged from 20 to 64 years).

El-Gendy et al. [16] studied 20 individuals with type 2 diabetes who fasted for four weeks during Ramadan. They found that fasting had little effect on ACR, decreasing it by 3.9 and 5.6% in the diabetic and control groups, respectively.

Ramadan did not significantly change the GFR of CKD patients without diabetes, according to **El-Wakil et al. [17]** (baseline eGFR 33.321.1 ml/min/1.73m2). However, the study only included a small sample size (15 participants).

After fasting throughout Ramadan, diabetic retinopathy considerably improved in 74 diabetic patients, ages 20 to 64, according to Kamar et al. [15]. They fasted for an average of fourteen hours. Restricting fluid consumption during the fast, particularly if it is prolonged, could be the reason for this. Furthermore, perspiration in humid, muggy conditions and in people who exercise vigorously might exacerbate this. All of these may lessen retinal exudation even if they increase the risk of thrombosis.

Shabrawy [18] determined that the overall frequency of hospitalizations for stroke is not increased by fasting throughout Ramadan. Despite this, ischemic strokes are occurring more frequently than hemorrhagic strokes. In terms of diabetes patients (N = 90) as well as the entire study population (N = 220), he found that there was no significant difference in random blood glucose or HbA1C during Ramadan compared to other months ($P > 0.05$). This finding may suggest that fasting during Ramadan does not significantly affect glycemic control.

Patients who fast in hotter countries or for extended periods of time (more than 18 hours in temperate nations during the summer) run the danger of being dehydrated, which can be made worse by unchecked hyperglycemia that results in osmotic diuresis. Dehydration can manifest in T2 diabetic patients as hypotension, fatigue, syncope, hemoconcentration, and hypercoagulability, which increases the risk of thrombosis and strokes. While in T2 diabetes, fasting can lower platelet sensitivity to clopidogrel, this may be due to an increase in glycaemic levels during Ramadan. But according to reports, there is no difference in the incidence of acute cardiac disease among T2 diabetes patients during Ramadan compared to other times**[19].**

Abushady et al. [12] additionally said that there was a marginally significant increase in the DN4 questionnaire score (p =

0.046) in relation to the impact of Ramadan fasting on neuropathic pain as assessed by the DN4 Q. By the end of Ramadan, they also discovered a significant improvement in glycemic indices, fructosamine (p=0.02) and FBS (p<0.001), along with a significant decrease in hypoglycemia episodes.

According to research by **Fakhrzadeh et al. [20],** fasting plasma glucose significantly decreased in both men and women who observed the Ramadan fast.

Khaled et al. [21] found that obese women with type 2 diabetes mellitus experienced significant reductions in their fasting blood glucose and HbA1c levels after Ramadan fasting.

In a research by **El-Hawary et al. [22]** on T1DM kids who fasted for 29 days in Ramadan 1434/2013 and got thorough pre-Ramadan training, they found a significant decrease in post-Ramadan fructosamine levels (p 0.001).

Patients with appropriate baseline glycemic control did not exhibit substantial changes in FBG following Ramadan, according to **Lessan et al. [23].** They used continuous glucose monitoring prior to, throughout, and following Ramadan in a study including 63 participants.

In a study involving 122 people with type 2 diabetes, **Sahin et al. [24]** similarly showed that there was no change in PPBG after Ramadan fasting.

In a study examining the impact of fasting on glycemic control during Ramadan, **Bouguerra et al. [25]** discovered that patients whose pre-Ramadan fructosamine levels were higher than 340 micromol/l had higher plasma fasting glucose and serum fructosamine (p<0.003), while those whose pre-Ramadan fructosamine levels were lower than 340 micromol/l had no change in glycemic control.

Abushady et al. [12] concluded that although glycemia improved, 50% of the population investigated had a significant rise in UAC ratio and a drop in eGFR during Ramadan fasting, though still within normal range. Respecting the decision of an individual with type 1 diabetes to fast during Ramadan is crucial. As long as they are otherwise stable and healthy, there is some evidence to support the concept that they can do so without risk. However, during pre-Ramadan health education, type 1 diabetics with microalbuminuria should be counseled on appropriate hydration and dietary protein modification. They should also receive specialized instruction on controlling their blood sugar levels and be closely monitored by a doctor.

Effect of Ramadan fasting on glycemic control:

Hypoglycemia

One well-known risk factor for the onset of hypoglycemia is reduced food consumption. Hypoglycemia is thought to be responsible for 2-4% of type 1 diabetes patients' deaths. Although the exact amount of hypoglycemia's contribution to type 2 diabetes mortality is unknown, it is generally believed to be a rare cause of death for patients with this condition. Patients with type 2 diabetes have significantly lower rates of

hypoglycemia than those with type 1 diabetes, and these rates are further reduced in those with type 2 diabetes who are on oral medication.**[26, 27].**

According to multiple studies, there was very little chance of severe hypoglycemia during Ramadan. The frequency of mild hypoglycemia episodes in the 21 insulin pump-using individuals was 33 throughout the course of the entire month. There was no statistically significant difference between the hypoglycemic episodes that occurred prior to and during Ramadan, and none of them broke their fast early. Additionally, as the month came to a conclusion, the incidence dropped **[28].**

Lessan et al.'s [23] investigation, in contrast, found that the insulin group's low blood glucose index (3.4–3.9) indicated a considerably higher risk of hypoglycemia ($p < 0.05$). However, as was already indicated, there were numerous limitations to this study. Similarly, severe hypoglycemia was considerably higher in the insulin group (0.14 episodes/month in Ramadan vs. 0.03 episodes/month in other month; $P = 0.0174$) in the EPIDIAR research, which involved 1070 patients from 13 different countries. This study's strengths are its diverse range of study centers and sizable sample size. However, recall bias affected two thirds of the patients in the EPIDIAR research, and they either increased or maintained their insulin dosage throughout Ramadan, which could account for the elevated incidence of severe hypoglycemia **[29].**

The general agreement among experts is to lower the daily insulin dosage by 20–50% during Ramadan in order to lower the risk of hypoglycemia. As predicted, the majority of hypoglycemia episodes happen before iftar. Less hypoglycemia happens when using CSII compared to CI, Lispro compared to ordinary insulin, basal-bolus compared to premixed insulin, and Humalog Mix 50 compared to Human insulin Mix 30. During fasting, continuous monitoring of capillary glucose can also help prevent severe hypoglycemia. It is strongly advised against fasting for patients who are at high risk of hypoglycemia, such as those with severe comorbid conditions, extensive renal or hepatic impairment, frequent hypoglycemic episodes, or hypoglycemia unawareness**[28].**

Hyperglycemia

Iftar, the major meal of Ramadan, is often a high-calorie, high-carbohydrate meal. It is therefore anticipated that hyperglycemia will happen soon after this meal. Two studies looked at post-Iftar hyperglycemia **[23, 30].** According to a study by **Ahmedani et al. [31],** hyperglycemia is more common during the pre-sohur phase. None of the examined studies included any documentation of diabetic ketoacidotic events. In two investigations, hyperglycemia was more common than hypoglycemia.

According to Egyptian studies, Ramadan fasting does not significantly affect glycemic management, as seen by the non-significant changes in HBA1C and mean fasting blood glucose during Ramadan compared to other months ($P > 0.05$) **[19]**.

According to a research by **Lessan et al. [23],** hyperglycemia was more common in the insulin group (13.9 7.7 mmol/L) than in the non-fasting group (8.1 6.3 mmol/L; $p < 0.04$). This can be a sign of elevated hypoglycemia in the insulin group and, consequently, hypoglycemia associated with correction. In their study, **Khalil et al. [32]** examined 21 patients using insulin pumps, and they reported 801 instances of postprandial hyperglycemia in them. Nevertheless, there was no mention of the incidence of severe hyperglycemia and no active comparative control group. **Al-Khawari et al. [30]** discovered that basal-bolus and insulin Lispro were superior to regular insulin in lowering episodes of hyperglycemia. Nevertheless, the definitions of hyperglycemia used in these investigations varied.

A systematic review by **Loh et al. [4]** studied the safety of Ramadan fasting in young patients with type 1 diabetes on 1,699 patients treated with either CSII or non-CSII (including premixed and multiple daily insulin injections) regimen., they reported that The CSII-treated group (n = 203) was older (22.9 ± 6.9 vs 17.8 ± 4.0 years), and had longer diabetes duration (116.7 ± 66.5 vs 74.8 ± 59.2 months) and lower glycated hemoglobin (7.8 ± 1.1% vs 9.1 ± 2.0%) at baseline than the non-CSII-treated group (n = 1,496).

The non-CSII-treated group had less non-severe hypoglycemia than the CSII-treated group (22%, 95% CI 13–34 vs 35%, 95% CI 17–55). Of the non-CSII-treated group, 7.1% (95% CI 5.8–8.5) developed severe hypoglycemia, but none from the CSII-treated group did. The non-CSII-treated group was more likely to develop hyperglycemia (12%, 95% CI 3–25 vs 8.8%, 95% CI 0–31) and ketosis (2.5%, 95% CI 1.0–4.6 vs 1.6%, 95% CI 0.1–4.7), and discontinue fasting (55%, 95% CI 34–76 vs 31%, 95% CI 9–60) than the CSII-treated group. They concluded that the CSII regimen had lower rates of severe hypoglycemia and hyperglycemia/ketosis, but a higher rate of non-severe hyperglycemia than premixed/MDI regimens. These suggest that appropriate patient selection with regular, supervised fine-tuning of the basal insulin rate with intensive glucose monitoring might mitigate the residual hypoglycemia risk during Ramadan.

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