Review Article

Management of Type 2 diabetes in Ramadan: Low-ratio premix insulin working group practical advice

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ABSTRACT

The challenge of insulin use during Ramadan could be minimized, if people with diabetes are metabolically stable and are provided with structured education for at least 2–3 months pre-Ramadan. Although, American diabetes association (ADA) recommendations 2010 and South Asian Consensus Guideline 2012 deal with management of diabetes in Ramadan and changes in insulin dosage, no specific guidance on widely prescribed low-ratio premix insulin is currently available. Hence, the working group for insulin therapy in Ramadan, after collective analysis, evaluation, and opinion from clinical practice, have formulated a practical advice to empower physicians with pre-Ramadan preparation, dose adjustment, and treatment algorithm for self-titration of low-ratio premix insulin.

Key words: Hyperglycemia, hypoglycemia, low-ratio premix insulin, ramadan, type 2 diabetes

Introduction

Fasting in Ramadan, the ninth month of Islamic Lunar Hijri calendar, is practiced safely by the majority of Muslims with type 2 diabetes (T2DM) across the globe. However, fasting can cause profound changes in dietary habits and life style. The common practice is to consume one large meal after sunset and one lighter meal before dawn.[1] In many cases, sedentary lifestyle and change in sleep pattern during Ramadan may alter energy metabolism in people with T2DM.[2]

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed that in some people with T2DM, during Ramadan fasting, the risk of severe hypoglycemia (defined as hospitalization due to hypoglycemia) increased 7.5-fold (from 0.4 to 3 events/100 people/month). The study also revealed that excessive reduction in dosage of insulin to prevent hypoglycemia, and dietary indiscretion practised by some patients during non-fasting periods, lead to postprandial glycemic excursion/severe hyperglycemia (before Ramadan 0.01 ± 0.05 episodes, during Ramadan 0.05 ± 0.35 episodes per patient per month, $P < 0.0001$).[3] Similarly, an increase in hyperglycemic episodes was also noted in another study conducted by the Benghazi Diabetes and Endocrine Centre (BDEC) on 493 T2DM patients fasting during Ramadan where

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10.7% experienced hyperglycemia.[4] Therefore, appropriate treatment adjustments including insulin regimen are necessary to avoid both hypo- and hyperglycemia during Ramadan fasting.

In order to address the specific challenges, associated with insulin use during Ramadan, a group of leading diabetes experts (from North Africa, Europe, Middle East, South Africa, and India) formed a working group for insulin therapy in Ramadan. Low-ratio premix insulin (Premix Insulin with Rapid component equal or less than 30%) is one of the most widely prescribed insulin globally. In general, insulin use during Ramadan could pose a challenge but this may be minimized, if people with diabetes are metabolically stable and are provided with structured education for at least 2-3 months pre-Ramadan. Furthermore, there are no large studies to guide the titration and dosage adjustment of the low-ratio premix insulin during Ramadan fasting. Although, recommendations and guidelines (ADA, 2010 and South Asian Consensus Guideline, 2012) deal with the management of diabetes in Ramadan or changes in insulin dosage, specific guidance on widely prescribed low-ratio premix insulin is largely absent.[5,6]

Therefore, in October 2013, during the first meeting of the working group for insulin therapy in Ramadan, it was decided to conduct a collective analysis and evaluation of the opinions from clinical practice, on strategies to optimize low-ratio premix insulin therapy during Ramadan fasting and publish it as a practical advice document.

Objective

The objective of this working group practical advice is to empower the physicians and diabetes educators with guidance for optimising management of individuals with T2DM on low-ratio premix insulin during Ramadan period. This work does not focus on Type 1 DM or other insulin regimens. The practical advice is structured as:

- Pre-Ramadan preparation
- Dose adjustment of low-ratio premix insulin
- Treatment algorithm for self-titration on low-ratio premix insulin.

Methodology

The Working Group for Insulin therapy in Ramadan, in October 2013, discussed and developed the practical advice for use of low-ratio premix during Ramadan. This document was then reviewed and endorsed by an extended working group of over 50 experts from North Africa, Europe, Middle East, South Africa, and India.

Ramadan low-ratio premix insulin practical advice

In patients taking low-ratio premix insulin who intend fasting, the following recommendations should be considered:

Pre-Ramadan preparation for patients on low-ratio premix insulin

A pre-Ramadan preparation period of at least 2–3 months is advisable in order to ensure safe fasting. This will include:

Pre-Ramadan individualized medical assessment

The working group advises observance of the current ADA recommendations[5] with specific attention to patients' overall well-being and the importance of good glycemic control, blood pressure, and lipid management. The understanding of patients' experiences of fasting, amendments of medications, extent of success, and problems encountered during a previous Ramadan is of paramount importance. Special attention should be devoted to an individualized risk assessment of patient with T2DM on low-ratio premix insulin who wishes to fast during Ramadan.

Structured education for patients on low-ratio premix insulin

Focus should be placed on factors like frequency of glucose monitoring during fasting and non-fasting hours, meal planning, meal choices, and physical activity to avoid hypoglycemia as well as post-prandial hyperglycemia. It is prudent to impart education both to the patient and his/her family. The advice could also be extended to those who do not wish to fast.

All means of communication of the relevant information could be used, including the media, the internet and written information as well as individual and group counselling by diabetes educators and physicians.

The structured education will include the advice on the importance of home blood glucose monitoring, when to break the fast, meal, and exercise planning.[5,7]

- Blood Glucose Monitoring (BGM): It is essential for patients to have the ability to monitor their blood glucose levels multiple times daily. It must be emphasized to patients that testing via BGM does not break the fast. BGM during Ramadan is advised for detection and prevention of hypo- and hyperglycemia. Indeed, insulin dose titration and dosage adjustment should be based on pre-meal blood glucose levels. The frequency of BGM for people on low-ratio premix insulin is dependent on the risk of hypoglycemia and their level of glycemic control:
    i. High risk group: This includes people with higher risk of hypoglycemia and/or poor glycemic control.

Whilst these patients should be advised against fasting during Ramadan, BGM should be done at the following times should they insist on fasting:
1. Pre-Suhur
2. 2 hours post-Suhur
3. Midday
4. Pre-Iftar
5. 2 hours post-Iftar
6. Whenever symptoms of hypoglycemia occur

A midnight blood glucose measurement could also be considered for many people with T2DM which may help in optimising premix insulin dose.

ii. Low risk group: It is advisable to do BGM at the following times during a day
1. Pre-Suhur
2. Midday
3. Pre-Iftar
4. Whenever symptoms of hypoglycemia occur

- Diet: The diet during Ramadan should be a healthy balanced diet. Food high in carbohydrates and saturated fat should be avoided or reduced in quantity. It is advisable to increase fluid intake during non-fasting hours. The fluid choice should be water or low-calorie drinks.
- Exercise: Regular light and moderate exercise is advisable. Rigorous exercise is not recommended during fasting hours due to potential risk of hypoglycemia. Prayers should be considered as part of the daily exercise regimen because they involve standing, bowing, prostrating, and sitting.
- Breaking the fast: The standard advice as per the ADA–Ramadan recommendations should be followed.[5] Studies have shown that many people continue to fast even after they experience a hypoglycemic episode. Patients should be educated on breaking the fast if they experience any hypoglycemic episode.[8] In case of hyperglycemia (BG > 300 mg/dl or 16.6 mmol/l), patients should break the fast if they are symptomatic or if the ketosis is present or if the hyperglycemia is due to reasons other than a heavy meal. Otherwise, patients should be advised to repeat BG testing after 1 to 2 hrs and break the fast if hyperglycemia persists or worsens.

Trial fast in pre-Ramadan period

A trial fast for 3 consecutive days before Ramadan should be advised. A trial fast mimicking Ramadan can be helpful in detecting hypoglycemia risk and creates the possibility for guiding the self-titration of premix insulin dosage, using a titration algorithm. It may also help to identify fasting or postprandial hyperglycemia. Though it may give an insight into the patient's response to premix insulin during Ramadan, findings should be carefully extrapolated to the Ramadan fasting, because of the difference in duration of fast. Many people fast on the 13th, 14th, and 15th day of Shaabaan. Therefore, these fasts could be used as a trial prior to the Ramadan fast.

Dose adjustment of low-ratio premix insulin during Ramadan

The management plan during Ramadan should be individualized. First the glycemic control of the patient needs to be ascertained. The dosage of premix insulin during Ramadan will depend on the meal size as well as composition, post meal fasting period and according to individual blood glucose targets. Although, the majority of patients are on conventional twice daily premix insulin regimen, few patients on premix insulin analogues may be using once daily dosing usually before supper.[9]

Studies have looked into the preference between analogue and human premix insulin during the fasting month. Soewondo *et al*. (2009), in 152 patients showed that analogue mix 30 significantly reduced all glycemic indices, i.e. fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2-hr PPG), and glycosylated hemoglobin (HbA1c). There were no significant changes in body weight and body mass index (BMI), with significant reduction in hypoglycemic episodes in patients after three months of treatment.[10] Similarly, another study which compared human insulin 30/70 with analogue Mix 25 during Ramadan, found that premix analogue resulted in better average daily glycemia and blood glucose control.[11] This favorable outcome in Ramadan fasting could be related to the pharmacodynamics of low-ratio premix analogues compared to human insulin, as well as to the meal time flexibility where unlike for human insulin a person, after a long fasting day can eat immediately after analogue insulin injection. Also, analogue insulins are less likely to cause post-pradial hypoglycemia.

The following points are considered as general practical advice:

A. If the patient is on once daily premix insulin in combination with oral glucose lowering drugs (OGLDs) in the pre-Ramadan period, then same dosage should be given at the sunset meal (Iftar) and can be titrated further as per the algorithm listed below [Table 1]. The dose of OGLDs should be optimized as per the standard recommendations of ADA.[5]

B. If the patient on once daily premix insulin is uncontrolled, then dosage should be uptitrated as per the algorithm given below [Table 1]. If after titration, the pre-meal/fasting blood glucose is not controlled, advise the patient to break the fast and start premix insulin twice daily.

C. If, during the pre-Ramadan period, the patient is on twice daily premix insulin then prescribe the usual morning dose at the sunset meal (Iftar) and half the usual evening dose at pre-dawn (suhur), e.g. if 30/70 premix insulin is prescribed 30 units in the morning and 20 units in the evening before Ramadan, then the recommended dose during Ramadan will be 30 units pre-Iftar and 10 units at pre-Suhur.

D. If the patient on twice daily premix insulin is uncontrolled and has before dinner blood glucose >300 mg/dl (16.6 mmol/L) in the pre-Ramadan period, then prescribe the usual morning dose at the sunset meal (Iftar) and the usual evening dose at pre-dawn (suhur), e.g. if 30/70 premix insulin is prescribed 30 units in the morning and 20 units in the evening before Ramadan, then the recommended dose during Ramadan will be 30 units pre-Iftar and 20 units at pre-Suhur.

E. If the patient is on thrice daily insulin, omit the afternoon dose and titrate the pre-Iftar and pre-Suhur dose as described above for twice daily premix regimen.

F. Dosage adjustments should be done based on home BGM data.

G. The preference of premix insulin analogue instead of human insulin can be considered when
   - immediate injection before a meal is preferred or
   - frequent hypoglycemia is a concern or
   - there are marked postprandial blood glucose excursions.

H. While switching from human premix to analogue premix insulin, the dose of analogue insulin at pre-Iftar should be 20 to 30% lower than the morning human insulin dose pre-Ramadan. Pre-Suhur dose should be 40% lower than the evening dose pre-Ramadan. Further dose adjustment to be decided as per the BGM data.

Treatment algorithm for self-titration on low-ratio premix insulin

- It is advisable to titrate insulin dose every 3 days.
- The lowest of the three readings on three consecutive days should be considered to up titrate the insulin dose. The timing of BGM is described in the algorithm [Table 1].
- Hypoglycemia is defined as blood sugar below 70 gm/dl (3.9 mmol/L) or symptoms of hypoglycemia.
- If hypoglycemia is noted on two (any time of the day) out of three consecutive days, fasting must be stopped and insulin dose should be reduced as described in the algorithm [Table 1]. Fasting should be stopped even if the hypoglycemia occurs close to the time of Iftar [Figure 1].
- If blood glucose is >300 mg/dl or 16.6 mmol/L, ketones in blood or urine should be checked and the patient should break the fast [Figure 1].
- Patients should avoid fasting on sick days.

Conclusion

This document provides practical guidance for usage of low-ratio premix insulin during Ramadan (summarized in Figure 2). Patients on low-ratio premix insulin who insist on fasting should be assessed before Ramadan and educated about physical activity, meal planning, blood glucose monitoring, dosage and timing of medications. This document provides a simple titration algorithm which will help patients to perform home BGM and self-titration. Moreover, continued efforts are needed towards formulation of evidence based guideline for the use of low-ratio premix insulin during Ramadan. While this document is based on the use of low-ratio premix insulin, higher ratios (e.g. premix 50/50) may be preferable during fasting, since the higher quick-acting component will cover the Suhur meal and the lower intermediate-acting component (compared to the 70% or 75% low-ratio premix) will minimize the risk of afternoon hypoglycemia.[12]

Appendix A: Working group members

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Table 1: Algorithm for self-titration of premix insulin during ramadan

Fasting/pre-iftar/pre-suhur BG	Premix insulin units*
<70 mg/dl (3.9 mmol/L) or symptoms	Break the fast and down titrate
<90 mg/dl (5.0 mmol/L)	−2 IU
90-126 mg/dl (5.0-7.0 mmol/L)	No change
>126 mg/dl (7.0 mmol/L)	+2 IU
>300 mg/dl (16.6 mmol/L)	Break the fast and increase dose by 4 units and check for ketones

*Pre-iftar dose to be adjusted based on pre-suhur BG and pre-suhur dose to be adjusted based on pre-Iftar BG levels

- History of previous years fasting and behaviour in Ramadan can help in reducing the hypoglycemic events
- Focussed education to patient and at least one family member during pre-Ramadan period
- Assessment of hypoglycemia pattern during previous Ramadan
- Knowledge of emergency management of hypoglycemic episode
- Avoid exercise at the peak of insulin dose
- Excessive physical activity should be avoided, particularly few hours before the sunset meal
- Monitor blood glucose 4-5 times a day

Figure 1: Avoiding hypoglycemic episodes while on Premix insulin during Ramadan

Pre-Ramadan Assessment

- Arrange for pre-Ramadan visit 2-3 months before Ramadan
- History of previous years fasting and behaviour in Ramadan can help
- Risk stratification for the individual including current diabetes control, other diabetes related complications, general health and social circumstances
- Ramadan-focussed education to patient and family members
  - o Blood glucose monitoring techniques and frequency
  - o When to stop the fast

BGM	
High Risk Group	**Low Risk Group**
Pre-Suhur	Pre-Suhur
2hrs post-Suhur	Midday
Midday	Pre-Iftar
Pre-Iftar	If symptoms of hypoglycaemia appear
2hrs post-Iftar	
If symptoms of hypoglycaemia appear	

Fasting/Pre-Iftar/ Pre-Suhur BG	Premix Insulin Units*
< 70 mg/dl (3.9 mmol/L) or Symptoms	Break the fast and down titrate
< 90 mg/dl (5.0 mmol/L)	-2 IU
90-126 mg/dl (5.0-7.0 mmol/L)	No change
>126 mg/dl (7.0 mmol/L)	+2 IU
>300 mg/dl (16.7 mmol/L)	Break the fast and increase dose by 4 units and check for ketones

*Pre-Iftar dose to be adjusted based on pre-Suhur BG and pre-Suhur dose to be adjusted based on pre-Iftar BG levels

Remember

- It is advisable to do insulin dose titration every three days
- A minimum of two readings on two consecutive days is required to titrate the insulin dose
- Hypoglycaemia is defined as blood sugar below 70 mg/dl (3.9 mmol/L) or symptoms of hypoglycaemia. Fasting must be broken if hypoglycaemia occurs
- If hypoglycaemia is noted on two days (any time of the day) out of three, insulin dose should be itrated down
- If blood glucose is high on two occasions in two consecutive days, titrate the insulin dose as per the lowest value
- If blood glucose is >300 mg/dl or 16.66 mmol/L, ketones in blood or urine should be checked and the fast should be broken for that day

Premix Insulin Dose and Frequency Adjustment during Ramadan

Type of Treatment	Pre-Iftar (Sunset Meal)	Pre-Suhur (Dawn Meal)	Comments
OGLD (Oral glucose lowering drugs)	-	-	Adjust as per ADA Recommendations
Once daily premix Insulin	Give same dose as pre-Ramadan	nil	• Titrate dose as per algorithm • If poor control, break the fast & consider adding a dose at Suhur
Twice daily premix Insulin	Give the usual morning dose	Give half the usual evening dose	-
Thrice daily premix Insulin	Give the usual morning dose	Give half the usual evening dose	Omit mid day dose

When to change from Human to Analogue low-ratio premix insulin?

- If immediate injection before the meal is preferred
- If frequent hypoglycaemia or marked postprandial blood glucose excursions

Remember

- Pre-Iftar dose should be 20 to 30% lower than the morning human insulin dose pre-Ramadan
- Pre-Suhur dose should be 60% of the pre-Ramadan evening dose
- Further dose adjustments will be decided according to BGM

Figure 2: Low-ratio premix insulin during Ramadan–practical advice summary

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