Risk stratification of persons on premixed insulin in Ramadan

Sanjay Kalra,[1] Fatema Jawad,[2] Zafar Ahmed Latif,[3] Md Faruque Pathan[4]

Abstract

The International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance, has recently published practical guidelines on the management of diabetes and Ramadan .The risk stratification categorizes all persons wishing to fast into three groups, based upon potential risk. In spite of evidence to the contrary, all persons using premixed insulin are categorized as having high risk. In this article, we present data from randomized controlled trials, and discuss the placement of premixed insulin in the risk stratification framework.

Keywords: Insulin biphasic aspart (BIAsp), Biphasic lispro (LisproMix), Insulin degludec aspart (IDegAsp), Insulin detemir.

Introduction

The International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance, has recently published practical guidelines on the management of diabetes and Ramadan.[1] This exhaustive publication explains the physiology of fasting, suggests a framework for risk stratification, describes the process of pre-Ramadan evaluation, and guides the reader in the modification of therapy during Ramadan.

The IDF-DAR Practical guidelines propose a triage of persons wishing to fast. The triage is based upon scientific, clinical and practical considerations, and enjoys religious sanction from the Mofty of Egypt. The guidelines, however, clearly state that regional discussions are needed to develop medico-religious opinion on this aspect.[1] In this article, we discuss the placement of premixed insulin in the risk stratification framework.

Risk Stratification

Category 1 (very high risk) includes persons with poorly controlled type 1 diabetes, persons with advanced macro-vascular disease, advanced renal disease (chronic kidney disease stage 4 and 5), acute illness, history of acute metabolic decompensation, women with pregnancy/gestational diabetes mellitus (GDM). The only mention made of glucose-lowering therapy is with regards to GDM, where women on insulin or sulfonylurea therapy are listed in very high risk category. This goes against religious teachings which exempt all pregnant women from fasting.[2]

Category 2 (high risk) and category 3 (moderate/low risk) are defined by clinical and therapeutic considerations. High risk category includes persons with well controlled type 1 diabetes, well controlled type 2 diabetes on "multiple dose insulin or mixed insulin", and type 2 diabetes with sustained poor glycaemic control. It also includes persons performing intense physical labour, those with additional comorbid factors, stable macrovascular complications, and CKD stage 3. Pregnant women controlled with diet and /or metformin are included in this category.

Category 3 lists well controlled type 2 diabetes treated with lifestyle therapy, metformin, acarbose, thiazolidinediones, second generation sulfonylureas, incretin based therapy, SGLT2 inhibitors and basal insulin.

IDF-DAR Guidelines on Insulin Use

The guidelines published by IDF-DAR contain pragmatic advice for the modification of insulin doses and regimes during Ramadan. They include suggestions regarding dose titration of premixed insulin, and suggest glucose monitoring every 3 days, using a simple 4-2-0-2-4 unit algorithm.

This advice is based upon a comprehensive review of literature, including 7 references related to insulin. Of these, 4 have studied various premixed regimes. The data obtained from these studies clearly demonstrates the safety of premixed insulin during Ramadan, when used with simple dose modification and titration.

Premixed Insulin Analogues in Ramadan

Mulitple randomized controlled trials have assessed the safety and efficacy of premixed insulins during Ramadan (Table).

[1]Department of Endocrinology, Bharti Hospital, Karnal, India, [2]Department of Diabetology, SIUT, Karachi, Pakistan, [3]BIRDEM, Dhaka, Bangladesh, [4]Department of Endocrinology, BIRDEM, Dhaka, Bangladesh.
Correspondence: Sanjay Kalra. Email: brideknl@gmail.com

Table: Mulitple randomized controlled trials have assessed the safety and efficacy of premixed insulins during Ramadan.

Trial (Reference)	Objectives	Number of patients enrolled/Trial arms	Results		Weight
			Efficacy	Safety	
Multicentre, open-label prospective study in patients with T2DM switched or continued with BIAsp at least 1 month before Ramadan (Soewondo et al, 2009)[3]	To evaluate the safety and efficacy of BIAsp in type 2 diabetic patients before, during, and after Ramadan fasting in normal clinical practice.	n=152 / No Comparator Additional medications - OHAs (not all patients)	All glycaemic indices significantly reduced	Reduced hypoglycaemia compared to baseline but not significant	No significant changes in weight or BMI
A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan (Mattoo et al, 2003)[4]	To compare insulin lispro Mix25 and human insulin 30/70 with regard to their effect on morning and evening postprandial glucose (PPG) control, and on average daily blood-glucose (BG), in patients with Type 2 diabetes who wish to fast during Ramadan	Treatment sequences: Group-1 :Insulin lispro Mix25 for first 2 weeks of Ramadan and then human insulin 30/70 for the next 2 weeks (n=79) Group-2: Human insulin 30/70 for first 2 weeks of Ramadan and then Insulin lispro Mix25for the next 2 weeks (n=72) Both given BID with morning and evening meals Additional medications - NR	Daily glycaemia (measured as the average of the four BG values, mmol/L): Overall: lower with insulin lispro Mix25 than human insulin 30/70, 9.5 vs 10.1 (p=0.004) Pre-evening meal: lower with insulin lispro Mix25 than human insulin 30/70, 7.1 vs 7.5 (p=0.034) 2 hrs post-evening meal: lower with insulin lispro Mix25 than human insulin 30/70, 10.5 vs 11.6 (p=0.0001)	Mean number of hypoglycaemic episodes per patient per 14 days: Similar in the two groups (0.49 ±0.9 for insulin lispro Mix25 and 0.49 ±0.8 for human insulin 30/70; P=0.725)	No significant change in body weight in any patient
An open label, controlled, multicentre, cluster randomised study in patients with T2DM on premix preparations or basal and rapid-acting insulin ± metformin and/or SU (Shehadeh et al, 2015)[5]	To assess the effect of insulin detemir and biphasic insulin aspart 30 compared to standard care	Insulin detemir with suhoor + BIAsp 30 with iftar(n=127) Standard care (n=128) (Premixed or intermediate-acting insulin twice daily. When possible, patients were changed to long-acting or intermediate insulin in the evening and short- or rapid-acting insulin with meal) Additional medications - Metformin/SU (not all patients)	Treatment intervention with insulin detemir and BIAsp 30 was non-inferior to standard care	Hypoglycaemia was significantly more common in the control group [6 (4.8%) vs. 24(21.4%), p ? 0.001]	
Comparison of Lispro Mix 50 with biphasic human insulin 30 in type 2 diabetes patients during Ramadan (Hui et al, 2009)[6]	To compare hypoglycaemic events, glycated haemoglobin (HbA1c) and changes in body weight in Muslim patients with Type 2 diabetes after receiving Lispro Mix 50 and biphasic human insulin 30 twice daily during Ramadan fasting	Group-1: Biphasic human insulin 30 at Suhoor and Lispro Mix50 at Iftar (n=26) Group-2: Biphasic human insulin 30 BID (n=26) Additional medications - NR	HbA1c change: Group-1 reduction of 0.48% (p = 0.0001), Group-2 increase of 0.28% (p = 0.007). [LSM difference 0.40%, p = 0.0004, 95% confidence limits (0.19%, 0.62%)]	Mean number of hypoglycaemic events during Ramadan compared with before Ramadan: Group-1: a small reduction of 0.04 (p = 0.81) Group-2: an increase of 0.15 (p = 0.43), Differences between the groups were not statistically significant	No significant difference in weight changes between groups
Efficacy and Safety analysis of IDegAsp compared with BIAsp 30: A Phase 3, Multicentre, International, Open-label, Randomized, Treat-to-target Trial in Patients with Type 2 Diabetes Fasting during Ramadan (M Hassanein et al, 2017)[7]	To compare the efficacy and safety of two insulin analogues (IDegAsp versus BIAsp 30)	IDegAsp (n=131) BIAsp (n=132) Both given BID with morning and evening meals Additional medications — ±OAD, SU/glinides discontinued	IDegAsp was non-inferior to BIAsp 30 in HbA1c reduction from baseline to end of Ramadan	Overall and nocturnal hypoglycemia Complete study : 74% and 83% lower with IDegAsp vs. BIAsp 30 During Ramadan: 62% and 74% lower with IDegAsp vs. BIAsp 30	

OHA: Oral hypoglycaemia agents; NR: Not reported; BMI: Body mass index; LSM: Least squares (adjusted) means; BID: Twice daily; IDegAsp: Insulin degludec/insulin aspart; BIAsp 30: Biphasic insulin aspart 30/70; SU: Suphonylureas.

Premixed Insulin Twice Daily

Soewondo et al[3] performed a multicenter, prospective study to evaluate the efficacy and safety of using biphasic insulin aspart 30 (BIAsp 30) during Ramadan as monotherapy, or in combination with an oral hypoglycaemic agent, in persons with type 2 diabetes. A total of 152 participants, either naïve to, or already using BIAsp 30 were enrolled, with an average age of 54 years and mean diabetes duration of 9.4 years. Treatment with BIAsp 30 significantly reduced fasting and postprandial glucose as compared to baseline levels. Significant reduction of HbA1c was also found between baseline and end-of study levels. Daytime and nocturnal hypoglycaemic events were reduced non-significantly, and there were no significant changes in body weight/ body mass index before and after treatment with BIAsp 30.

Mattoo et al carried out an open label, multicenter, randomized, cross-over study comparing insulin lispro Mix25 [25% short-acting lispro/75% intermediate-acting lispro protamine] and human insulin 30/70 [30% short-acting soluble human insulin/70% intermediate acting NPH]) , in participants with type 2 diabetes, who chose to fast during Ramadan. The authors[4] found that insulin lispro Mix25 achieved better average daily glycaemia, and better glucose control before and after the evening meal compared to human insulin 30/70. Rate of hypoglycaemia were found to be similar in both the groups.

Basal Insulin + Premixed Insulin, Each Once Daily

Shehadeh et al,[5] through an open label, prospective, controlled multicenter cluster non-inferiority randomized study, assessed the use of insulin detemir and BIAsp 30 during Ramadan. Insulin dose in the intervention group was 60% of the usual daily dose, of which 40% was dosed as insulin detemir at sunrise and 60% as BIAsp 30 before dinner. Standard care was provided in the other group wherein when possible, patients were changed to long-acting or intermediate insulin in the evening and short- or rapid-acting insulin with meals. The intervention was non-inferior to standard care as assessed by mean 4 point-SMBG during days 23-30 of treatment. Hypoglycaemia event rate was lower in the intervention group.

Reverse Heteromix Regime [50:50 At Iftar, 25:75 At Suhur]

Hui et al[6] studied the effects of insulin lispro Mix50 [50% short-acting lispro/50% intermediate-acting lispro protamine] and human insulin 30/70 on glycaemic control during Ramadan. Patients on twice daily human insulin 30/70 before Ramadan were included. In Group-1, the evening dose of human insulin 30/70 was changed to insulin lispro Mix50 2-weeks prior to Ramadan and the same was continued during Ramadan. Patients in Group-2, however, continued with twice daily dose of human insulin 30/70. Patients in Group-1 had a mean HbA1c reduction of 0.48% (p= 0.0001) before and after Ramadan, whereas those in Group-2 had a mean HbA1c increase of 0.28% (p= 0.007). Also, Group-1 was associated with a small, though non-significant, reduction of 0.04 in the mean number of hypoglycaemic events during Ramadan compared with before Ramadan, whereas Group-2 was associated with an insignificant increase of 0.15.

Co-Formulation Insulin Degludec/Aspart

Hassanein et al[7] have used IDegAsp, a new co-formulation of insulin degludec and insulin aspart, which is associated with reduced risk of hypoglycaemia compared with BIAsp 30 due to the flat pharmacokinetic profile and long duration of action of insulin degludec. Patients with type 2 diabetes, who intended to fast and were on basal, pre-mixed or self-mixed insulin ± oral antidiabetic drugs for ≥90 days, were randomized (1:1) to IDegAsp or BIAsp 30, both given twice daily. Treatment duration was up to 28 weeks (treatment initiation, 8-20 weeks pre-Ramadan; 4 weeks during Ramadan; and 4 weeks post - Ramadan,. At the start of Ramadan, a 30-50% reduction of one of the two doses of both insulins was recommended. In total, 263 patients were randomized to IDegAsp (n=131) or BIAsp 30 (n=132). IDegAsp was non-inferior to BIAsp 30 in HbA1c reduction from baseline to end of Ramadan. During the 28-week treatment period, rates of overall and nocturnal hypoglycaemia, respectively, were 74% and 83% lower with IDegAsp vs. BIAsp 30. During the month of Ramadan, rates of overall, nocturnal and overall daytime hypoglycaemia, respectively, were 62%, 74% and 56% lower with IDegAsp versus BIAsp 30. In a high-risk population of patients with T2D fasting during Ramadan similar efficacy of IDegAsp and BIAsp 30 in controlling blood glucose during and after Ramadan was seen, however, IDegAsp was associated with lower rates of overall and nocturnal hypoglycaemia vs. BIAsp 30.

South Asian Guidelines

South Asian guidelines on the use of premixed insulin in Ramadan (2012)[8] were updated in 2016[9] to include the use of IDegAsp during this month. A single centre experience on the use of IDeg and IDegAsp during Ramadan has been published.[10] Anecdotal experience from Bangladesh and India, two countries with a large Ramadan-observing population, suggests that IDegAsp is effective and well tolerated by persons with type 2 diabetes during Ramadan. In fact, its pharmacokinetic properties make it the most suitable, out of all dual action

formulations, for use in persons with type 1 diabetes who wish to fast during Ramadan.

Summary

We reiterate that the decision to fast during Ramadan must be based on multiple psychosocial, religious[11] and biomedical factors, rather than just on the type of therapy received. Irrespective of treatment regimens being followed, Ramadan fasting should be undertaken under medical supervision, following precautions as underlined in the IDF-DAR guidelines. Based upon published evidence, persons well controlled on modern premixed insulin analogues should be stratified as having moderate/low risk. This will help reduce unfounded concerns in minds of both physicians and persons with diabetes. We concur with the authors of IDF-DAR guidelines that more research, and more discussion, is needed to ensure optimal care of people with diabetes who wish to fast during Ramadan.

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