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. 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. 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 macrovascular 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.

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

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

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Objectives</th>
<th>Number of patients enrolled/Trial arms</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicentre, open-label prospective study in patients with T2DM switched or continued with BIAsp at least 1 month before Ramadan (Soewondo et al, 2009)</td>
<td>To evaluate the safety and efficacy of BIAsp in type 2 diabetic patients before, during, and after Ramadan fasting in normal clinical practice.</td>
<td>n=152 / No Comparator</td>
<td>All glycaemic indices significantly reduced</td>
<td>Reduced hypoglycaemia compared to baseline but not significant</td>
<td>No significant changes in weight or BMI</td>
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<tr>
<td>A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan (Mattoo et al, 2003)</td>
<td>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</td>
<td>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 Mix25 for the next 2 weeks (n=72) Both given BIAs with morning and evening meals</td>
<td>Additional medications - OHAs (not all patients)</td>
<td>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)</td>
<td>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)</td>
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<tr>
<td>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)</td>
<td>To assess the effect of insulin detemir and biphasic insulin aspart 30 compared to standard care</td>
<td>Insulin detemir with suhoor + BIAsp 30 with iftar (n=127)</td>
<td>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)</td>
<td>Additional medications - Metformin/SU (not all patients)</td>
<td>Treatment intervention with insulin detemir and BIAsp 30 was non-inferior to standard care</td>
</tr>
<tr>
<td>Comparison of Lispro Mix 50 with biphasic human insulin 30 in type 2 diabetes patients during Ramadan (Hui et al, 2009)</td>
<td>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</td>
<td>Group-1: Biphasic human insulin 30 at Suhoor and Lispro Mix50 at Iftar (n=26) Group-2: Biphasic human insulin 30 at Suhoor (n=26)</td>
<td>Additional medications - NR</td>
<td>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%)]</td>
<td>Mean number of hypoglycaemic events during Ramadan compared with before Ramadan: Group-1: a small reduction of 0.04 (p = 0.87) Group-2: an increase of 0.15 (p = 0.43), Differences between the groups were not statistically significant Overall and nocturnal hypoglycaemia Complete study: 74% and 83% lower with IDegAsp vs. BIAsp 30 During Ramadan: 62% and 74% lower with IDegAsp vs. BIAsp 30</td>
</tr>
<tr>
<td>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)</td>
<td>To compare the efficacy and safety of two insulin analogues (IDegAsp versus BIAsp 30)</td>
<td>IDegAsp (n=131) BIAsp (n=132)</td>
<td>Both given BIAs with morning and evening meals</td>
<td>IDegAsp was non-inferior to BIAsp 30 in HbA1c reduction from baseline to end of Ramadan</td>
<td>No significant differences in body mass index, BMI, or BMI percentile between groups.</td>
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</table>
Premixed Insulin Twice Daily
Soewondo et al. 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 naive 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 lab, 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 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. 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. 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. 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, premixed or self-mixed insulin ± oral anti-diabetic 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) were updated in 2016 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. 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 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.

References