DIABETES MELLITUS AND FASTING DURING RAMADAN

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ABSTRACT

Objective:
To review how commonly do diabetic Muslims fast, how safe is it to fast, who should not fast, and what is the optimal therapeutic regimen during Ramadan.

Methods:
Articles were identified from a Medline search on 19 Nov 2010 using MESH terms "diabetes mellitus", "Islam" and "fasting" for articles from 1979 to date. Hand search of references of review articles was also done. Randomized controlled and observational trials were shortlisted and critically appraised.

Results:
15 articles were shortlisted for review. Fasting is common among Muslim type 2 diabetics and to a lesser extent for type 1 diabetics. Fasting is generally safe for type 2 diabetics without complications. Hardly any evidence exists on the safety of fasting for high risk patients. There is some evidence that switching from soluble insulin to insulin Lispro may be beneficial. There is also some evidence that pioglitazone may improve glycaemia in poorly controlled diabetics without increasing the risk of hypoglycaemia.

Conclusion:
Fasting may be done safely for selected diabetic patients in Ramadan. Treatment should be individualized.

Keywords: diabetes mellitus, fasting, Ramadan

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INTRODUCTION

Singapore is a multicultural and multi-religious society with a significant proportion of Muslims. According to the National Census 2000, there are 371,660 Muslims in Singapore, who make up almost 15% of the population. Virtually all Malays and slightly over a quarter of all Indians practice Islam. In the National Health Survey 2004, the prevalence of diabetes mellitus was 15.3% of Indians and 11.0% of Malays. The control of diabetes in Muslim patients is particularly challenging when it comes to the fasting month of Ramadan. Until recently, little was known about the glycaemic control for fasting, diabetic Muslim patients during the month of Ramadan, whether fasting is safe for this population and what it the optimal therapeutic regimen during Ramadan. A number of reviews have been published in recent years ..... perhaps highlighting the need to consolidate evidence in an area which has not had high priority in the field of diabetes research.

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Background to fasting in Ramadan

Sawm or fasting in the month of Ramadan is one of the five pillars of Islam. It is an obligation for every adult Muslim man and woman to fast. In Islam, fasting goes beyond the mere physical act of abstinence from food but also carries great moral and spiritual significance. There are exemptions for those who are not in a condition to fast, especially when fasting may lead to harmful consequences. These include ill persons, the old and weak, pregnant and nursing mothers. Children, who have not reached the age of puberty, are not required to fast but are not forbidden to do so.

Fasting involves abstaining from any food, drink, smoking and oral medications from dawn to sunset. Insulin injections, blood taking, using inhalers for asthma and vaccinations do not invalidate the fast. Muslims who fast generally have two meals a day during this month. One at sunset called Iftar (in Arabic) and one at predawn called Suhur. Majlis Ugama Islam Singapura or MUIS, the only Islamic governing body in Singapore, gives guidance on fasting which is available from their website at www.muis.gov.sg.

OBJECTIVE

To review and critically appraise the available evidence with regards to the following:

a. How commonly do Muslim diabetics fast in Ramadan?
b. Is it safe for diabetics to fast during Ramadan?
c. Which patients should be advised not to fast?
d. For those who fast, what is the optimal therapeutic regimen?

METHODS

A Medline search was conducted on 19 Nov 2010 using MESH terms "diabetes mellitus", "Islam" and "fasting" for articles from 1979 to date. This yielded 76 articles. Titles and abstracts were reviewed for relevance and full articles were obtained. Randomized trials and observational studies were included. Brief reports, case reports and case series were excluded. Studies solely on biochemical markers without clinical outcomes and articles not in the English language were also excluded. As only one database was used, a hand search of relevant studies referenced in other reviews was also conducted. Full texts of shortlisted articles were obtained except for one, for which only

the abstract was available (described in table 3). Evidence was evaluated using the checklists and grading levels in the Scottish Intercollegiate Guidelines Network 50: A guidelines developer's handbook (revised edition January 2008). See Annex A.

RESULTS

15 articles were shortlisted for this review.

How commonly do Muslim diabetics fast in Ramadan?

No substantial data was available until the large epidemiological study by the EPIDIAR (Epidemiology of Diabetes and Ramadan) group. This was a cluster sampled, interviewer conducted, questionnaire on 12,243 Muslim diabetic patients in 13 countries for the month of Ramadan in 2001. In this study, 42.8% of type I and 78.7% of type II diabetics fasted for at least 15 days during the month of Ramadan. There were marked differences between countries in the proportion who fasted, ranging from 9.4% to 71.6% for type I diabetics and 57.8% to 89.8% for type II diabetics. The average number of fasting days was 23 days and 27 days for type I and type II diabetics respectively.

A more recent questionnaire survey conducted in Pakistan found that 327 of 453 diabetic subjects (72.2%) fasted during the month of Ramadan. Sex distribution was fairly equal and the mean age was 50.3 years. The vast majority of those who fasted were type II diabetics (96.3%) and subjects fasted for an average of 25 days.

No local data is available but it would be reasonable to assume that fasting is common among Muslim type 2 diabetics and perhaps less so for type 1.

Is it safe for diabetics to fast during Ramadan?

The biggest concern for diabetics who fast during Ramadan is the risk of hypoglycaemia. On the other hand, the excessive consumption of sweet and fried foods, prepared traditionally for Ramadan, especially with the Iftar meal may instead predispose to hyperglycaemia.

The EPIDIAR study defined severe hypoglycaemia as hypoglycaemia leading to hospitalization. Rates of severe hypoglycaemic episodes was significantly higher during Ramadan compared to the other months of the year, 0.14 vs 0.03 episodes/month/patient for type 1 and 0.03 vs 0.004 episodes/month/patient for type 2 respectively. A significant percentage of patients changed their drug regimens themselves with detrimental effects. One in four of those on oral antidiabetic drugs and one in three of those on insulin changed doses during Ramadan. Severe hypoglycaemic episodes were associated with change in oral antidiabetic drug dose, change in insulin dose and change in level of physical activity. Severe hyperglycaemia but not hypoglycaemia, was associated with changes in food or sugar intake.[8] (Level 3)

The study from Pakistan found a prevalence of 21.7% for hypoglycaemia and 19.8% for hyperglycaemia during Ramadan. The prevalence of severe hypoglycaemia and severe hyperglycaemia were 4% and 8% respectively. In contrast to the EPIDIAR study, this study did not find any relationship between hypoglycaemia or hyperglycaemia and changes in medication timing, diet and physical activity.[9] (Level 3)

The data from the above two studies have some drawbacks. The EPIDIAR study used historical controls to determine if complication rates were higher during Ramadan. The results of this retrospective survey are also dependent on patient recall which is not necessarily reliable. The reporting of glycaemic symptoms in both studies was subjective but the Pakistan study did have some blood glucose levels on record, with a mean of 73mg/dL (4.1mmol/L) for hypoglycaemia and 277mg/dL (15.4mmol/L) for hyperglycaemia.

One recent study found an increased number of hypoglycaemic events during Ramadan as compared to non-fasting periods, but the incidence of severe hypoglycaemia was low[20].

The EPIDIAR group also collected data on diabetes management. Only 68% and 62% of type I and type II diabetics respectively who fasted, received recommendations from health care providers.[8]

It would seem that patient education prior to the start of Ramadan might have a place in improving patient safety. This hypothesis was tested in a recent retrospective cohort study on type II diabetics. In this study, 57 patients attended a 2-hour education programme while 54 patients in the control group were invited but did not attend. There was a significant decrease in hypoglycaemic events in the education group compared to the control group which had a four-fold increase in hypoglycaemic events ($p<0.001$). The absolute risk reduction in hypoglycaemic events by patient education was calculated at 58.2%. However, it was not clear from the study whether this effect was due to education or due to reductions in sulphonylurea dose. There may have been selection bias with patients in the education group being more motivated to maintain good glycaemic control. (Level 2-)

The risk of hypoglycaemia does appear to be raised during Ramadan (Level 3). The main reasons for this could be the lack of education to patients on management issues, inadequate attendance and monitoring during Ramadan and patients adjusting their diets and medications of their own accord.

There is no local data on the safety of fasting during Ramadan.

Which patients should be advised not to fast?

As a follow on to the EPIDIAR study, the American Diabetic Association (ADA) published a workgroup report making recommendations on fasting in Ramadan. The recommendations were based on expert opinion rather than hard data. Their emphasis was that the decision to fast is a personal one and should be made after ample discussion of the

associated risks with the attending physician. They suggested categorizing patients according to their risk profile (see Table 1). In addition, those with brittle control or unwilling or unable to monitor glycaemia should be strongly discouraged from fasting. Pregnant women should also be strongly advised not to fast. (Level 4)

Table 1. Categories of risks in patients with type 1 or type 2 diabetes who fast during Ramadan

Very high risk
Severe hypoglycaemia within the last 3 months prior to Ramadan
Patient with a history of recurrent hypoglycaemia
Patients with hypoglycaemia unawareness
Patients with sustained poor glycaemic control
Ketoacidosis within the last 3 months prior to Ramadan
Type 1 diabetes
Acute illness
Hyperosmolar hyperglycaemic coma within the previous 3 months
Patients who perform intense physical labour
Pregnancy
Patients on chronic dialysis
High risk
Patients with moderate hyperglycaemia (average blood glucose between 150 and 300 mg/dl, A1C 7.5–9.0%)
Patients with renal insufficiency
Patients with advanced macrovascular complications
People living alone that are treated with insulin or sulfonylureas
Patients living alone
Patients with co-morbid conditions that present additional risk factors
Old age with ill health
Drugs that may affect mentation
Moderate risk
Well-controlled patients treated with short-acting insulin secretagogues such as repaglinide or nateglinide
Low risk
Well-controlled patients treated with diet alone, metformin, or a thiazolidinedione who are otherwise healthy

Source: American Diabetic Association[11]

Most of the trials in this review had exclusion criteria for high risk patients e.g. those with cardiac or renal failure, recurrent hypoglycaemia. There is therefore hardly any evidence on fasting amongst high risk populations.

Only one study identified predictors for hypoglycaemia during Ramadan[20], although this was not the main objective of the study. Hypoglycaemic events were analysed as the number of events rather than as rates. Fasting blood glucose at the start of Ramadan correlated with the risk of hypoglycaemic events during Ramadan, Odds Ratio OR 0.984 (Confidence Interval CI 0.976-0.992) (p<0.0002) while HbA1c before Ramadan correlated with asymptomatic hypoglycemic events during Ramadan OR 0.575 (CI 0.396-0.835) (p=0.0036). No predictive model was derived and validated from these findings. On multivariate analysis, two factors were found to predict a higher risk of hypoglycaemic events: subjects in countries with stricter Ramadan observance (Indonesia, Malaysia, Saudi Arabia) OR 3.24 (95%CI 1.70-6.36) (p=0.0004) and low waist circumference (<90cm) OR 2.75 (95%CI 1.27-5.95) (p=0.01). Fasting blood glucose >6.7mmol/L just before Ramadan had a protective effect against hypoglycaemic events OR 0.48 (95%CI 0.24-0.95) (p=0.03). It was not clear if all the available data were considered in the bivariate and multivariate anaylsis for predicting hypoglycaemic events. (Level 2+)

For those who fast, what is the optimal therapeutic regimen?

The ADA workgroup[11] suggested that care of the fasting diabetic must be highly individualized. Medical assessment and education should take place before the start of fasting. There should be frequent monitoring of glycaemia, especially those on insulin. A healthy balanced diet should be maintained and a constant body mass maintained. Complex carbohydrates are recommended at the predawn meal, which should be taken as late as possible and simple carbohydrates at the sunset meal. Fluid intake should be increased in the non-fasting hours. A normal level of activity should be maintained, avoiding excessive activity in the hours before the sunset meal. The fast should be broken if glucose levels fall below 60mg/dl or 3.3mmol/L or if below 70mg/dl or 3.9mmol/L in the few hours after the start of the fast (especially those on insulin or secretagogues) or if above 300mg/dl or 16.7mmol/L. (Level 4)

The following therapeutic regimens were suggested by the ADA workgroup. (Level 4)

Type 1 Diabetes
Therapeutic options:

1. NPH insulin BD and short acting insulin before meals.
2. Ultralente BD with short acting insulin before meals.
3. Insulin glargine OD or insulin determir BD.
4. Intermediate acting insulin BD with insulin lispro before meals.
5. Subcutaneous insulin pump.

Type 2 Diabetes
Recommended changes:

1. Diet control – to take 2 to 3 smaller meals and modify exercise.
2. Metformin – 2/3 daily dose at sunset, 1/3 daily dose at dawn.
3. Glitazones – no change is required.
4. Sulphonylureas – treatment should individualized and use with caution.
   a. Once daily before the sunset meal or
   b. Half the usual morning dose at the predawn meal and full dose at the sunset meal.
5. Short acting secretagogues – may be safer than sulphonylureas
6. Premixed insulin 70/30 – Usual morning dose at sunset meal and half the usual evening dose at predawn meal. Consider changing to glargine or determir plus lispro or aspart.

Studies of therapeutic options during fasting in Ramadan have been done almost exclusively in type 2 diabetics. Only one trial was conducted on type 1 diabetics[14]. The methodological quality of trials was variable. The common weaknesses were the lack of non-fasting controls, lack of blinding, lack of adjustment for confounding factors (e.g. diet, activity), lack of intention-to-treat analysis, heterogeneous interventions (variable drug regimens & dosages) and heterogeneous comparison groups. A few studies had non-fasting control groups but the control groups were neither randomly allocated nor matched[12,18,19]. Only two studies had biochemical inclusion criteria[18,19]. The majority had exclusion criteria such as renal, liver or cardiac impairments, severe diabetic complications and recurrent hypoglycaemia. Most studies relied on hypoglycaemic symptom reporting without biochemical confirmation. Only two studies had routine capillary glucose checked during fasting hours[18,20], while the others did not, primarily for religious reasons. The definition of severe hypoglycaemia was variable and ranged from hypoglycaemia requiring assistance from another person to hypoglycaemia requiring hospital admission.

1. Insulin & Insulin Analogues

Two randomized studies comparing insulin lispro and soluble insulin were identified. Both studies had similar designs, comparing insulin lispro and soluble insulin with a crossover 14 days after the start of Ramadan. The trial by Akram and the Ramadan Study Group[13] on 70 type 2 DM participants was of good methodological quality and showed that post-meal glucose excursion was significantly lower with insulin lispro than with soluble insulin. Although the number of patients having hypoglycaemic events were similar in both groups, those on Lispro had significantly fewer hypoglycaemic episodes. No severe hypoglycaemic events were reported (Level 1++). The second trial on participants with type 1 DM, showed similar results but was methodologically less robust[14] (Level 1-).

Matoo et al[15] from the Ramadan Study Group also showed in a randomized trial that using Lispro Mix 25 resulted in lower glucose excursion after the evening meal compared with Humulin 30/70, without any difference in rates of hypoglycaemia. (Level 1+)

The evidence of improved diabetic control in a cohort trial comparing Humalog Mix 50 and Insulin Mix 30 was less convincing as it was unclear if both groups were comparable at treatment allocation[22]. (Level 2-)

2. Sulphonylureas

In a study of 591 type 2 diabetic subjects[12], two different glibenclamide dose regimens were compared along with a self-selected, non-fasting control group. Fasting subjects were randomized to one of two regimens: normal daily dose with dosage pattern reversed (morning dose switched to evening and vice versa); or dosage pattern reversed but daily dose reduced by 25%. There were no significant differences in fructosamine levels, percentage of glycated haemoglobin and hypoglycaemic events between the three groups. However, it should be noted that patients in this study had very poor diabetic control, the baseline glycated haemoglobin level ranging from 13.2% to 14.3% between the three groups. (Level 1+)

More studies involving sulphonylureas are discussed below.

3. Biguanides and alpha-glucosidase inhibitors

There were no trials which studied the use of these agents during Ramadan but metformin is generally considered to be safe[11].

4. Meglitinides

In a randomized controlled trial by the Ramadan Study Group[16], repaglinide produced greater decreases in fructosamine levels and lower rates of hypoglycaemic events compared with glibenclamide. However, the groups were not comparable at baseline and drug dosages were not handled in a similar manner. (Level 1-)

Two cohort studies comparing fasting and non-fasting groups did not find any significant difference in glucose parameters between groups. Cesur et al[18] studied the use of glimepiride, repaglinide or glargine, in addition to metformin during Ramadan. It was unclear if the comparison groups were similar at baseline or if any drug adjustments were made in the control group. The number of patients experiencing hypoglycaemia was similar in both groups. Bakiner et al[19] studied repaglinide and glargine but the subject numbers was small and intention-to-treat analysis was not performed. No hypoglycaemic events were reported. (Level 2-)

A study comparing repaglinide and glimepiride was identified but the full text could not be obtained for this review. (see table 3)

5. Thiazolidinediones

Hyperglycaemia is also a problem during Ramadan and some studies look at how glycaemic control could be improved. In a small randomized controlled trial[17], adding pioglitazone negated the rise in fructosamine levels which was seen in the control group, without increasing the incidence of hypoglycaemic events (Level 1++). The subjects in this trial had somewhat poor diabetic control at baseline.

6. Incretin Mimetics and Dipeptidyl peptidase-4 (DPP-4) inhibitors

The therapeutic arsenal in diabetes has expanded in recent years with the addition of incretin mimetics and Dipeptidyl peptidase-4 (DPP-4) inhibitors. A small study[21] showed that the incidence of hypoglycaemic events during Ramadan was lower in the vildagliptin group as compared to the gliclazide group with both groups having similar declines in HbA1c. However, it was not clear that the subjects in each group were similar at treatment allocation. (Level 2-)

No studies on incretin mimetics were found.

Table 2. Summary of trials on therapeutics

Name/Year	Study Design	Subjects	Results	Level of Evidence
Belkhadir[12] 1993	Randomized controlled trial Usual or 75% daily dose glibenclamide with reversed dosage pattern with non-fasting control group	591 Type 2 DM	Change in fructosamine level from start to end of Ramadan Full dose group 367±80µmol/L to 381±96µmol/L 75% dose group 359±82µmol/L to 376±98µmol/L Non-fasting group 396±91µmol/L to 400±102µmol/L Number of hypoglycaemic events Full dose group (n=183) 14 75% dose group (n=182) 10 Non-fasting group (n=177) 11	1+
Akram[13] 1999	Open label Randomized Crossover Insulin Lispro or soluble insulin BD with crossover after 14 days + NPH insulin BD	70 Type 2 DM	Rise in blood glucose 2hr after sunset meal Lispro group 2.6±0.4mmol/L Soluble insulin group 4.0±0.5mmol/L (p<0.008) Hypoglycaemia frequency (episodes/patient/14 days) Lispro group 1.3±0.1 (p<0.002) Soluble insulin group 2.6±0.2 No severe hypoglycaemic events.	1++
Kadiri[14] 2001	Open label Randomized Crossover Insulin Lispro or soluble insulin BD with crossover after 14 days + NPH insulin BD	64 Type 1 DM	Rise in blood glucose 2hr after sunset meal Lispro group 2.50±0.46mmol/L Regular human insulin group 3.47±0.49mmol/L (p=0.026) Hypoglycaemia incidence Lispro group 15 patients (23.4%) Regular human insulin group 31 patients (48.4%) (p=0.004) Hypoglycaemia frequency (episodes/patient/30days) Lispro group 0.70±0.19 Regular human insulin group 2.25±0.36 (p<0.001)	1-
Matoo[15] 2003	Open label Randomized Crossover Lispro Mix25 or Humulin 30/70 with crossover after 14 days	151 Type 2 DM	Mean blood glucose evening glucose excursion Lispro Mix 25 group 3.4±2.9 Humulin 30/70 group 4.0±3.2 (p=0.007) Hypoglycaemia frequency (episodes/patient/14 days) Lispro Mix25 group 0.4±0.9 Humulin 30/70 group 0.4±0.8 (p=0.725)	1+
Mafauzy[16] 2003	Randomized Controlled Trial Repaglinide or glibenclamide	235 Type 2 DM	Change in fructosamine level from start to end of Ramadan Repaglinide group 389.69±84.6 to 370.89±86.43µmol/l Glibenclamide group 365.99±75.89 to 358.59±70.10µmol/l Hypoglycaemia frequency (episodes/patient/30 days) Repaglinide group 0.03 Glibenclamide group 0.05	1-
Vasan[17] 2006	Randomized Controlled Trial Pioglitazone or placebo + convential oral hypoglycaemic agents	86 Type 2 DM	Fructosamine levels 2 weeks after Ramadan Pioglitazone group 336.45±76.20µmol/L Placebo group 381.94±112.99µmol/L (p=0.04) Number of hypoglycaemic events 39 in pioglitazone group & 32 in placebo group. (p=0.21) Number of severe hypoglycaemic events 0 in pioglitazone group & 2 in placebo group.	1++
Cesur[18] 2007	Prospective cohort with non-fasting control Glimepiride or repaglinide or glargine + metformin	65 Type 2 DM	No significant difference in comparison of changes in fructosamine levels between fasting and non-fasting groups. Significantly higher post-prandial blood glucose in non-fasting group than fasting group at post-Ramadan and one month post-Ramadan. (p<0.05 and p<0.001) No significant difference in incidence of hypoglycaemia between fasting (12.2%) and non-fasting groups (12.5%).	2-
Bakiner[19] 2009	Prospective cohort with non-fasting controls RepaglinideTDS and glargine ON	19 Type 2 DM	No significant differences between groups in fasting blood glucose post-prandial glucose and fructosamine levels. No hypoglycaemic events reported from either group.	2-
Salti[20] 2009	Prospective cohort with non-fasting self controls Glimepiride OM and glargine ON	349 Type 2 DM	Number of hypoglycaemic events 346 during Ramadan vs 156 pre-Ramadan (p<0.001) and 153 post-Ramadan (p=0.0002) Not analyzed as rates. 1 episode of severe hypoglycaemia in each of the three study periods	2+

Devendra[21] 2009	Prospective cohort	52	Mean number of hypoglycaemic events before and after Ramadan Vildagliptin 0.42±0.5 to 0.08±0.3 ↓ Gliclazide 0.27±0.5 to 0.92±0.9 ↑ Least squares means difference between groups -0.66 (95%CI -1.20 to -0.13, p=0.0168)	2-
	Vildagliptin or Gliclazide BD + metformin	Type 2 DM	Hypoglycaemia incidence Vildagliptin group 7.7% Gliclazide group 61.5% Mean difference -53.8% (95%CI -74.9 to -26.3, p<0.0001)	
			Number of severe hypoglycaemic events 1 in gliclazide group. None in vildagliptin group.	
			Similar reductions in HbA1c in both groups.	
Hui[22] 2010	Prospective cohort	52	Mean number of hypoglycaemic events during and before Ramadan Humalog Mix 50 group 0.46±0.65 to 0.42±0.58 Mixtard 30 group 0.42±0.58 to 0.58±0.81 Not statistically significant. Least squares means difference between groups 0.135 (95%CI -0.26 to 0.43, p=0.36).	2-
	Mixtard 30 at predawn & Humalog Mix 50 at sunset or Mixtard 30 BD	Type 2 DM	Mean HbA1c Reduction in Humalog Mix 50 group 0.48% (p=0.0001) Increase in Mixtard 30 group 0.28% (p=0.007) Least squares means difference between groups 0.40% (95%CI 0.19-0.62, p=0.0004)	

Table 3. Summary of studies with only abstract available

Name	Description of study
Anwar	Open label comparative trial on repaglinide and glimepiride in 41 subjects. Glucose excursion was better for repaglinide in the morning but better for glimepiride in the afternoon and evening.

Discussion

There are inherent difficulties in conducting studies on fasting amongst diabetic Muslims in Ramadan. Each study should ideally include a non-fasting control group but randomization into fasting and non-fasting groups cannot be done for ethical reasons. Non-fasting controls would then be heterogeneous with respect to the study group. The option taken by some studies is to use the same study cohort during non-fasting months as a control, but there are many other confounding factors which occur during Ramadan. Confounders which are not easy to account for include accessibility to medical care, level of activity, diet and religious factors. Checking and documenting each hypoglycaemic episode biochemically is difficult for logistical and religious reasons hence studies are reliant on self reporting of symptoms.

Although the trial on education[10] did not convincingly demonstrate that it could reduce the risk of hypoglycaemia, recent studies on drug therapeutics have usually included a component of education for all patients in preparation for Ramadan. As such, education on diet, activity and drug modification, recognizing and managing complications, should be provided to patients who intend to fast.

Insulin Lispro seems to be better than soluble insulin for diabetics who fast during Ramadan, probably because of a more rapid onset of action (within 15 minutes of administration), earlier peak levels (30 to 90 minutes) and shorter duration of action (less than 5 hours). It is more costly than soluble insulin and this should be considered.

Repaglinide, with a rapid onset of action and short duration of action, should in theory be superior to sulphonylureas, but so far the evidence has not been robust enough to support it. Overall, no oral agent has been proven to be of greater benefit or safer than any other.

Most studies have concentrated on using alternative or additional agents, but it makes more sense to adjust existing medications to avoid adding costs to the patient. Only one study examined how the dosage pattern of usual medications could be modified for Ramadan[12]. Although it showed how two different patterns of glibenclamide dosing were safe, the study population had high glycaemic indices and the results may not be generalized to populations with good control.

Given that the therapeutic options and study populations in the studies are so varied, it would follow that management of each diabetic patient wanting to fast for Ramadan should be individualized.

There are limitations with this review. Firstly, critical analysis of trials should have two reviewers and a third adjudicator in cases of disagreement. Secondly, only English language articles

were reviewed. There may be more data given that countries with predominantly Muslim populations may not publish studies in the English language or in western scientific journals. Unpublished results have been presented at international conferences but were not available for this review.

There is certainly still a lot more research to be conducted on this subject. Future studies should examine:

a. Predictive models, including biochemical markers, for fasting safely during Ramadan.
b. Optimal dosage pattern modifications.
c. Non-pharmacological aspects of diabetic control, including diet, activity modification and patient education.

Recommendations

1. The management of each diabetic patient wanting to fast for Ramadan should be individualized. (GPP)

2. There is insufficient evidence on the safety for fasting for Type 1 diabetics. There is also hardly any evidence on the safety of fasting for high risk patients such as those with cardiac or renal failure, recurrent hypoglycaemia or in pregnancy. It would be prudent to advise against fasting in these populations. The risk stratification table by the ADA (see above) may be useful in counseling patients on their risk. (Grade D, Level 4)

3. Although the risk of hypoglycaemia in Type 2 diabetics may be higher during Ramadan, those with good compliance and no complications may be able to fast safely. (Grade C, Level 2+)

4. Although there is insufficient evidence to show that patient education can reduce the risk of hypoglycaemia, it should nonetheless be provided for patients who wish to fast. (Grade D, Level 4)

5. In addition to the therapeutic options recommended by the ADA11, the following may be considered in Type 2 diabetics:
   a. Insulin lispro reduces the glucose excursion and frequency of hypoglycaemia as compared to soluble insulin. Consider switching soluble to a rapidly acting insulin such as insulin lispro for the duration of Ramadan. (Grade B, Level 2++).
   b. Pioglitazone may improve glycaemic control without increasing the risk of hypoglycaemia. Consider adding a thiazolidinedione for those with suboptimal glycaemic control. (Grade B, Level 1+).

ANNEX A

Scottish Intercollegiate Guidelines Network
Key to evidence statements and grades of recommendations

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion
Grades of recommendations	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
Good practice points	
☑	Recommended best practice based on the clinical experience of the guideline development group

REFERENCES

1. National Census 2000.
2. National Health Survey 2004. Ministry of Health, Singapore.
3. Benaji B, Mounib N, Roky R et al. Diabetes and Ramadan: Review of the Literature. Diabetes Res Clin Pract 2006;73:117-25.
4. Kobeissy A, Zantout MS, Azar ST. Suggested Insulin Regimens for Patients with Type 1 Diabetes Mellitus Who Wish to Fast During the Month of Ramadan. Clin Ther 2008;30:1408-15.
5. Hui E, Bravis V, Hassanein M et al. Management of people with diabetes wanting to fast during Ramadan. BMJ 2010;340:1407-11.
6. Karamat MA, Syed A, Hanif W. Review of diabetes management and guidelines during Ramadan. J R Soc Med 2010;103:139-47.
7. Hui E, Devendra D. Diabetes and fasting during Ramadan. Diabetes Metab Res Rev 2010;26:606-10.
8. Salti I, Benard E, Detournay B, Bianchi-Biscay M, et al. The EPIDIAR Study Group: A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care 2004; 27:2306-11.
9. Ahmadani MY, Riaz M, Fawwad A et al. Glycaemic trend during Ramadan in fasting diabetic subjects: A study from Pakistan. Pak J Biol Sci 2008; 11(16):2044-7.
10. Bravis V, Hui E, Salih S et al. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with type 2 diabetes who fast during Ramadan. Diabet Med 2010;27:327-31.
11. Al-Arouj M, Bouguerra R, Buse J, Hafez S, et al. Recommendations for management of diabetes during Ramadan. Diabetes Care 2005;28:2305-11.
12. Belkhadir J, Ghomari HE, Klöcker, N et al. Muslims with non-insulin dependent diabetes fasting during Ramadan: treatment with glibenclamide. BMJ 1993;307:292-5.
13. Akram J, De Verga V, Ramadan Study Group. Insulin Lispro (Lys(B28),Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. Diabet Med 1999;16:861-6.
14. Kadiri A, Al-Nakhi A, El-Ghazali S et al. Treatment of type I diabetes with insulin lispro during Ramadan. Diabetes Metab (Paris) 2001; 27:482-6.
15. Mattoo V, Milicevic Z, Malone JK. A comparison of insulin lispro Mix25TM and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. Diabetes Res Clin Pract 2003; 59:137-43.
16. Mafauzy. Repaglinide versus glibenclamide treatment of Type 2 diabetes during Ramadan fasting. Diabetes Res Clin Pract 2002; 58:45-53.
17. Vasan S, Thomas N, Bharani et al. A double-blind, randomized, multicenter study evaluating the effects of pioglitazone in fasting Muslim subjects during Ramadan. Int J Diabetes Dev Ctries 2006;26:70-6.
18. Cesur M, Corapcioglu D, Gursoy A et al. A comparison of glycemic effects of glimepiride, repaglinide, and insulin glargine in type 2 diabetes mellitus during Ramadan fasting. Diabetes Res Clin Pract 2007; 75:141-7.
19. Bakiner O, Ertorer ME, Bozkirli E et al. Repaglinide plus single-dose insulin glargine: a safe regimen for low-risk type 2 diabetic patients who insist on fasting in Ramadan. Acta Diabetol 2009;46:63-5.
20. Salti I; Diabetes and Ramadan Study Group. Efficacy and safety of insulin glargine and glimepiride in subjects with Type 2 diabetes before, during and after the period of fasting in Ramadan. Diabet Med. 2009;12:1255-61.
21. Devendra D, Gohel B, Bravis V et al. Vildagliptin therapy and hypoglycaemia in Muslim type 2 diabetes patients during Ramadan. Int J Clin Pract. 2009 Oct;63(10):1446-50.
22. Hui E, Bravis V, Salih S et al. Comparison of 28 Humalog Mix 50 with human insulin Mix 30 in type 2 diabetes patients during Ramadan. Int J Clin Pract 2010;64:1095-9.
23. Anwar A, Azmi KN, Hamidon BB, Khalid BA. An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan. Med J Malaysia. 2006. Int J Clin Pract. 2009 Oct;63(10):1446-50.