A Prospective Cohort Study on the Effect of Various Risk Factors on Hypoglycaemia in Diabetics Who Fast During Ramadan

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SUMMARY

Muslim diabetics who fast during Ramadan are at risk of hypoglycaemia, and previous consensus guidelines have highlighted certain risk factors. This prospective cohort study aims to determine the relative risk (RR) of hypoglycaemia during Ramadan fasting compared with a non-fasting period of equivalent length, and to ascertain which risk factors are clinically significant. From the results, Ramadan fasting carries a RR of hypoglycaemia of 1.60 (95% CI 1.05 to 2.43). Good metabolic control (HbA1c < 8%) and old age (> 60 years) increased RR more than twice, while taking breakfast prior to fasting reduces RR to less than half.

KEY WORDS:
Cohort Studies, Fasting, Hypoglycemia, Islam, Risk Assessment, Type 2 Diabetes Mellitus

INTRODUCTION

The prevalence of diabetes in Malaysia has been increasing steadily as a result of urbanisation and socioeconomic change. It is estimated that there are at present approximately 1.2 million diabetics in the country, a large proportion of which are observant Muslims who fast during the month of Ramadan[1]. In the large EPIDAR study which was conducted across 13 countries with large Muslim populations, it was found that 43% of type 1 diabetics and 79% of type 2 diabetics fast during Ramadan. Less than half of these altered their treatment regime to accommodate the change in meal pattern, and the incidence of severe hypoglycaemia increased 4.7-fold in type 1 diabetics, and 7.5-fold in type 2 diabetics. Among the countries surveyed, Malaysia had one of the highest rates of diabetics who fasted during Ramadan[2].

Both the American Diabetes Association and the International Consensus Meeting on diabetes and Ramadan (Morocco, 1995) have identified patient groups who are at particular risk of hypoglycaemia when fasting (Table I)[3,4]. This list of risk factors is based mostly on expert opinion and it would be useful to confirm their significance in a properly designed study. Furthermore, an estimate of their relative contribution to the development of hypoglycaemia would allow targeted intervention prior to initiating fasting with a view to reducing complications.

MATERIALS AND METHODS

Study Objectives

The primary objective of this study was to compare the rate of hypoglycaemia during the Ramadan fasting months of 2007-2008 (1428-1429 Hijrah) with the non-fasting period immediately prior to it. The secondary objective was to determine the risk factors for hypoglycaemia and correlate them with the rate of hypoglycaemia while fasting during Ramadan.

Inclusion and Exclusion Criteria

Only patients who had been previously diagnosed with diabetes mellitus (both type 1 and 2) and who intended to fast during the Ramadan months of 2007-2008 (1428-1429 Hijrah) were included. Diabetics younger than 18 years were excluded from the study as children have a different risk profile for hypoglycaemia as compared with adults. In addition, this would avoid potential difficulties in obtaining consent from parents or guardians. Pregnant women were also excluded from the study as they are more prone to hypoglycaemia and do not normally fast. Those unable to be contacted by telephone were excluded as this would prevent adequate follow-up during the study period. Patients with intercurrent illness aside from hypoglycaemia requiring admission to hospital along with those who were unable to complete at least three weeks of fasting during the study period were excluded at the point of data analysis.

Data Collection

The study population consisted of Muslim diabetic volunteers who were recruited from the specialist medical clinic of Kuala Lumpur General Hospital in August 2007 and August 2008. Informed consent was obtained by trained interviewers using a consent form approved by the Malaysian Ministry of Health Ethics Review Board in accordance with current guidelines on Good Clinical Practice and the Declaration of Helsinki.

A questionnaire was filled by the interviewer at the point of initial recruitment detailing the various risk factors for hypoglycaemia, along with general demographic and background information. The most recent laboratory HbA1c value within the three month period prior to recruitment was used as an indicator of current metabolic control. The patient was asked if there was an intention to change the evening meal size, the level of physical activity, medication regime, and any special precautions taken to treat hypoglycaemia.

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For each study patient, a printed calendar chart was provided covering the period of 12th August to 12th October 2007 or 1st September to 2nd November 2008, detailing a fixed non-fasting period of four weeks, and a subsequent fasting period of four weeks during Ramadan. Patients were advised to document on the chart episodes of hypoglycaemia encountered during this period, and if the assistance of another person was required during the episode. For this study, severe hypoglycaemia was defined as a hypoglycaemic episode severe enough to require the assistance of another person. Hospital admissions for hypoglycaemia were documented on the chart noting the period of inpatient stay. Changes in diabetic medication were also charted, along with any break in fasting and the reason(s) for breaking the fast. A contact telephone number was given so that queries can be clarified promptly by one of the study personnel. Counselling was provided about the symptoms of hypoglycaemia along with appropriate self-management.

Patients who agreed to be in the study were reminded by telephone just prior to the start of the non-fasting period and just before commencement of Ramadan fasting. After Ramadan, they were also contacted to remind them to post the completed calendar chart back to the study centre for analysis. A pre-addressed and stamped envelope was provided to each subject for this purpose.

Analysis

Analysis of the primary objective was done by estimating the relative risk (RR) of hypoglycaemia comparing the four week non-fasting period with the equivalent Ramadan fasting period. The total number of hypoglycaemic episodes for all patients along with the total number of days during the non-fasting and fasting periods was counted. If patients were unable to fast on certain days for any reason aside from hypoglycaemia, these days were excluded from analysis and the duration of the fasting period shortened accordingly. Patients who aborted fasting because of hypoglycaemia were counted as having hypoglycaemia on that day. The rate of hypoglycaemia was obtained by dividing the total number of days patients experienced hypoglycaemic symptoms with the duration of the non-fasting or fasting period as appropriate. The RR of hypoglycaemia for Ramadan fasting was calculated by dividing the rate of hypoglycaemia for the fasting period by the rate for the non-fasting period.

Analysis of the secondary objective was done using Unpaired T-Tests with the rate of hypoglycaemia during the fasting period as the dependent variable, and with groups defined according to the 10 predictors noted in Table I. The first seven predictors were based on expert opinion while the final three predictors were precautions that patients take to avert hypoglycaemia. The type of diabetes was not used as a predictor as the prevalence of type 1 diabetes in the local population is low [1]. Severe hypoglycaemia and recurrent hypoglycaemia were grouped together as a single predictor. The RR for each of the predictors was obtained and considered significant when less than 0.5 or greater than 2.

Based on the null hypothesis that there is no difference in the rate of hypoglycaemia between the groups defined by the predictors, power analysis for a two-tailed Unpaired T-Test showed that for a 5% type I error rate (alpha-level 0.05), 20% type II error rate (80% power), and a maximum allocation ratio of 2.5, with an ability to detect a large difference (Cohen's d = 0.8), a sample size of 64 patients was needed. A low cut-off for the allocation ratio was used to ensure that only clinically important predictors were selected. Normality of data was tested using the Kolmogorov-Smirnov test against a normal distribution, while equality of variances was tested with Levene's test. False discovery rate (FDR) control with the Simes procedure was used to reduce type I errors when performing multiple pairwise testing. Predictors with an allocation ratio greater than 2.5 were not analysed to reduce the likelihood of a type II error. Planning for a maximum 50% drop-out rate, a minimum of 128 patients was targeted for recruitment to achieve adequate statistical power.

All computations were performed using SPSS for Windows version 13.0 (SPSS Inc, Chicago, Illinois, USA). Statistical tests were two-tailed and conducted at 5% level of significance unless stated otherwise. Power analysis was done using the program G*power 3 (Faul & Erdfelder, Bonn University 2007) [6].

RESULTS

Over the study period, a total of 135 patients were recruited. Of these, 121 patients had documented HbA1c values within three months prior to recruitment. Only 67 patients returned the printed calendar chart after study completion even with telephone reminders. Of these, a further six patients were excluded due to inability to complete at least three weeks of fasting, two of which were for hospital admission for non-diabetic conditions, with no reason given for the other four patients. All of the remaining 61 patients had type 2 diabetes. None of the patients were admitted to hospital for hypoglycaemia, or had hypoglycaemia requiring the intervention of a third party.

For the primary objective, there were a total of 35 hypoglycaemic episodes during the non-fasting period and 55 episodes during the fasting period for the 61 patients analysed. The total number of non-fasting days was 1708, and the number of fasting days was 1680. The average rate of hypoglycaemia during the four week non-fasting period was 0.0205 episodes per patient per day, while the rate of hypoglycaemia during the fasting period was 0.0327 episodes per patient per day. The RR of hypoglycaemia for Ramadan fasting was 1.60 (95% CI 1.05 to 2.43). Histogram plots showed that the majority of patients had no documented hypoglycaemic episodes. Of the 61 patients, 37 had no documented episodes of hypoglycaemia, 12 had more hypoglycaemia during the fasting period, 9 had more hypoglycaemia in the non-fasting period, while three had the same number of episodes during both periods (Fig. 1).

For the secondary objective, only 6 of the 10 predictors had an allocation ratio less than 2.5 (Table I). For an alpha-level of 0.05, after FDR adjustment for 6 multiple comparisons, a significant p-value should be less than 0.03. Unpaired T-Tests did not show significant results for any of these 6 predictors.

Looking at the means for these predictors, a history of severe or recurrent hypoglycaemia did not affect hypoglycaemia

Table I: Risk Factors for Hypoglycaemia When Fasting

No	Risk Factor (Predictor)	Yes	No	Allocation Ratio
1*	Recent history of severe hypoglycaemia			
1*	History of recurrent hypoglycaemia	40	95	2.38**
2	Patients with hypoglycaemic unawareness	19	116	6.1
-*	Type 1 diabetes	3	132	44.0
3	Patients who perform manual labour	6	129	21.5
4	Well controlled diabetes (HbA1c < 8%)	53	68	1.3**
5	Patients who live alone	9	126	14.0
6	Elderly (> 60 years old)	49	83	1.69**
7	Patients on insulin or sulphonylurea treatment	110	24	4.6
8	Take breakfast before starting fast	79	56	1.41**
9	Carry sweets when going out	42	93	2.21**
10	Reduce exercise	74	61	1.21**

* Severe hypoglycaemia and recurrent hypoglycaemia are grouped into a single risk factor, while type 1 diabetes is not used as a predictor as the local prevalence is low.

** Only predictors with an allocation ratio less than 2.5 are analysed to reduce the likelihood of a Type II error.

Table II: Unpaired T-Test Comparing Predictors With Rate of Fasting Hypoglycaemia

No	Risk Factor (Predictor) Allocation Ratio < 2.5	Mean(Yes)	Mean (No)	Rel. Risk	t-Score	p-Value
		Events per Patient per Day				
1	Recent history of severe hypoglycaemia					
1	History of recurrent hypoglycaemia	0.0234	0.0362	0.64	-0.601	0.550
4	Well controlled diabetes (HbA1c < 8%)	0.0459	0.0197	2.33	-1.245**	0.224
6	Elderly (> 60 years old)	0.0523	0.0244	2.14	1.113**	0.278
8	Take breakfast before starting fast	0.0207	0.0541	0.38	-1.622**	0.115
9	Carry sweets when going out	0.0339	0.0330	1.03	0.047	0.962
10	Reduce exercise	0.0281	0.0390	0.72	-0.602	0.549

* after FDR adjustment for 6 comparisons, a significant p-value is < 0.03

** the t-test for unequal variances was used instead when indicated by a significant Levene's test

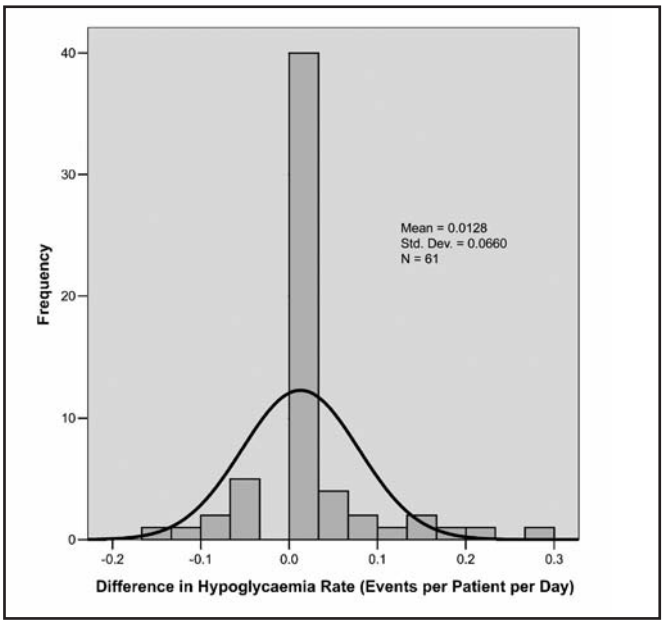

Fig. 1: Histogram of the Difference in Hypoglycaemia Rate Between Fasting and Non-Fasting Periods.

during Ramadan. Carrying sweets when going out of the house and reducing exercise also did not protect against hypoglycaemia. However, diabetics with good metabolic control (HbA1c <8%) and elderly diabetics had more than twice the risk of developing hypoglycaemia during the fasting month. In addition, having breakfast before fasting reduced the risk of hypoglycaemia more than two-fold (Table II).

The data set was reanalysed excluding 37 patients who did not report a single episode of hypoglycaemia. This made no difference to results for the primary objective and gave only a marginal improvement in results for the secondary objective.

DISCUSSION

While the rate of hypoglycaemia was 1.6 times higher during the fasting compared to non-fasting periods, the difference was smaller than indicated in the EPIDAR study 2. On closer examination of the data, more than 60% of patients had no documented episodes of hypoglycaemia, and the number of patients who had more hypoglycaemia during the non-fasting period (15%) was almost as many as those who had more hypoglycaemia during the fasting period (20%) (Fig. 1). To account for the possibility that some patients may have misunderstood instructions and not recorded hypoglycaemic episodes, the data set was reanalysed excluding patients who did not report any episodes of hypoglycaemia, but this did not alter the findings. As all of the patients included in the analysis had type 2 diabetes, these findings do not apply to type 1 diabetics.

From this, we can conclude that for patients with type 2 diabetes in the population which we studied, fasting during Ramadan increases the rate of hypoglycaemia by 1.6-fold. This is in contrast to the EPIDAR study which showed a large 7.5-fold difference in the rate of severe hypoglycaemia[2]. There are a number of possible reasons for this discrepancy. The first is that the EPIDAR study is retrospective, which can lead to significant recall bias as patients are more likely to recall episodes of hypoglycaemia when they are fasted. Moreover, this is compounded by their definition of severe

hypoglycaemia which only covers hospital admissions, leading to further bias as patients are more likely to be admitted to hospital when having hypoglycaemia while fasting.

In contrast, the current study is prospective and none of the patients documented any episodes of severe hypoglycaemia whether managed at home by family members or requiring hospital admission. Based on the rate of severe hypoglycaemia of 0.03 episodes per patient per month during the fasting month in the EPIDAR study, we would expect two patients in our cohort to be admitted to hospital for hypoglycaemia during the study period [2]. While the numbers are too small to draw any statistical inference, the authors suspect that counselling about symptoms and management of hypoglycaemia and provision of a printed chart in this study may have enabled patients to self-manage episodes early, thus avoiding severe hypoglycaemia.

For the six predictors of hypoglycaemia with an allocation ratio less than 2.5, only three of them were found to have a significant effect (RR < 0.5 or > 2). Patients with good metabolic control (HbA1c <8%) had an increased risk (RR = 2.3) of developing hypoglycaemia when fasting, and this is consistent with results from the Kumamoto study in type 2 diabetes which showed that intensive metabolic control increased the risk of developing symptomatic hypoglycaemia by 1.6 times[7]. Interestingly just like in our study, no patients in the Kumamoto cohort developed severe hypoglycaemia.

Being elderly (> 60 years old) also carried an increased risk of developing hypoglycaemia (RR = 2.1) when fasting. This is likely due to the diminished counter-regulatory response and reduction in autonomic symptoms in the elderly with hypoglycaemia [8]. Of the precautions to avert hypoglycaemia that were studied, only taking breakfast prior to fasting significantly reduced the risk of hypoglycaemia (RR = 0.38). A reduction in exercise did have a small effect on reducing hypoglycaemia (RR = 0.72), and this was consistent with findings from the EPIDAR study [2].

None of the six predictors showed significant p-values as the sample size was too small to detect the differences seen. Based on the difference in rate of fasting hypoglycaemia of 0.0334 episodes per patient per day for the risk factor with the lowest p-value (Table II), standard deviation of 0.0700, an FDR-adjusted alpha-level of 0.03, and an allocation ratio of 2.5, a minimum of 172 subjects would have been needed to demonstrate significance.

The main limitation of this study was that the sample size was inadequate to demonstrate a significant difference for the predictors looked at. Compounding this problem was the low rate of return of 50% for the completed calendar chart.

CONCLUSIONS

From the results of this prospective cohort study, we conclude that fasting during Ramadan increases the rate of symptomatic hypoglycaemia for patients with type 2 diabetes about 1.6-fold. Based on the RR for the predictors of hypoglycaemia, we suggest that elderly patients older than 60 years and those having good metabolic control with HbA1c less than 8% be counselled of the risk of hypoglycaemia during fasting. All patients should have their breakfast prior to starting the fast. Finally, it would be sensible for clinicians to advise their patients on how to identify the symptoms of hypoglycaemia, along with the appropriate management.

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