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Research: Treatment

Multi-country retrospective observational study of the management and outcomes of patients with Type 2 diabetes during Ramadan in 2010 (CREED)

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Abstract

Aim To describe the characteristics and management of patients with diabetes who chose to fast during Ramadan in 2010.

Methods This was a multi-country, retrospective, observational study, supplemented with physician and patient questionnaires, with data captured before, during and after Ramadan. A total of 508 physicians in 13 countries enrolled 3777 patients and a total of 3394 evaluable cases were analysed. We report on the subset of patients with Type 2 diabetes, which included 3250 patients (95.8%).

Results Oral anti-hyperglycaemic therapy was the predominant pre-Ramadan therapy for most patients (76.6%). The treatment regimen was modified before Ramadan for 39.3% of all patients (34.9% for patients on oral drugs alone, 47.1% for patients on injectable drugs alone). Almost all physicians (96.2%) reported providing fasting-specific advice to patients and 62.6% report using guidelines or recommendations for the management of diabetes during Ramadan. In all, 64% of patients reported fasting everyday of Ramadan and 94.2% fasted for at least 15 days.

Conclusions Physicians have increasingly adopted multiple approaches to the management of fasting during Ramadan, including the adoption of international and/or national guidelines, providing fasting-specific advice and adjusting treatment regimens, such that patients are able to fast for a greater number of days without acute complications. Additional research is needed to explore physician and patient beliefs and practices to inform the evidence-based management of diabetes while fasting, both during and outside of Ramadan, and to identify and address barriers to the universal uptake of techniques to facilitate that management.

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Introduction

Fasting during Ramadan, the holy month of the Islamic lunar calendar, is an obligatory practice for healthy adult Muslims. Although potentially exempt from the obligation, the majority of Muslim patients with diabetes also choose to fast. The authors of the multi-country Epidemiology of Diabetes and Ramadan 1422/2001 (EPIDIAR) study reported that 78.7% of patients with Type 2 diabetes fasted for at least 15 days during Ramadan [1]. Combining the EPIDIAR results with a 2010 global Muslim population estimate of 1.6 billion [2] and an updated estimated global prevalence of Type 2 diabetes—8.3% among adults [3]—it can be estimated that there are at least 132 million Muslims worldwide with diabetes, of whom more than 100 million may fast during Ramadan. Furthermore, economic development, and the associated decreased physical activity and high-calorie diets, are projected to contribute to an 'obesogenic' environment in countries with large Muslim populations, increasing the number of people with diabetes. Projected population growth and epidemiological trends suggest that understanding the management of patients with diabetes who fast during Ramadan remains critical.

The EPIDIAR study also identified a need for more intensive education before fasting, for the dissemination

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of guidelines and for further studies assessing the impact of fasting on morbidity and mortality [1]. Since publication of the study results, there has been increasing awareness that fasting during Ramadan represents a global medical issue, prompting the development of recommendations for the management of diabetes during Ramadan [4,5] and structured education programmes [6]. Additionally, a collaboration of medical experts and religious scholars provided important religious guidance via a decree issued in April 2009 [7].

New published data, new pharmacological agents and clear religious guidance may have changed both the management and outcomes of patients with diabetes who fast during Ramadan. In keeping with the recommendations of the EPIDIAR study group, we conducted a multi-country study to describe the characteristics, and multiple approaches to the management of patients with diabetes who fasted during Ramadan 2010. The primary objective was to evaluate the percentage of patients who had a change in diabetes treatment regimen before and during Ramadan in 2010/1431.

Study design and methods

The Multi-Country Retrospective Observational Study of the Management and Outcomes of Patients with Diabetes during Ramadan (the CREED study) was conducted simultaneously in 13 countries (Table 1). In each country, physicians involved in the management of Muslim patients with diabetes were selected from the OneKey® database [8]. In countries with limited database representation, local resources were used to solicit physicians' participation. There was no stratification based on specialty or type of practice for physician recruitment.

Physicians were asked to enroll patients with Type 1, Type 2 or gestational diabetes, who were aged ≥ 18 years old on the first day of Ramadan 2010, who were prescribed medication for diabetes, of any type, alone or in combination, and who fasted for any period of time during Ramadan 2010, with at least one documented visit to his/her primary diabetes healthcare practitioner in the 3 calendar months before Ramadan in 2010, and at least one documented visit in the calendar month after Ramadan in 2010. Each participating patient signed an informed consent form before enrolment. The study was approved by the appropriate ethics committees in accordance with local regulations.

Table 1 The CREED observational study: participation by country of patients with Type 2 diabetes

Region/ Country	Physicians (N = 508), n	Patients (N = 3250), n	Overall contribution to study population, %
Asia			25.1
India	31	271	8.3
Indonesia	66	259	8.0
Malaysia	32	286	8.8
Europe			20.7
France	39	139	4.3
Germany	32	190	5.8
UK	14	91	2.8
Turkey	24	252	7.8
Middle East			26.9
Kingdom of Saudi Arabia	36	248	7.6
Kuwait	14	211	6.5
United Arab Emirates	33	417	12.8
North Africa			27.3
Algeria	75	370	11.4
Morocco	61	282	8.7
Tunisia	51	234	7.2

Data collection

Physician and patient data were collected using standardized questionnaires, translated into the local language if needed. For each patient, data before, during (if a visit occurred) and < 1 month after Ramadan were gathered from the patient's medical records and during a post-Ramadan face-to-face regularly scheduled visit with the physician.

Statistical analyses

Data analyses were performed using SAS® (Statistical Analysis System, Cary, NC, USA) version 9.2 for Windows. Descriptive statistics including frequency, mean, median, standard deviation and extreme values were determined for continuous variables and absolute and relative frequencies for categorical data. Logistic regressions were performed to determine factors associated with the number of days fasted during Ramadan (< 15 vs ≥ 15 days), with changes in diabetes treatment regimen during Ramadan, and with occurrence of complications during Ramadan. Univariate analyses were performed to select a first set of covariates to be tested for inclusion in a multivariate model ($P < 0.25$). The final logistic regression model was obtained by using a backward selection with a threshold level of 0.05.

Results

A total of 3777 patients were enrolled retrospectively in the study (March to June 2011), for whom 3476 case report forms were received and recorded in the database. After reviewing all forms for minimum data quality requirements, a total of 3394 evaluable cases were used for analysis. Because of inconsistencies between patient demographics, diagnosis and treatment, 82 reported cases were excluded from the analysis (51 patients with gestational diabetes, 30 patients with Type 1 diabetes treated only with oral medication and one patient with Type 2 diabetes with no reported treatment). The Type 2 diabetes subset included 3250 patients (95.8%). Table 2 shows the baseline

Table 2 Demographic and clinical features of patients

	Type 2 diabetes
n	3,250
Sex: male/female, %	48.5/51.5
Mean ± SD age, years	56.9 ± 10.7
Mean ± sd time since diagnosis, years	8.4 ± 6.3
Mean ± SD weight, kg	77.2 ± 15.2
Mean ± sd BMI, kg/m²	28.7 ± 5.5
Mean ± SD HbA_{1c}, mmol/mol (%)	60 ± 17.5 (7.6 ± 1.6)
Occupation/working status, *n* (%)	
Active full-time worker	915 (28.3)
Active part-time worker	266 (8.2)
Non-active worker	709 (21.9)
Student	5 (0.2%)
Retired	810 (25.0)
Other	534 (16.5)
Diabetes complications, *n* (%)	
Neuropathy	643 (19.8)
Retinopathy	404 (12.4)
Nephropathy	360 (11.1)
Coronary artery disease	334 (10.3)
Diabetic foot complications	127 (3.9)
Peripheral arterial disease	111 (3.4)
Cerebrovascular disease	67 (2.1)
Comorbidity, *n* (%)	
Hypertension	2020 (62.1)
Dyslipidaemia	1840 (56.6)
Physician-reported risk status (ADA criteria), %	
Low	33.3
Moderate	31.4
High	31.5
Very high	3.8
Pre-Ramadan anti-hyperglycaemic regimens	
Oral, *n* (%)	2490 (76.6)
Monotherapy, %	28.8
Two-drug combination, %	37.7
Three-drug combination, %	9.5
Injectable only, *n* (%)	140 (5.1)
Oral + injectable, *n* (%)	595 (18.3)

ADA, American Diabetes Association.

demographic and clinical characteristics of the studied population. Country-specific CREED data and outcomes are provided in the Supporting Information (Appendix S1).

Physician management of diabetes during Ramadan

Specific physician approaches to patient education and the use of guidelines are shown in Table 3. Inter-country differences in the use of fasting-specific guidelines were notable, ranging from 28% in France to 88% in Indonesia.

Patient demographic and clinical features

The overall demographic and clinical features of the study population are shown in Table 2. The population had a mean age of 57 years and had been diagnosed with diabetes for 8.4 years. Three quarters (74.6%) of patients had a documented HbA_{1c} assay in the 3 months before Ramadan: the mean value was 60 mmol/mol (7.6%). The three most prevalent complications of diabetes were neuropathy (19.8%), retinopathy (12.4%) and nephropathy (11.1%). As with previous studies [1], there was considerable variability between countries and regions. The prevalence of neuropathy ranged from 7.2% in France to 35.5% in Indonesia. The frequency of hypertension (75.5%) and dyslipidaemia (84.9%) was highest in the United Arab Emirates.

Physicians were asked to assess the risk of adverse events for each patient, using American Diabetes Association recommendations [4]. Physicians reported 64.7% of patients to be at low or moderate risk. Again, there was wide variability between countries; physicians in Malaysia reported that only 43.4% of patients could be considered low or moderate risk, while physicians in Germany considered 84.7% of their patients to be in those categories.

Patients were treated with oral antidiabetic drugs alone (76.6%), injectable drugs alone (5.1%), or a combination of an oral antidiabetic drug and an injectable drug (18.3%). Biguanides, alone or in combination, were used by 82.9% of all patients, with monotherapy (17.9%) and combination therapy with a sulphonylurea drug (29.8%) being the most frequent regimens. Patients on injectable drugs alone (all insulin) were prescribed a variety of injection regimens; 8.0% once daily, 54.0% twice daily, 19.7% three times a day and 18.3% four times daily. A total of 23 patients (0.7%) were treated with exenatide or liraglutide, all in combination with another anti-hyperglycaemic agent.

Diabetes during Ramadan

Specific lifestyle and treatment changes implemented for Ramadan are shown in Table 4. Physicians reported a change in diabetes treatment regimens for 39.3% of patients. Irrespective of pre-Ramadan regimens, changes in frequency of administration (74.8%) were more frequent than changes in total daily dose, or a change in drug, defined as an addition, discontinuation or switch. Treatment regimen changes as a method of managing diabetes during Ramadan varied by country; only 13% of patients in France had changes to their pre-Ramadan therapy, while 64% of all patients in Kuwait had a treatment change.

Fasting practice during Ramadan

Table 5 shows the fasting practices both during and outside Ramadan. In all, 94% of patients with Type 2 diabetes in the CREED study reported fasting for at least 15 days during Ramadan. The mean number of fasting days was 27 for the overall study population and ranged from 20.2 (Turkey) to 28.8 days (Saudi Arabia and Algeria). Notably, 30% of patients in the CREED study reported fasting outside of Ramadan, with significant intercountry differences ranging from 8% in India to 46% in Malaysia.

Table 3 Physician management of diabetes during Ramadan

	Total (N = 508), n (%)
Advice given to fasting patients	
Missing	11
No	19 (3.9)
Yes	478 (96.2)
If yes,	
Advice given according to type of diabetes:	
No	46 (9.62)
Yes	432 (90.38)
Advice given according to medication regimen::	
No	39 (8.2)
Yes	439 (91.8)
Advice given for:	
Self-monitoring of glucose	389 (81.4)
Hypoglycaemia	429 (89.8)
Hyperglycaemia	321 (67.2)
Food intake	418 (87.5)
Other	111 (23.2)
Use of one or more guidelines or recommendations for management of diabetes during Ramadan	318 (62.6)
If used, specific recommendations*	
ADA 2005 recommendations	124 (39.0)
ADA 2010 recommendations	131 (41.2)
Local guidelines or recommendations	116 (36.5)
Other guidelines or recommendations	42 (13.2)
Use of one or more Ramadan-focused education programmes	342 (67.3)
If used, specific programmes*	
International	49 (14.3)
National	106 (31.0)
Local	99 (29.0)
Provided by pharmaceutical manufacturer	66 (19.3)
Other	67 (19.6)
If used, education programme is provided by*	
One-on-one counselling with physician	279 (81.6)
One-on-one counselling with nurse or nurse educator	83 (24.3)
In group sessions	66 (19.3)
Via take-home written material/brochure	130 (38.0)

ADA, American Diabetes Association.
*Physicians could specify the use of more than one guideline and education programme.

Table 4 Treatment and diet changes implemented for Ramadan

	Patients with Type 2 diabetes, n (%)	
Total number of patients	3250	
Patients with changes (overall)*	1276	(39.3)
Patients on OAD alone (n = 2490)	869	(34.9)
Patients on injectable therapy alone (n = 140)	66	(47.1)
Patients on injectable + oral therapy (n = 595)	322	(54.1)
Nature of treatment changes, overall study population		
Number of patients with changes	1276	
Change in drug†	261	(20.4)
Changes in total daily dose	471	(36.9)
Changes in frequency of administration	955	(74.8)
Nature of treatment change, patients on OAD only		
Number of patients with changes	869	
Change in drug†	164	(18.9)
Changes in total daily dose	278	(32.0)
Changes in frequency of administration	635	(73.1)
Nature of treatment changes, patients on injectable therapy alone		
Number of patients with changes	66	
Change in drug†	5	(7.6)
Changes in total daily dose	31	(47.0)
Changes in frequency of administration	55	(83.3)
Nature of treatment changes, patients on injectable + OAD		
Number of patients with changes	322	
Discontinuation of a therapy (OAD or injectable)	84	(26.1)
Changes in the frequency for administration	249	(77.3)
Average number of meals consumed each day during Ramadan		
1	54	(1.7)
2	2076	(64.1)
3	1030	(31.8)
4 or more	79	(2.4)
Change in size of meals	1657	(51.7)
Eat smaller meals	662	(40.5)
Eat larger meals	972	(59.5)
Predominant change in the type of meals		
Eat more carbohydrate	1084	(61.8)
Eat more protein	1032	(58.9)
Eat more fat	690	(39.4)

OAD, oral antidiabetic drug.
*Physicians could assign the change to more than one category.
†Change defined as discontinuation of a drug, addition of a drug, switching from one drug to another.

Hypoglycaemia and hospitalization during Ramadan

Patient-reported episodes of hypoglycaemia during the month of Ramadan and associated severity are reported in Table 6. During Ramadan, 8.8% of patients reported at least one episode of hypoglycaemia (mean 1.8, range 1–9). Most of the events required either assistance (51.4%) and/or stopping the fast (47.8%). Hospitalization during Ramadan was rare. A total of 15 patients (0.5%) each reported one hospitalization during the month, with only seven of those being related to diabetes.

Regression analyses

The results of the logistic regression analyses are shown in Tables 7 and 8. Fasting for < 15 days was more likely for patients treated by specialists (vs general practitioners), for women (vs men), patients treated with injectable drugs alone (vs oral antidiabetic drugs alone), for patients with high levels of LDL cholesterol (reference < 2.5 mmol/l), for patients not given diabetes education (vs those given diabetes education), and for patients with comorbidities before Ramadan (vs those without).

A change in diabetes treatment regimen during Ramadan was more likely for patients being treated by other specialists (vs general practitioner), patients with a BMI > 25 kg/m^2 (vs ≤ 18.5 kg/m^2), patients on an injectable plus oral regimen (vs an oral antidiabetic drug alone) and patients with a

Table 5 Patient fasting practice during Ramadan

	Patients with Type 2 diabetes, *n* (%)
Total number of patients, *n* (%)	3250
Patients who fasted every day during Ramadan, *n* (%)	2043 (63.6)
Mean ± sd overall number of days fasted	27.2 ± 6.0
Fasted < 15 days, *n* (%)	187 (5.9)
Fasted ≥ 15 days, *n* (%)	3024 (94.2)
Fast outside of Ramadan, *n* (%)	967 (29.9)
Mean ± SD number of days fasted according to ADA risk status*	
Low risk	27.3 ± 6.0
Moderate risk	26.8 ± 6.1
High risk	27.2 ± 6.0
Very high risk	24.4 ± 7.9

ADA, American Diabetes Association.
*For the overall study population, including 144 patients with Type 1 diabetes.

Table 6 Hypoglycaemia during Ramadan

	Patients with Type 2 diabetes
Total number of patients	3250
Patients reporting at least one episode, *n* (%)	285 (8.8)
Number of episodes of hypoglycaemia, *n* (%)	524
Mean ± sd	1.8 ± 1.3
Range	1–9
Severity of hypoglycaemia, *n* (%)	
Necessitated stopping fast	249 (47.8)
Required assistance	268 (51.4)

pre-Ramadan HbA_{1c} level > 64 mmol/mol (8%) [vs < 48 mmol/mol (6.5%)].

There were no identifiable factors associated with the occurrence of complications during Ramadan.

Discussion

The CREED study provides an important update on the characteristics and management of patients with diabetes who chose to fast during Ramadan in 2010. The CREED study was not meant to replicate the landmark EPIDIAR study in either design or conduct. The two studies have notable differences, and comparison of results between the studies has limitations. To provide the present update, however, it was necessary to compare the results of the studies and report and discuss the differences observed.

While the EPIDIAR study focused on countries with predominantly Muslim populations from East/North Africa, the Middle East and Asia-Pacific countries, the CREED study also included European patients in countries with minority Muslim populations. The two studies were conducted in seven common countries.

The age of patients and time since diagnosis were similar in the two studies, 56.9 vs 54.0 years and 8.4 vs 7.6 years in the CREED and EPIDIAR studies, respectively. Patients in the CREED study presented with a higher BMI (28.7 vs 27.2 kg/m^2). The proportion of patients with Type 2 diabetes was slightly higher in the CREED than in the EPIDIAR study (95.8 vs 91.3%), perhaps because of the increasing prevalence of Type 2 diabetes [9], but perhaps also because of a difference in the age structure of targeted countries, which might have been influenced by the inclusion of European countries with older populations. Additionally, this could be a consequence of the CREED study inclusion criteria, whereby a greater proportion of patients with Type 2 diabetes intended to fast, compared with patients with Type 1 diabetes.

The three most frequent diabetes complications were the same for both studies, but the overall prevalence of each complication was lower in the CREED study (neuropathy, 19.8 vs 27.8%; retinopathy, 12.4 vs 19.7%; nephropathy, 11.1 vs 12.1%). The prevalence of two common comorbidities was higher in the CREED study (hypertension, 62.1 vs 48.8%; dyslipidaemia, 56.6 vs 32.5%). The lower prevalence of complications observed in the present cohort may be explained by changes in the management of patients with diabetes since the EPIDIAR study was conducted, but the bias introduced by the inclusion of countries with differential access to newer medications must also be considered.

To our knowledge, we are the first to report on physicians' perception of the risk of adverse events in patients with diabetes who fast during Ramadan. As noted earlier, an interesting finding was that there appears to be inter-country and perhaps regional differences in physician-perceived risk. In general, physicians in Europe reported a higher percentage of patients in the low- and medium-risk category (ranging from 64.9% in the UK to 84.8% in Germany) than physicians in Asia (ranging from 43.4% in Malaysia to 79.1% Indonesia). This might be explained by differences in baseline treatment regimens; for example, there was much higher use of sulphonylurea drugs in Malaysia (61.2% of all patients) compared with Germany (20.0% of patients); however, other factors, including the number and extent of baseline risk factors, may explain the difference.

The use of fasting-specific advice appears to have greatly increased. In all, 96% of investigators in the CREED study reported providing fasting-specific advice concerning self-care, in line with American Diabetes Association recommendations for pre-Ramadan educational counselling. When specific guidelines were referenced, ~40% of physicians reported using the American Diabetes Association 2005 and/or American Diabetes Association 2010 recommendations, which were not available to EPIDIAR investigators. By comparison, physicians in the EPIDIAR study reported that

Table 7 Logistic regression analysis to determine factors associated with increased risk of fasting < 15 days

	Univariate models						Multivariate model					
Variables	*N*	Events†	OR	[95% CI]	*P*	Global *P*	*N*	Events†	OR	[95% CI]	*P*	Global *P*
Type of diabetes						< 0.001*						
Type 1	144	27	–	–	–							
Type 2	3250	187	0.26	[0.17; 0.41]	< 0.001*							
Specialty of physicians						0.001*						< 0.001*
General practitioner	1171	50	–	–	–		389	16	–	–	–	
Endocrinologist	305	27	1.36	[0.80; 2.31]	0.257		199	22	4.04	[1.98; 8.26]	< 0.001*	
Diabetologist	489	33	0.63	[0.40; 0.98]	0.042*		227	16	2.17	[1.03; 4.61]	0.043*	
Internist	823	71	1.32	[0.86; 2.02]	0.210		369	39	2.51	[1.36; 4.66]	0.003*	
Other	552	32	0.87	[0.52; 1.43]	0.572		176	7	0.91	[0.36; 2.32]	0.846	
Location of the physician site						0.013*						
Office-based	1877	102	–	–	–							
Hospital-based	1451	111	1.43	[1.08; 1.88]	0.013*							
Sex of patients						0.002*						0.006*
Male	1647	81	–	–	–		684	38	–	–	–	
Female	1733	131	1.58	[1.18; 2.10]	0.002*		676	62	1.85	[1.19; 2.86]	0.006*	
Age of patients						0.152						
19–49 years	795	56	–	–	–							
49–57 years	854	41	0.67	[0.44; 1.02]	0.062							
57–64 years	861	54	0.90	[0.61; 1.32]	0.578							
64–96 years	854	63	1.06	[0.73; 1.53]	0.775							
BMI						0.087						
≤ 18.5 kg/m²	40	4	–	–	–							
18.5–25 kg/m²	748	64	0.57	[0.19; 1.66]	0.300							
25–30 kg/m²	1379	84	0.85	[0.29; 2.48]	0.772							
> 30 kg/m²	837	49	0.59	[0.21; 1.70]	0.329							
Diabetes treatment during Ramadan						< 0.001*						< 0.001*
OADs alone	2480	130	–	–	–		1013	66	–	–	–	
Injectable agents alone	265	44	0.28	[0.19; 0.40]	< 0.001*		93	19	3.87	[2.13; 7.06]	< 0.001*	
OADs + injectable agents	582	37	0.34	[0.21; 0.54]	< 0.001*		254	15	0.97	[0.53; 1.77]	0.919	
Diabetes education						0.006*						< 0.001*
No	1129	90	–	–	–		422	47	–	–	–	
Yes	2265	124	0.67	[0.51; 0.89]	0.006*		938	53	0.40	[0.25; 0.64]	< 0.001*	
Time from diagnosis, years	3045	196	1.00	[0.97; 1.02]	0.756	0.756						
Blood pressure before Ramadan						0.074						
Normal	351	30	–	–	–							
Prehypertension	1613	99	0.70	[0.46; 1.07]	0.099							
Stage 1 hypertension	906	46	0.57	[0.35; 0.92]	0.021*							
Stage 2 hypertension	380	30	0.91	[0.54; 1.54]	0.729							
LDL cholesterol						< 0.001*						0.002*
< 2.5 mmol/l	552	17	–	–	–		430	16	–	–	–	
≥ 2.5 mmol/l	1142	95	2.84	[1.68; 4.81]	< 0.001*		930	84	2.43	[1.38; 4.27]	0.002*	
HDL cholesterol						0.396						
< 1 mmol/l	486	28	–	–	–							
≥ 1 mmol/l	1187	82	1.21	[0.78; 1.89]	0.396							

Table 7 (*Continued*)

Variables	Univariate models						Multivariate model					
	N	Events†	OR	[95% CI]	*P*	Global *P*	*N*	Events†	OR	[95% CI]	*P*	Global *P*
Triglycerides						0.003*						
< 2.5 mmol/l	1798	99	–	–	–							
≥ 2.5 mmol/l	409	39	1.80	[1.22; 2.65]	0.003*							
Comorbidities before Ramadan						0.035*						0.033*
No	554	46	–	–	–		214	24	–	–	–	
Yes	2840	168	0.69	[0.49; 0.97]	0.035*		1146	76	0.57	[0.34; 0.96]	0.033*	

OR, odds ratio.
*$P \leq 0.05$.
†Number of patients who fasted for < 15 days during Ramadan.

62% of patients with Type 2 diabetes were provided with fasting- and diabetes-specific guidelines.

Oral anti-hyperglycaemic therapy alone was the predominant baseline therapy in the CREED study (76.6%), similar to that in the EPIDIAR study (78.4%); however, the use of oral monotherapy has decreased, while the use of two or more oral drugs in combination has increased, reflective of modern diabetes management. Approximately 25% of patients in the EPIDIAR study changed their pre-Ramadan oral anti-hyperglycaemic dose, while 35% of patients in the CREED study on oral therapy alone had a change in dose or frequency before Ramadan. Similarly, 35.9% of patients in the EPIDIAR study experienced some change in insulin dose, while ~ 50% of patients in the CREED study who were on injectable therapies had a change to their baseline regimen. Regardless of baseline therapy, when changes in pre-Ramadan regimens did occur, they were most often changes in period of administration, consistent with American Diabetes Association recommendations.

A total of 94% of patients in the CREED study reported fasting for ≥ 15 days during Ramadan, compared with 78.7% of patients in the EPIDIAR study. We have previously noted the many changes that have occurred since 2001 that certainly may have influenced the ability of a patient to complete his/her fast, but are unable to establish a causal relationship with any specific change.

We also believe we are the first to report on the extent of non-obligatory fasting outside of Ramadan. Notably, 30% of patients in the CREED study reported fasting outside of Ramadan, with significant inter-country differences ranging from 8% in India to 46% in Malaysia. It is important to note that a large number of patients fast frequently throughout the year and this should potentially be considered in ongoing patient management and treatment selection.

When compared with recent studies [10–12], the incidence of patient-reported hypoglycaemia in the CREED study during the month of Ramadan was low: 8.8% of patients reported at least one episode. Notably, however, these were prospective, often diary-based studies, primarily focused on event rates associated with sulphonylurea use, with or without a comparison with hypoglycaemia event rates associated with the use of dipeptidyl peptidase-4 inhibitors. Reported rates for hypoglycaemia ranged from 0.0 to 6.7% for dipeptidyl peptidase-4 inhibitors and from 13.2 to 41.7% for sulphonylurea therapy [10,12]. A more appropriate comparison might be made with a prospective observational study that also examined the role of drug therapy change, glucose monitoring and patient education on acute diabetic complications in patients with diabetes fasting during the month of Ramadan [13]. The authors reported a symptomatic hypoglycaemia rate of 6.36% and either improvement or non-deterioration in glycaemic control with fasting. In the CREED study, 61.2% of

Table 8 Logistic regression analysis to determine factors associated with changes in diabetes treatment regimen during Ramadan

	Univariate models						Multivariate model					
Variables	N	Events†	OR	[95% CI]	*P*	Global *P*	N	Events†	OR	[95% CI]	*P*	Global *P*
Type of diabetes						< 0.001*						0.036*
Type 1	144	72	–	–	–		91	48	–	–	–	
Type 2	3250	994	0.44	[0.32; 0.62]	< 0.001*		2008	629	0.56	[0.33; 0.96]	0.036*	
Specialty of physicians						0.016*						0.019*
General practitioner	1171	351	–	–	–		646	190	–	–	–	
Endocrinologist	305	105	0.98	[0.81; 1.19]	0.829		254	85	1.07	[0.77; 1.47]	0.698	
Diabetologist	489	150	1.38	[1.12; 1.71]	0.003*		368	109	0.90	[0.67; 1.20]	0.454	
Internist	823	243	1.03	[0.82; 1.30]	0.777		501	162	1.12	[0.87; 1.45]	0.388	
Other	552	205	1.23	[0.94; 1.60]	0.134		330	131	1.51	[1.13; 2.01]	0.005*	
Location of the physician site						0.480						
Office-based	1877	605	–	–	–							
Hospital-based	1451	451	0.95	[0.82; 1.10]	0.480							
Sex of patients						0.767						
Male	1647	521	–	–	–							
Female	1733	540	0.98	[0.85; 1.13]	0.767							
Age of patients						0.233						
19–49 years	795	241	–	–	–							
49–57 years	854	248	0.94	[0.76; 1.16]	0.571							
57–64 years	861	281	1.11	[0.90; 1.37]	0.310							
64–96 years	854	282	1.13	[0.92; 1.40]	0.238							
BMI						0.131						0.026*
≤ 18.5 kg/m²	40	16	–	–	–		19	11	–	–	–	
18.5–25 kg/m²	748	266	0.68	[0.36; 1.30]	0.244		499	177	0.41	[0.16; 1.07]	0.068	
25–30 kg/m²	1379	433	0.83	[0.43; 1.59]	0.569		976	306	0.35	[0.13; 0.91]	0.031*	
> 30 kg/m²	837	261	0.69	[0.36; 1.31]	0.251		605	183	0.31	[0.12; 0.80]	0.016*	
Diabetes treatment before Ramadan						< 0.001*						< 0.001*
- OADs alone	2490	691	–	–	–		1515	420	–	–	–	
Injectable agents alone	246	93	0.63	[0.48; 0.83]	< 0.001*		166	69	1.26	[0.83; 1.91]	0.273	
OADs +injectable agents	632	274	1.26	[0.93; 1.70]	0.135		418	188	1.92	[1.51; 2.43]	< 0.001*	
Diabetes education						0.323						
No	1129	342	–	–	–							
Yes	2265	724	1.08	[0.93; 1.26]	0.323							
Time from diagnosis, years	3079	957	1.02	[1.01; 1.03]	< 0.001*	< 0.001*						
Blood pressure before Ramadan						0.059						
Normal	351	100	–	–	–							
Prehypertension	1613	510	1.16	[0.90; 1.50]	0.251							
Stage 1 hypertension	906	281	1.13	[0.86; 1.48]	0.382							
Stage 2 hypertension	380	142	1.50	[1.10; 2.04]	0.011*							
HbA_{1c}						< 0.001*						0.002*
< 48 mmol/mol (6.5%)	431	111	–	–	–		358	93	–	–	–	
48–64 mmol/mol (6.5–8%)	1269	375	1.79	[1.39; 2.32]	< 0.001*		1078	325	1.19	[0.90; 1.56]	0.218	
> 64 mmol/mol (8%)	827	317	1.21	[0.94; 1.55]	0.132		663	259	1.60	[1.19; 2.15]	0.002*	
LDL cholesterol						0.274						
< 2.5 mmol/l	552	161	–	–	–							

Table 8 (*Continued*)

Variables	Univariate models N	Events†	OR	[95% CI]	*P*	Global *P*	Multivariate model N	Events†	OR	[95% CI]	*P*	Global *P*
≥ 2.5 mmol/l	1142	363	1.13	[0.91; 1.41]	0.274							
HDL cholesterol						0.373						
< 1 mmol/L	486	154	–	–	–							
≥ 1 mmol/L	1187	350	0.90	[0.72; 1.13]	0.373							
Triglycerides						0.655						
< 2.5 mmol/l	1798	560	–	–	–							
≥ 2.5 mmol/l	409	132	1.05	[0.84; 1.33]	0.655							
Comorbidities before Ramadan						0.841						
No	554	176	–	–	–							
Yes	2840	890	0.98	[0.81; 1.19]	0.841							

OR, odds ratio.
*$P \leq 0.05$.
†Number of patients with changes in diabetes treatment regimen during Ramadan.

patients had a recorded HbA_{1c} value in the post-Ramadan period: the mean was 58 mmol/mol (7.5%), which was similar to the pre-Ramadan mean of 60 mmol/mol (7.6%). Together, these two studies provide encouraging data to suggest that, with appropriate multiple-approach management, the majority of patients with diabetes who choose to fast during Ramadan can safely fast for the majority, if not all, of the month.

The present study has several limitations. The data are derived from a convenience sample of largely urban physician practices and included only patients with a physician visit both before and after Ramadan 2010. No data were collected on the characteristics and outcomes associated with patients who chose to fast but did not present to a healthcare professional before fasting. The retrospective observational design of the study is subject to recall bias and does not allow causal inferences. This might particularly affect the validity of patient-reported hypoglycaemia; however, we would argue that this bias is somewhat mitigated when looking specifically at hypoglycaemic episodes during Ramadan. In this case, patients may be acutely aware of past events, particularly those which required a break in fasting, as they would be required to compensate for the broken fast after Ramadan.

The present study provided an important update on the characteristics and management of patients with diabetes who chose to fast during Ramadan. Despite religious and medical guidance that may otherwise exempt some from the obligation to fast, a large number of Muslim patients will attempt to fast. A large number of patients can and do fast the majority, if not all, of the month of Ramadan. Nevertheless, we have identified variable uptake of methods of assisting in the management of these patients between individual countries. Identifying and removing barriers to uptake may allow even more patients to fast safely. In addition, there is some evidence to suggest that physicians may have different perceptions of the potential risk associated with prolonged fasting. Lastly, there is a large number of patients with diabetes who fast in a non-obligatory or intermittent fashion, again with much difference between countries.

There is still a need to explore physician and patient perceptions and practices to inform the evidence-based management of diabetes during fasting, both prolonged and intermittent, and to identify and address barriers to the universal uptake of methods to help manage those patients. We would encourage the use of clinical and/or well-designed prospective, observational trials to address these needs.

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Competing interests

S.M.B., D.T., K.S.B., A.T. and A.J. are employees of Eli Lilly and Company. M. H. has received honoraria for lectures and advisory boards from Eli Lilly, and honoraria for lectures from Takeda, Novo-Nordisk, Merck Sharpe & Dohme Ltd, Boehringer Ingelheim, Novartis, and Sanofi-Aventis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Characteristics and management of patients in CREED by country.