Evaluation of glycaemic control and diabetes treatment strategies during the religious fasting period of Ramadan

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Elaine Yin Lam Hui BSc MRCP

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Abstract

Evaluation of glycaemic control and diabetes treatment strategies during the religious fasting period of Ramadan

Ramadan is one of the longest periods of religious fasting. Muslims abstain from food and drink from sunrise to sunset for the month of Ramadan. In patients with diabetes, dietary changes during Ramadan can influence the glycaemic control. Since Ramadan is a key part of the Islamic faith, many Muslims with diabetes are willing to endure the hardship and choose to fast.

The thesis included discussions on the physiology and the practice of fasting in different religious groups. The current evidence for the optimum diabetes management during Ramadan was reviewed and recommendations were made based on randomised, comparison and observational studies and expert consensus.

The practice of fasting among pregnant women with diabetes was assessed in North West London in a questionnaire-based survey. Only 10% of women fasted. Having diabetes and hypoglycaemia were the likely deterrent factors. Imams (religious advisors) were as important as healthcare professionals in advising about fasting.

The glycaemic variability in patients with diabetes who followed the recommendations for optimal diabetes management was studied using continuous glucose monitoring. The glycaemic variability during fasting and non-fasting periods of Ramadan was similar, suggesting that pre-Ramadan assessment was useful in negating glycaemic excursions during Ramadan.

Changing to Humalog Mix 50 insulin at Iftar (sunset meal) in type 2 diabetes patients that were on twice daily Human Mixtard 30 insulin minimised their risk of hypoglycaemia without compromising their glycaemic control during Ramadan. The incretin-based therapies were more suitable than gliclazide when considering an add-on to metformin for type 2 diabetes patients who planned to fast for Ramadan.

In summary, the main aim of pre-Ramadan assessment and therapeutic adjustments is to allow patients with type 2 diabetes to fast safely during Ramadan.

Contents

Title Page			1
Copyright Declaration			2
Acknowledgements			3
Abstract			4
Contents			5-12
Chapter 1			13-32
Introduction			13
1.1	Overview of diabetes		13
1.2	Complications of diabetes		17
1.3	Religions and fasting		19
	1.3.1	Islam	19
		1.3.1.1 The month of Ramadan	20
		1.3.1.2 The impact of Ramadan fasting in the Northern Hemisphere	20
		1.3.1.3 Metabolic changes during fasting	21
		1.3.1.4 Effects of fasting on glycaemic control	24
		1.3.1.5 Risks of fasting for people with diabetes	24
		1.3.1.6 Effects of fasting on caloric intake	25
		1.3.1.7 Effects of fasting on weight and body mass index	26
		1.3.1.8 Effects of fasting on lipid profile	26
	1.3.2	Judaism	27
	1.3.3	Hinduism	29
	1.3.4	Buddhism	30
	1.3.5	Christianity	30
1.4	Aims		32

Chapter 2 33-45

Review of diabetes management during Ramadan 33

2.1 Management of people with diabetes planning to fast during Ramadan 33

2.1.1 Assessment before Ramadan 33

2.1.2 Ramadan focused education 34

2.2 Managing type 2 diabetes patients fasting for Ramadan 36

2.2.1 People taking oral hypoglycaemic agents 36

2.2.1.1 Metformin 36

2.2.1.2 Acarbose 37

2.2.1.3 Rapid acting insulin secretagogues 37

2.2.1.4 Sulphonylureas 38

2.2.1.5 Thiazolidinediones 40

2.2.1.6 Dipeptidyl peptidase-4 inhibitors 40

2.2.1.7 Glucagon-like peptide-1 receptor agonists 40

2.2.2 Patients taking insulin 41

2.2.2.1 Single basal insulin and oral combined treatment 41

2.2.2.2 Premixed insulins 42

2.3 Fasting during pregnancy 42

2.4 Managing type 1 diabetes patients fasting for Ramadan 43

Chapter 3 46-64

Fasting among pregnant women with diabetes during Ramadan 46

3.1 Health beliefs of Muslim women about Ramadan fasting during pregnancy 46

3.1.1 Fasting during Ramadan amongst healthy pregnant women 46

3.2 Effects of fasting in pregnancy in the non-diabetic population 48

3.3 Effects of fasting in pregnant population with diabetes 54

3.4 The practice of Ramadan fasting in pregnant women with diabetes 54

3.4.1 Methods 55

3.4.2 Results 56

3.4.3 Discussion 60

Chapter 4 65-78

Low glycaemic variability in type 2 diabetes subjects following pre-Ramadan assessment and adjustments for fasting during Ramadan 65

4.1 The role of continuous glucose monitoring for fasting people with diabetes 65

4.1.1 Glucose variability and diabetes complication risk 66

4.2 Impact of pre-Ramadan assessment on glycaemic variability: Methods 68

4.2.1 Subject characteristics 68

4.2.2 Study procedure and data collection 68

4.2.3 Outcome measures 69

4.3 Results 70

4.3.1 Individual glycaemic variability 70

4.3.2 Glycaemic variability during fasting and non-fasting periods 73

4.4 Discussion 75

4.5 Conclusion 78

Chapter 5 79-90

Glucagon-like peptide-1 receptor agonist and dipeptidyl peptidase-4 inhibitor therapies in type 2 diabetes patients during Ramadan 79

5.1 Incretin hormones: from physiology to therapeutic use during Ramadan 79

5.2 Glucagon-like peptide-1 receptor agonist and glycaemic control during Ramadan 81

5.2.1 GLP-1R agonist: Method 81

5.2.2 GLP-1R agonist: Results 82

5.2.3 GLP-1R agonist: Discussion 85

5.3 Dipeptidyl peptidase-4 inhibitor and glycaemic control during Ramadan 87

5.3.1 Hypoglycaemia 87

5.3.2 Safety and adverse events 89

5.3.3 Recommendations during Ramadan 90

Chapter 6 91-108

Insulin regimens in type 2 diabetes patients during Ramadan 91

6.1 Different options of insulin regimens during Ramadan 91

6.1.1 Switching insulin doses Suhur to Iftar, and vice versa 91

6.1.2 Long-acting insulin and oral hypoglycaemic agents 93

6.1.3 Once or twice daily neutral protamine hagedorn insulin 94

6.1.4 Basal bolus regimen 94

6.1.5 Mixed insulin regimens 95

6.1.6 Proposed insulin regimen – Mixtard 30 at Suhur, Humalog Mix 50 at Iftar 96

6.2 Comparison of Humalog Mix 50 with human insulin Mix 30 in type 2 diabetes patients during Ramadan 96

6.2.1 Aim 96

6.2.2 Methods 97

6.2.3 Results 99

6.2.4 Discussion 104

6.2.4.1 Hypoglycaemia 104

6.2.4.2 Weight Change 105

6.2.4.3 Glycaemic control 106

Chapter 7 109-121

Advances, challenges, and future directions in Ramadan research 109

7.1 Advances in research on Ramadan 109

7.1.1 Increasing awareness of Ramadan in medical conditions 109

7.1.2 Increasing awareness in Muslim and non-Muslim countries 110

7.1.3 Advances in diabetes research 111

7.1.3.1 Structured education for both healthcare professionals and patients 111

7.1.3.2 Evidence-based recommendations to Muslims with diabetes 113

7.2 Challenges in Ramadan studies 114
7.2.1 Geographical and cultural differences 114
7.2.2 Physiological adaptation during the month of fasting 115
7.2.3 Limitations and bias 116
7.3 Future directions in Ramadan research 117
7.3.1 The ‘Ramadan model’: initiation of lifestyle modification 117
7.3.2 Ramadan and other diabetes complications 118
7.3.3 Ramadan and cardiovascular outcomes 120
7.4 Summary and conclusion 121

References 122-146

Chapter 8 147-148
Appendix 1 147
Appendix 2 148
2.1 Declaration of originality 148
2.2 Supervision 148
2.3 Authors 148

Chapter 9 149
Publications 149

List of Tables

Chapter 1 Tables

1.1	Classification of the different types of diabetes mellitus depending on the causes of impaired glycaemia	17
1.2	The number of fasting hours during the month of Ramadan in consecutive years in the United Kingdom based on Greenwich Mean Time	21
1.3	A summary of the major fasting days across different religions	31

Chapter 2 Tables

2.1	Expert recommendations for risk stratification in patients with type 1 or type 2 diabetes who fast during Ramadan	34
2.2	Four key areas in Ramadan-focused education	35
2.3	An approach to oral treatment of type 2 diabetes in Ramadan	45

Chapter 3 Tables

3.1	A summary of the effect of Ramadan fasting in healthy pregnant women and their neonates	53
3.2	Characteristics of the pregnant women with diabetes	57
3.3	Characteristics of the women who fasted during pregnancy	57
3.4	Glycaemic control in the women who fasted during pregnancy	58
3.5	Experience of hypoglycaemia during previous Ramadan periods in non-fasting women	59
3.6	Comparison between the pregnant women with diabetes who fasted and who did not fast during Ramadan	59

Chapter 4 Tables

4.1	The baseline characteristics of the six participants who completed the continuous glucose monitoring during Ramadan	70
4.2	The adjustments in timing and dosage of the participants' medications pre-Ramadan and the mean tissue glucose during continuous glucose monitoring	71

4.3 Percentage of time spent above, within and below target glucose range 73
4.4 The parameters of blood glucose control and glycaemic variability of the participants during the fasting and non-fasting hours of Ramadan 74
4.5 The pros and cons of each measure of glycaemic variability 76

Chapter 5 Tables

5.1 Biological actions of endogenous GLP-1, GLP-1R agonist and DPP-4 inhibitor in relation to the pathophysiology of type 2 diabetes 80
5.2 Baseline characteristics of the participants 82
5.3 Changes in outcome measures during Ramadan in participants taking exenatide and gliclazide with or without metformin 84

Chapter 6 Tables

6.1 Suggested changes in insulin regimens during Ramadan 92
6.2 Baseline characteristics of the participants 101
6.3a Change in outcome measures during Ramadan in participants receiving Mix 30 before sunrise and Mix 50 after sunset (the Mix 50 group) 102
6.3b Change in outcome measures during Ramadan in participants receiving Mix 30 twice daily (the Mix 30 group) 102
6.4 The onset and duration of different insulins 108

Chapter 7 Tables

7.1 Article metrics: an indication of how often the Ramadan review article has been assessed month by month 112

List of Figures

Chapter 3 Figure

3.1	Percentage of healthy women fasted during pregnancy	48

Chapter 5 Figures

5.1	The mean changes in HbA1c	83
5.2	The mean changes in weight	84

Chapter 6 Figures

6.1	HbA1c (%) of the Mix 50 group before and after Ramadan	103
6.2	Weight (kg) of the Mix 50 group before and after Ramadan	103
6.3	HbA1c (%) of the Mix 30 group before and after Ramadan	103
6.4	Weight (kg) of the Mix 30 group before and after Ramadan	104

Chapter 1: introduction

1.1 Overview of Diabetes

Diabetes Mellitus is a group of metabolic disorders resulting in hyperglycaemia due to defects in insulin secretion and/or insulin action. The long-term effects of hyperglycaemia include damage to multiple organs, in particular, the heart, kidneys, eyes, nerves, and blood vessels.

The earliest descriptions that resembled the features of diabetes were found in the Ebers papyrus (1550 BC), the ancient Egyptian document relating to the practice of medicine. During the 9^{th} – 11^{th} centuries AD, Arabian physician, Shaikh-Ul-Rais Bu Ali Ibne Sina (960 – 1037 AD) described the clinical features of diabetes and noted two complications of the disease, namely gangrene and sexual dysfunction. Another Arabian physician, Musa Bin Maimoon (1135 – 1209 AD), proposed that diabetes was caused by the sweet water of river Nile. The term 'diabetes' was first coined by Aretaeus (81 -138 AD), meaning to 'Siphon' – a melting down of the flesh and limbs into urine. Thomas Willis (1621 – 1675 AD) added the term 'mellitus', observing the presence of sugar in the urine and blood of diabetes patients[1].

In modern times, the diagnostic criteria of diabetes mellitus is based on glucose criteria, either the fasting plasma glucose (FPG), or the 75-g oral glucose tolerance test when blood is taken for glucose determination at baseline and 2 hours after a 75 grams of oral glucose challenge. Its diagnosis was previously made according to the World Health Organisation (WHO) criteria using a FPG and subsequent 75-g OGTT as updated in 2006[2], or the American Diabetes Association (ADA) criteria as updated in 2005[3]. The WHO criteria classified diabetes mellitus as a FPG $\geq$ 7.0

mmol/l (126 mg/dl) or a 2-hour venous plasma glucose ≥ 11.1 mmol/l (200 mg/dl). More recently, the International Expert Committee of the ADA issued a statement proposing an HbA1c level of 6.5% (48 mmol/mol) as a diagnostic level for the diagnosis of diabetes mellitus. The cut-point of 6.5% was chosen as levels above 6.5% were associated with an increased incidence of diabetes retinopathy[4], as are the diagnostic threshold for FPG and 2-hr PG[4]. Subsequently, the ADA has updated its diagnostic criteria of diabetes to include: FPG 7.0 mmol/l (126 mg/dl), or a 2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl), HbA1c > 6.5% , or having symptoms of hyperglycaemia with a random plasma glucose of ≥ 11.1 mmol/l (200 mg/dl)[5]. The test should be performed in a laboratory using a method that is National Glycohaemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. The use of HbA1c as a diagnostic test has the advantages of not relying on a fasting sample and smaller intra-individual measurement variability. However, HbA1c measurements can be misleading in conditions that alter red cell survival, such as haemoglobinopathies, anaemia (both iron deficient and haemolytic anaemias), and renal failure. Another disadvantage is the discrepancies in HbA1c between individuals from different races and also individuals of different ages.

Type 1 diabetes is caused by the autoimmune destruction of the β-cells of the pancreas, leading to absolute insulin deficiency. The autoimmune destruction of the β-cells is characterised by the presence of islet cell auto-antibodies, glutamic acid decarboxylase (GAD 65) antibodies, autoantibodies to insulin and tyrosine phosphatase IA-2, IAA. These autoantibodies are present in 85-90% of individuals at the onset of fasting hyperglycaemia. Zinc T8 autoantibodies were found in 26% of type 1 diabetes subjects previously classified as autoantibody-negative on the basis

of other markers (GAD, IA-2, IAA, ICA)[6]. Absolute insulin deficiency manifests clinically as hyperglycaemia and ketoacidosis. Individuals usually present in childhood or adolescence, but can present at any age. The rate of β-cell destruction is also variable among individuals, with some patients dependent on insulin for survival at the outset, and others may retain sufficient β-cells function to prevent ketoacidosis for years.

Type 2 diabetes results from a combination of insulin resistance and relative insulin deficiency of varying degrees. It accounts for 90 – 95% of adults with diabetes. Autoimmune destruction of β-cells does not occur, but specific causes for this type of diabetes are unknown. It is often associated with obesity which leads to insulin resistance. Adequate glycaemic control can be achieved with weight loss, physical exercise, with or without oral anti-diabetic medication. Insulin is not required for survival, at least in the early stage of the disease, but is sometimes needed later on in patients with poor glycaemic control. Ketoacidosis does not usually occur in patients with type 2 diabetes, but some patients, such as those from African origin, can present in a subtype of diabetes known as ketosis-prone atypical diabetes. It is characterised by ketosis or ketoacidosis at presentation in individuals with an otherwise type 2 phenotype. Insulin-free near-normoglycaemia is achieved by oral hypoglycaemic agents after initial insulin treatment within days or weeks. Islet cell auto-antibodies are absent but the cause of the acute onset and remission is not fully elucidated. Viral infections, such as human herpes virus 8, may contribute to the acute presentation of ketosis-prone diabetes[7]. On the other hand, patients who were initially diagnosed as type 2 diabetes but presented with ketoacidosis may actually be unrecognised latent autoimmune diabetes in adults (LADA). It is characterised by

adult onset, presence of islet cell auto-antibodies, and rapid decline in β-cell function, requiring long-term insulin treatment shortly after diagnosis (Table 1.1).

Gestational diabetes (GDM) arises during pregnancy, usually in the second or third trimester and resolves after delivery. If untreated, GDM is associated with adverse maternal and foetal outcomes such as foetal malformation, macrosomia and pre-eclampsia. The number of undiagnosed patients with type 2 diabetes presenting in early pregnancy is also on the rise, as the ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age.

Other types of diabetes include: 1) maturity-onset diabetes of the young (MODY), characterised by monogenic defects in β-cell leading to impaired insulin secretion and the absence of islet cell auto-antibodies. Patients present at an early age, usually before 25 years of age, and are treated with sulphonylurea, which facilitates insulin secretion in MODY cases involving mutations in the genes encoding hepatocyte nuclear factor 1 homeobox A (HNF1A) and 4 (HNF4); 2) diseases that structurally damage the pancreas can also lead to diabetes, such as pancreatitis, cystic fibrosis, and haemochromatosis; 3) Endocrinopathies that are diabetogenic such as Acromegaly, Cushing's syndrome and glucagonoma. These diseases resulted from an excess in hormones that antagonise insulin action, namely growth hormone, cortisol and glucagon respectively. Patients with any types of diabetes may require insulin at some stage of their disease. Table 1.1 summarises the classification of diabetes mellitus according to the aetiology of the glycaemic impairment.

Types of Diabetes Mellitus	Aetiology	Insulin requirement
Type 1	β cell destruction	Absolute insulin deficiency
Type 2	Insulin resistance and insulin secretory defect of variable degrees	May require insulin for glycaemic control at a later stage
Other specific types: - Genetic defects of β cell function (Mature onset diabetes of the young, MODY)	Monogenic defects in genes, such as: hepatic nuclear factor-4 (MODY 1), glucokinase (GCK) (MODY2), hepatic nuclear factor-1A (MODY 3), insulin promoter factor (MODY4), mitochondrial DNA	Generally not requiring insulin: - Sensitive to sulphonylurea in HNF1A and HNF4 - Mild hyperglycaemia not requiring treatment in GCK - Require insulin at later stage and avoid metformin due to lactic acidosis in mitochondrial dysfunction
- Latent autoimmune diabetes in adults (LADA)	Autoimmune β cell destruction with variable progression of β cell failure from months to years	Require insulin for glycaemic control after initial insulin-free period
- Diseases of exocrine pancreas	Chronic pancreatitis, pancreatectomy, cystic fibrosis, haemochromatosis	Likely requiring insulin for glycaemic control
- Endocrinopathies	Excess hormones antagonising insulin action: Acromegaly (growth hormone) Cushing's syndrome (cortisol) Glucagonoma (glucagon) Phaeochromocytoma (catecholamines)	Likely requiring insulin for glycaemic control
Gestational Diabetes	Any degree of impaired glucose tolerance during pregnancy	May require insulin for control

Table 1.1 Classifications of the different types of diabetes mellitus depending on the causes of impaired glycaemia. (adapted from American Diabetes Association position statement, 2010[5]).

1.2 Complications of diabetes

Acute complications of uncontrolled diabetes include hyperglycaemia with ketoacidosis and (HHS) hyperosmolar non-ketotic state. Chronic hyperglycaemia leads to microvascular complications, namely retinopathy with threatening loss of vision; nephropathy leading to renal failure; peripheral neuropathy resulting in foot ulcers, amputations, and Charcot joints. Diabetes-related autonomic neuropathy can affect gastrointestinal delay, bladder instability and cardiovascular symptoms and sexual dysfunction. Macrovascular complications, including atherosclerotic

cardiovascular, peripheral arterial and cerebrovascular disease, account for morbidity and mortality in patients with uncontrolled diabetes.

The UK Prospective Diabetes Study (UKPDS) is a landmark multicentre randomised trial to study the glycaemic treatments of newly diagnosed type 2 diabetes patients. Over the course of 20 years, it has shown that intensive blood-glucose control with sulphonylurea or insulin, as compared to conventional treatment, reduced the risk of 'any diabetes-related endpoint' by 12% and microvascular disease by 25%[8]. The mean haemoglobin A1c (HbA1c) was 7.0% (53 mmol/mol) in the intensive-control group and 7.9% (63 mmol/mol) in the conventional-control group at the end of the follow-up period. Furthermore, intensive glucose control with metformin had risk reduction of 32% (95% CI 13-47, p=0.02) for any diabetes-related endpoints, including macrovascular complications and is associated with less weight gain and lower incidence of hypoglycaemia than insulin and sulphonylureas[9].

However, recent studies on the effect of intensive blood glucose control on cardiovascular outcomes have opened the debate on the optimal glycaemic target. In the ACCORD study[10], type 2 diabetes patients with either established cardiovascular disease or additional cardiovascular risk factors, targeting the blood glucose control to an HbA1c of less than 6% led to higher all-cause mortality, compared to targeting an HbA1c value of 7.0% - 7.9%. One of the reasons for the excess mortality is the higher risk of death from cardiovascular causes in the intensive-therapy group compared to the standard-therapy group in the treatment period of 3.7 years and in the follow-up period where both groups were treated in the standard approach targeting HbA1c of 7.0% - 7.9%[11].

Several other randomised control trials, such as ADVANCE[12] and VADT[13], did not find significant difference between the intensive and conventional glucose control groups in the incidence of cardiovascular events or all-cause mortality. However, non-glycaemic cardiovascular risk factors, such as lipid control, were not optimally controlled in the ACCORD study and VADT's study population was predominantly men.

It has become clear that an intensive treatment strategy should be initiated at an early stage of diabetes. In patients with long duration of diabetes or with established complications, it may be more reasonable to continue conventional control due to the increased cardiovascular risk associated with intensive treatment approach and weight gain associated with intensive augmentation with insulin therapy. Individual circumstances and the side effects of hypoglycaemic agents should be taken into account in the diabetes management on an individual basis.

1.3 Religions and fasting

One of the individual circumstances that can influence the management of diabetes includes fasting for religious reasons.

1.3.1 Islam

Islam is the second largest religion in the world with over 1 billion followers. 1,591,000 Muslims were recorded in the 2001 UK census, around 2.7% of the population. The Islamic month of Ramadan is one of the longest periods of fasting. The holy month of Ramadan is one of five main pillars of Islam.

The Five Pillars consist of:

- Shahadah: reciting the Muslim profession of faith
- Salat: performing ritual prayers five times each day
- Zakat: paying an alms (charity) tax to benefit the poor and the needy
- Sawm: fasting during the month of Ramadan
- Hajj: pilgrimage to Mecca

1.3.1.1 The month of Ramadan

Fasting during Ramadan involves abstaining from food and drink from dawn to sunset for approximately 30 days as it is based on a lunar calendar. Most people take two meals a day during Ramadan - Suhur (the meal before dawn) and Iftar (the meal after sunset). Although the Koran exempts sick people from the duty of fasting[14], many Muslims with diabetes may not perceive themselves as sick and are keen to fast. The majority of Muslim people with diabetes are passionate about fasting. A large epidemiological study of Muslims with diabetes in 13 Muslim countries (n=12,243), the EPIDIAR study, showed that 43% of patients with type 1 and 79% of those with type 2 diabetes fasted during Ramadan[15].

1.3.1.2 The impact of Ramadan fasting in the Northern Hemisphere

As the month of Ramadan follows the lunar calendar, the fasting month is brought forward by about 10 days each year, which means that the season in which Ramadan falls into, changes over time. For the next decade Ramadan will fall in the summer in the northern hemisphere (Table 1.3). As daylight hours vary considerably between summer and winter months in non-equatorial countries, the length of the fast (which lasts from dawn to sunset) increases in the summer to about 16-20

hours. People with diabetes who fast are at risk of adverse events and the risks may increase with longer fasting periods.

Year	Start date of Ramadan	Time fasting starts	Time fasting ends	Number of fasting hours
2000	28th November	05:40	15:58	10:18
2001	17th November	05:26	16:09	10:43
2002	6th November	05:10	16:25	11:16
2003	26th October	04:53	16:45	11:52
2004	15th October	05:35	18:08	12:33
2005	4th October	05:17	18:32	13:15
2006	23rd September	04:57	18:57	14:00
2007	13th September	04:37	19:20	14:43
2008	1st September	04:11	19:47	15:36
2009	22nd August	03:45	20:09	16:24
2010	11th August	03:10	20:33	17:23
2011	31st July	02:45	20:50	18:05
2012	20th July	02:38	21:07	18:29
2013	9th July	02:33	21:17	18:44

Table 1.2 The number of fasting hours during the month of Ramadan in consecutive years in the United Kingdom based on Greenwich Mean Time (Adapted from www.Ramadantimetable.co.uk).

1.3.1.3 Metabolic changes during fasting

Fasting involves partial or total abstinence from all oral intakes, or select abstinence from prohibited food. The response of fasting will depend on the size and the composition of the meal that is last ingested before fasting begins.

The initial stage of fasting is the post-absorptive period, which starts when all the ingested nutrients at the last meal have been absorbed from the small intestine. This can occur as soon as 3 – 4 hours or as long as 7 – 8 hours depending on the amount and type of food in the meal. It lasts for about 24 hours as the body adjusts to the absence of nutrients. Blood glucose is maintained in normal individuals as the liver glycogen store is hydrolysed and released as glucose into the circulation[16]. As the liver glycogen store is depleted, blood glucose begins to fall. This results in

hormonal changes, including a reduction in plasma insulin concentration and stimulation of glucagon, catecholamines, growth hormone, thyroid-stimulating hormone and corticosteroids. The net result is gluconeogenesis, a process to generate glucose from non-carbohydrate substrates. Substrates for gluconeogenesis include the carbon skeletons of some amino acids, lactate released by glycolysis in red blood cells and the glycerol released from adipose tissue.

The rate of carbohydrate utilisation is decreased in the fasted state and the rate of fat oxidation increases to meet energy demand. The limited carbohydrate store is reserved for the central nervous system and the erythrocytes, which rely solely on carbohydrate metabolism. Triglycerides reserve within the adipose tissue is mobilised in the process of lipolysis, leading to an increase in the circulating free fatty acids in the plasma that is available to the body as a source of fuel.

After a few days of fasting, ketone bodies, which are derived from the conversion of fat breakdown products, are increasingly used as a fuel as they can cross the blood-brain barrier to be used by the brain cells for energy.

While religious fasts are partaken mainly for spiritual purposes, they can potentially affect one’s physical health. In patients with diabetes, changes in meal frequency, daily physical activities and sleeping patterns during these religious fasts may influence the glycaemic and other biochemical parameters.

Intermittent fasting occurs during Ramadan. Food and drink are abstained during daylight hours on repeated days for a month, with no restrictions on intake during the hours of darkness.

A change in the timings of meals during Ramadan is accompanied by changes in circadian pattern. Studies on sleep patterns have demonstrated significant delays in bedtime and wake-up time during Ramadan in healthy subjects[17;18]. Body temperature, as a marker of circadian pattern, normally falls during sleep and rises at wake time. During Ramadan, there is a significant rise in body temperature at 23:00 and 00:00 hours and a significant reduction in daylight hours (09:00, 11:00, 13:00, and 16:00 hours), as compared to non-fasting period[19]. Melatonin, also a marker of circadian rhythm, has been shown to have a delayed night peak and a flatter slope of serum melatonin rise during Ramadan[20], which may be due to prolonged exposure to artificial light during Ramadan.

Changes in meal timing and daytime fasting have been shown to induce changes in the rhythmic patterns of various endocrine hormones, as compared to pre-Ramadan days[20]. During the non-Ramadan day (meals at 08:00, 12:00 and 19:00), serum cortisol levels rose during the early hours since midnight and peaked at 08:00, then gradually fell during the day. During the Ramadan day (meals at 19:00 and 01:00), there were two peaks, one at 8:00 and the other at 20:00 in the evening, i.e. at the time of the first meal following the daytime fasting period. In addition, there was a slower rise but higher morning peak during Ramadan than on the control day. This pattern is consistent with findings in subjects on a five-day total fast (water only), which showed a delayed maximum cortisol concentrations and increase in the mass of the glucocorticoid secretory bursts[21]. Prolactin also exhibited similar biphasic peaks at 08:00 and 20:00 during Ramadan[20].

Leptin, produced and secreted from fat adipocyte tissue, has a key role in regulating appetite and energy expenditure. It acts in the hypothalamus. When fat mass

increases, plasma leptin level increases, thus inhibiting food intake and increasing energy expenditure through integrated pathways of the hypothalamic neural circuits. Neuropeptide Y is one of the orexigenic hormones. Reduction in neuropeptide Y activity is associated with decrease in food intake. Fasting serum leptin levels were significantly raised and neuropeptide Y levels were reduced in healthy subjects fasting during Ramadan[22].

Periods of religious fasting are usually followed by celebratory feasting. Eid ul-Fitr marks the end of Ramadan and is usually celebrated with 3 days of prayers, family gatherings, and feasting with traditional Eid food such as murgh mussallam and mrouziya.

1.3.1.4 Effects of fasting on glycaemic control

Most Muslim religious authorities accept that if a person is advised by a trusted health professional, such as a doctor or nurse, that fasting is harmful to his or her health, then that person is exempted from fasting[23]. Several studies on people with diabetes, either diet controlled or on oral hypoglycaemic agents, have demonstrated no change in HbA1c or fructosamine levels[24;25] during Ramadan. Others have shown improvement[26] or deterioration[27] in glycaemic control in people taking oral hypoglycaemics or insulin during Ramadan. However, it is the variation in glycaemia leading to severe hypo- and hyperglycaemia that is the main issue for people with diabetes fasting for Ramadan.

1.3.1.5 Risks of fasting for people with diabetes

The risks of fasting include hypoglycaemia, hyperglycaemia, and dehydration. The EPIDIAR study found that the change in eating patterns during Ramadan increased

the risk of severe hypoglycaemia 4.7-fold (from 3 to 14 events per 100 people per month) in type 1 diabetes and 7.5-fold (from 0.4 to 3 events per 100 people per month) in type 2 diabetes. It also found a fivefold increase in the incidence of severe hyperglycaemia in patients with type 2 diabetes during Ramadan. A small observational study (n=41) conducted in 1998 found an increase in symptomatic hypoglycaemia[28], but other studies have not found a significant increase in the risk of hypoglycaemia during Ramadan in patients treated with oral hypoglycaemic medications or insulin[27;29]. One explanation for different findings among studies is that because Ramadan occurs in a different season every nine years, and the duration and temperature of fasting days change, rates of hypoglycaemia may vary according to the year in which the study was performed. The differences in methods and the small number of patients included in these studies would also explain the disparity of the results. Furthermore, the baseline HbA1c or fructosamine levels in the studies were not the same and the interventions instituted in the studies were different[28-30]. This would also explain the disparate results of hypoglycaemic rates.

1.3.1.6 Effects of fasting on caloric intake

Even though people abstain from any oral intake from sunrise to sunset, they take considerable amount of sweet and fried foods traditionally prepared for Ramadan during non-fasting hours, especially at the Iftar meal. An increase in daily caloric intake during Ramadan has been shown in healthy subjects[31;32]. However, some studies reported a decrease in daily caloric and carbohydrate intake in type 1 and type 2 diabetes patients[26;33]. These discrepancies between healthy and diabetes subjects may be due to diabetes patients being more health conscious about limiting their total food and carbohydrate intake. It could also be explained by the food habits

in different Islamic countries, as the former studies on healthy subjects were conducted in Tunisia and Algeria[31;32], whereas the latter relating to diabetes patients were performed in Malaysia[26;33].

1.3.1.7 Effects of fasting on weight and body mass index

In 120 well-controlled type 2 diabetes patients on diet or oral hypoglycaemic medications, weight and body mass index did not change before and fifteen days after Ramadan after receiving dietary advice and adjustment of the timing of their medications[34]. However, in type 2 diabetes women with high body mass index (BMI> 30kg/m^2), fasting during Ramadan resulted in a significant weight loss (-3.12 kg; $p < 0.01$), a decrease in meal frequency (from 4.3 ± 0.4 before to 2.2 ± 0.3 meals during Ramadan) as well as in energy intake (1823 ± 262 to 1488 ± 118 Kcal/d; $p < 0.001$)[35].

1.3.1.8 Effects of fasting on lipid profile

It was postulated that physiological adaptations during the month of fasting lead to an increase in reliance on fat as a source of fuel during daytime fasting[36]. In obese type 2 diabetes women, dietary fat consumption increased (from 25.36% before to 35.84% during Ramadan), especially saturated fats (231Kcal/d i.e. 43.25%) [35]. Total cholesterol intake, as well as total and LDL cholesterol concentration, also increased significantly in non-obese type 2 patients (n = 57)[37] and in type 2 patients with hyperlipidaemia on diet, fibrates or statins[38].

Over the coming decade, the number of fasting hours will progressively increase in the northern hemisphere as Ramadan falls in the summer months. This will have important implications for Muslims with diabetes who wish to fast. Hence, it is

important that both patients and their healthcare professionals are aware of the implications of Ramadan fasting in order to provide systematic advice on treatment adjustment to empower the patients in self-management of their disease.

1.3.2 Judaism

The world's Jewish population was estimated at 13,428,300 in 2010. Israel and the United States accounted for 82% of the total[39]. Europe has the largest estimated core Jewish population outside of North America and Israel, with an estimated 2.2 Jews per 1000 total population. The United Kingdom has a core Jewish population of 292,000, which included people that identified themselves as Jews in socio-demographic surveys; or who are identified as Jews by a respondent in the same household, and do not have another monotheistic religion.

The prevalence of adult-onset diabetes (diabetes presenting at $\geq$ 20 years of age) was 12% among Jews in Israel[40]. In the Ashkenazi Jewish population, single nucleotide polymorphisms (SNPs) in the hepatic nuclear factor 4A (HNF-4A) and Wolfram syndrome (WF1) genes were associated with predisposition for type 2 diabetes[41;42]. The unadjusted odds of being affected with Type 2 diabetes were 3 times greater in subjects with the HNF4A and WFS2 risk alleles than those without either[42].

Yom Kippur, the Day of Atonement, is one of the major annual fasting days in Judaism. No food and drink is consumed for twenty-five hours from sunset on the eve of the day to the dusk of the following day. All Jewish males 13 years or older and all females 12 years or older are required to fast. However, the Jewish law

exempts patients from fasting if it endangers their health[43]. Halakhic authorities (experts in Jewish law) recommend that all patients with diabetes who intend to fast should consult their doctors for assurance that fasting is safe and forbid type 1 diabetes patients to fast on Yom Kippur[44]. Yom Kippur differs from other Jewish fast days in that drawing blood and using electrical devices (such as blood glucose meters) are prohibited, unless needed to preserve sanctity of life[45]. If patients with diabetes decided to fast during Yom Kippur, it has been suggested that blood glucose monitoring should be done only if there are hypoglycaemic symptoms or upon arising on the morning of fast if there is a history of hypoglycaemic unawareness. Nonetheless, recent recommendations from Rabbis and diabetes specialists advocated that the use of capillary blood glucose testing with electronic meters during Yom Kippur is permissible in type 1 and type 2 diabetes patients when performed appropriately for patients' welfare and health[45;46]. Apart from the risk of hypoglycaemia, dehydration and subsequent hypotension may also compromise the 25-hour fast in patients with diabetes. If a patient with diabetes feels strongly about proceeding to fast despite physicians' advice not to, a compromise position may be recommended by the rabbi, whereby small quantities of food or drink can be taken at specified intervals throughout the day of Yom Kippur, rather than three daily meals[45].

Many Jews also observe additional fasts (tzomot) throughout the year. In Tisha B'Av, the ninth day of the month of Av in the Hebrew calendar, fasting also occurs for 25-hours from sunset to sunset. The other fasting days observed during the year mainly last from sunrise to sunset, i.e. daytime-only fast, namely the 10th of Tevet (Asarah B'Tevet); the fast of Tammuz; the fast of Gedaliah; and the fast of Esther.

1.3.3 Hinduism

Hinduism is the religion of over 900 million adherents worldwide with the majority in India and Nepal[47]. There are many festivals in Hinduism, with periods of feasting and fasting from one to nine days based on the lunar calendar. Fasting also varies from total abstinence of food and drink to omitting certain meals of the day or limiting some types of food. For instance, Monday is dedicated to the God Shiva when devotees of Shiva observe a fast all night and break the fast the next morning, and eat the food offerings (made from fruits of the season, root vegetables, and coconuts) offered to Shiva. Fasting on Tuesdays honours the Goddess Mariamman in Southern India, when devotees only have liquid, but not solid food, from sunrise to sunset. In Northern India, Tuesday fast is dedicated to Lord Hanuman, when only milk and fruit are allowed to be consumed between sunrise and sunset (Table 1.2).

The 2001 U.K. census recorded 559,000 Hindus, around 1% of the population in Britain. The prevalence of diabetes mellitus has rapidly increased in India in the past decades and a similar trend has been observed in South Asian migrants compared with other ethnic groups in host countries[48]. Understanding of the cultural practices of fasting and feasting is important to manage these people with diabetes or with high risk of developing diabetes and to prevent acute complications. For instance, appropriate advice about hypoglycaemia to patients who only takes beverages during fasting days is important to improve self-management of diabetes. Morning insulin doses may need to be reduced if the lunchtime meal is omitted when fasting for these festivals and evening doses may be increased during post-fast meals.

1.3.4 Buddhism

The two major sects of Buddhism are Theravada (mainly in Thailand, Cambodia and Sri Lanka) and Mahayana Buddhism (mainly in Tibet, China, Korea and Japan). All branches of Buddhism practice some periods of fasting, usually on full-moon days, as a method of purification. On the days of observance, the Uposatha days, lay Buddhists and monks observe the eight precepts usually once a week, which includes abstaining from eating after noon until the following day. High scores for Buddhist values were found to be correlated with better medication and dietary self-care in non-insulin dependent diabetes patients in Thailand[49].

1.3.5 Christianity

The largest proportion of religious affiliates in the U.K. still belonged to the Church of England, representing 20% of the respondents of the British social attitudes survey[50].

Fasting usually occurs in Lent; a forty-day period to commemorate the fast observed by Jesus Christ during his temptation in the desert and is marked by the period between Ash Wednesday and Easter. In the Roman Catholic Church, abstinence from meat is observed on Ash Wednesday and every Friday during Lent. For Eastern Orthodox and Greek-Catholic Christians, fasting during Lent includes refraining from all animal and dairy products for the entire period of Lent.

Religion	When they fast	How they fast	Why they fast
Islam	Ramadan, 9th month of the Muslim calendar	Abstain from food and drink from sunrise to sunset for the month of Ramadan	Commemorates when the Koran was first revealed to the Prophet Muhammad
Judaism	Yom Kippur and Tisha B'Av are the major days of fasting. Other days include Asarah B'Tevet, Tzom Tammuz, Tzom Gedaliah, Tzom Esther	On Yom Kippur and Tisha B'Av, food and drink is prohibited for a 25-hour period, from sunset to sunset. On other fast days, food and drink is prohibited only from sunrise to sunset.	Yom Kippur is the day of Atonement; Tisha B'Av is the day of the destruction of Jewish Temples
Hinduism	On days of new moon and during various festivals, e.g. Shivaratri, Saraswati Puja, and Durga Puja	Fasting varies from total abstinence from food and drink for 24-hours to abstinence from solid food, or particular food, e.g. meat or eggs	For the purpose of purification, meditation and sacrifice
Buddhism	On days of full moon and other days in general, depending on different sects of Buddhism	Abstain from solid food	For the purpose of purification and meditation
Christianity	Ash Wednesday, Good Friday, and all Fridays in Lent	Abstain from meat	Lent is the period between Ash Wednesday to Easter Sunday. Good Friday commemorates the day Christ died
Eastern Orthodox	Lent, Apostles' Fast, Dormition Fast (1st – 14th August), and the Nativity Fast (15th November – 24th December), and several fast days (Every Wednesday and Friday is a fast day)	Abstain from meat, dairy products and eggs on the day of fast. Fish is forbidden on some fast days.	Fast strengthens resistance to gluttony
Baha'i	Ala, the 19-day fast, from March 2 - 20	Abstain from food from sunrise to sunset	To reinvigorate the soul and bring a person closer to God

Table 1.3 A summary of the major fasting days across different religions

1.4 Aims

- To review the current evidence for optimum management of diabetic patients who wish to fast during Ramadan and to draw up recommendations for optimal diabetes management during Ramadan (chapter 2).
- To examine the practice of fasting amongst specific groups of Muslim patients with diabetes, in particularly pregnant women (chapter 3).
- To evaluate the impact of the pre-Ramadan assessment on glycaemic variability using continuous glucose monitoring (chapter 4).
- To evaluate the safety and efficacy, in terms of hypoglycaemic events and glycaemic control, of using the newer diabetic agents, including glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, as well as insulin treatments for patients with type 2 diabetes during Ramadan (chapter 5 and 6).
- To review the advances and challenges in the research on Ramadan fasting (chapter 7).

Chapter 2: Review of Diabetes Management during Ramadan

The evidence for optimum management of diabetic patients who wish to fast during Ramadan is reviewed in this chapter, drawing on a small evidence base comprising randomised trials, non-randomised comparison studies, and observational studies. This is combined with recommendations based on expert consensus.

2.1 Management of people with diabetes planning to fast during Ramadan

2.1.1 Assessment before Ramadan

Expert opinion recommends that if a patient has made it clear that they wish to fast during Ramadan, their primary care physicians and/or diabetes care specialists should assess whether they increase their health risk by doing so[51]. Table 2.1 outlines how patients planning to fast during Ramadan may be categorised as high, moderate, or low risk of adverse events. Patients classed as high risk are advised not to fast as it can lead to worsening diabetes control, resulting in, for example, severe hypoglycaemia and diabetes ketoacidosis. Patients at moderate risk can reduce their level of risk if they see a healthcare professional several months before Ramadan and make necessary changes to their diabetes treatment. Those at low risk can fast without healthcare advice. Patients who choose to fast despite advice not to do so need support to help them fast as safely as possible. It is worth noting that the ADA pre-Ramadan risk stratification is mainly based on expert opinions, rather than evidence-based research. More studies on the safety of fasting on subgroups of Muslims, such as patients with renal transplant or cardiac disease[52;53], are emerging and will help to refine the risk stratification profile for specific groups of

Muslims and to provide more evidence-based pre-Ramadan advice for these patients.

In case patients miss the opportunity for assessment before Ramadan, discussion with patients and provision of information packs that include advice on Ramadan fasting can be made available at diagnosis and also at annual diabetic review.

High risk patients
Severe and recurrent episodes of hypoglycaemia and unawareness
Patients with sustained poor glycaemic control
Ketoacidosis within the last 3 months prior to Ramadan
Hyperosmolar hyperglycaemic coma within the 3 months before Ramadan
Those with acute illness
Those who perform intense physical labour
Pregnant women
Those with comorbidities such as advanced macrovascular complications, renal disease on dialysis, cognitive dysfunction, uncontrolled epilepsy (particularly precipitated by hypoglycaemia)
Moderate risk
Well-controlled patients treated with short-acting insulin secretagogue, sulphonylurea, insulin, or on combination oral or oral plus insulin therapy
Low risk
Well-controlled patients treated with diet alone, monotherapy with metformin, DPP4 inhibitor or thiazolidinedione who are otherwise healthy

Table 2.1 Expert recommendations for risk stratification in patients with type 1 or type 2 diabetes who fast during Ramadan[51;54].

2.1.2 Ramadan focused education

Structured education interventions have been endorsed by the National Institute for Health and Clinical Excellence as important in empowering patients to improve their journey with diabetes[55]. In a observational study, patients who fasted during Ramadan without attending a structured education session had a fourfold increase in hypoglycaemic events, whereas those who attended an education programme focusing on Ramadan had a significant decrease in hypoglycaemic events[56]. It is therefore recommended that Muslim patients with diabetes attend some form of structured education intervention to increase their chance of being well when fasting

during Ramadan. Patients at high risk who plan to fast despite medical advice not to are also invited to attend structured education to support their self-management and decision to fast. Table 2.2 outlines suggested content of Ramadan focused education.

Table 2.2 Four key areas in Ramadan-focused education

Meal planning and dietary advice	• The diet during Ramadan should not differ from that of a healthy balanced diet • Slow energy-release foods (such as wheat, semolina, beans, rice) should be taken before and after fasting, whereas foods high in saturated fat (such as ghee, samosas and pakoras) should be minimised • Advise patients to use only a small amount of monounsaturated oils (such as rapeseed or olive oil) in cooking • Before and after fasting include high fibre foods such as wholegrain cereals, granary bread, brown rice; beans and pulses; fruit, vegetables, and salads
Exercise	• Light and moderate exercise on a regular basis is safe in Type 2 diabetes patients • Rigorous exercise is not recommended as the risk of hypoglycaemia is increased, particularly in patients taking sulphonylureas or insulin • Patients should be encouraged to continue their usual physical activity, especially during non-fasting periods • Tarawaih prayers (multiple prayers after the sunset meal) should be considered as part of the daily exercise regimen.
Blood glucose monitoring	• Blood glucose monitoring does not constitute the break of fast • All patients who fast should be provided with the means to monitor their blood glucose • Capillary blood glucose testing should be done when: ▪ The patient suspects they have symptoms of hypoglycaemia (subjective to the individual). Patients should be advised to break their fast if hypoglycaemia is confirmed on blood glucose testing ▪ The patient is unwell (e.g. has a fever) • Testing at other times may be useful only if patients are able and willing to adjust their diabetes treatment regimens, such as insulin dosage titration
Recognising and managing complications	• Patients should be aware of the warning symptoms of dehydration, hypoglycaemia and hyperglycaemia, and should stop the fast as soon as any complications or acute illness occur

2.2 Managing type 2 diabetes patients fasting for Ramadan

2.2.1 Patients taking oral hypoglycaemic agents

2.2.1.1 Metformin

Hypoglycaemia occurs in patients with type 2 diabetes taking metformin who are not fasting[8]. One of the mechanisms which metformin reduces hepatic gluconeogenesis, lowering blood glucose levels and potentially causing hypoglycaemia, is by inhibiting the expressions of hepatic gluconeogenic genes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), via AMP protein kinase (AMPK)-mediated upregulation of the transcription of the Small Heterodimer Partner (SHP) gene[57]. Metformin-induced increase in AMPK activity is also implicated in the stimulation of glucose uptake in skeletal muscle by directly phosphorylating the GLUT4 enhancer factor (GEF), increasing the transcription of the skeletal muscle glucose transporter, GLUT4[58]. Metformin also reduces fatty acid oxidation, thereby enhancing glucose oxidation and reducing the energy supply for gluconeogenesis via the glucose fatty acid (Randle) cycle[59]. Furthermore, the glucose-lowering effect of metformin may be explained by its local inhibition of intestinal glucose absorption via the AMPK-mediated pathway[59] involving intestinal glucose transporters, Sodium-dependent glucose transporter-1 (SGLT1) and GLUT2.

A systematic review reported that levels of risk for hypoglycaemia among people taking metformin who are not fasting range from 0% to 21%[60]. No data exist for the incidence of hypoglycaemia in people who fast for prolonged periods and take only metformin.

As iftar is usually the largest meal during Ramadan, expert consensus suggests that the metformin dose should be split such that two thirds of the dose is taken at iftar and one third at suhur (as the lunchtime dose during the daytime fast is not allowed). So for a regimen of, for example, metformin 500 mg three times a day, we recommend 500 mg at suhur and 1000 mg at iftar[54].

2.2.1.2 Acarbose

Acarbose inhibits the action of intestinal brush border alpha-glucosidases, which retards glucose absorption and modifies the secretion of insulin[61]. A randomised double-blind study showed that the risk of hypoglycaemia is low with this class of drugs[62], although we could not find any evidence that this is so during Ramadan. We suggest that it is acceptable to continue with the prescribed dose(s) of acarbose taken only with meals during fasting.

2.2.1.3 Rapid acting insulin secretagogues

An open label, multicentre, randomised study showed that repaglinide, a rapid acting insulin secretagogue, contributed to improved glycaemic control, with a lower number of hypoglycaemic events among fasting patients during Ramadan when compared with glibenclamide. Patients taking repaglinide lowered their fructosamine levels from baseline, and there were 0.03 hypoglycaemic events per patient per month in this group versus 0.05 events per patient per month in the glibenclamide group[63].

A small study compared repaglinide (n=27) with a group of patients taking a sulphonylurea [glimepiride (n=23) or gliclazide (n=17)]. Fructosamine, HbA1c, and body weight did not change significantly in either group from before to after

Ramadan. Hypoglycaemia was documented in only one patient who took glimepiride during Ramadan[25]. The evidence cited suggests that rapid acting insulin secretagogues taken at suhur and iftar are a safer alternative than glibenclamide for patients who fast. Both sulphonylureas and rapid acting insulin secretagogues act by increasing insulin secretion via the ATP-sensitive K+ channels of the pancreatic β-cells, activating the voltage-gated calcium channels to increase cytoplasmic calcium concentration and thereby stimulate the exocytosis of insulin. The difference is that they act on different binding sites and therefore, differs in their duration of action[64]. Repaglinide has been shown to enhance early phase insulin secretion more effectively than glimepiride and gliclazide MR[65] in a non-Ramadan study, without prolonging insulin secretion beyond the early phase. Repaglinide has a fast onset (peak in 30 – 60 minutes) and short duration of action of 1 hour, compared to gliclazide MR (gradual onset in 6 hours, duration of action of 24 hours). Therefore, it may be preferable in targeting the post-prandial hyperglycaemia without additional hypoglycaemia during fasting periods. However, comparison between repaglinide and long-acting gliclazide has not been performed during Ramadan.

2.2.1.4 Sulphonylureas

A large prospective observational study (n=332) by the GLIRA study group showed that changing once daily glimepiride from a morning dose taken with breakfast before Ramadan to an evening dose taken at iftar during Ramadan did not alter rates of hypoglycaemia or glycaemic control[30]. However, the rate of hypoglycaemia in patients taking glimepiride in the mornings during Ramadan was not studied, so whether that rate was higher than the rate in those taking glimepiride in the evenings was unknown. The incidence of hypoglycaemic events did not differ between a group

of patients taking once daily glimepiride (n=21) and a group taking twice daily repaglinide (n=20) (taken at suhur and iftar)[66].

A recent observational study has shown that 20% of patients on sulphonylurea and metformin experienced one or more symptomatic hypoglycaemic events during Ramadan. The hypoglycaemic risk varied across agents within this class, with incidences observed in subjects treated with glibenclamide (26%), glimepiride (17%), and gliclazide (14%), respectively[67].

If a sulphonylurea is being used during Ramadan, slow release preparation may have a better safety profile than glimepiride. In a non-Ramadan-related study, the GUIDE study (a double-blinded comparison of once-daily gliclazide MR and glimepiride), gliclazide MR demonstrated about 50% fewer hypoglycaemic events in comparison with glimepride[68]. In a Ramadan-related study, 136 type 2 diabetes males, with well-controlled diabetes and evening administration of gliclazide MR 60mg as monotherapy during fast, have been shown to have no weight gain or increase in hypoglycaemic events during Ramadan (5 episodes before and 3 episodes during Ramadan)[69].

Based on the above evidence, gliclazide or gliclazide MR appeared to have the lowest hypoglycaemic risk. During Ramadan, the recommendation would therefore be to change the timing of the once daily dose of sulphonylurea (such as glimepiride or gliclazide MR) from the usual morning dose to the evening (at iftar). With regard to gliclazide, patients are recommended take a larger dose at iftar than at suhur and that clinicians should consider reducing the prescribed dose for suhur if the patient's glycaemic control before Ramadan is stable (for example, change gliclazide 160 mg twice daily to 80 mg in the morning and 160 mg in the evening)[54].

2.2.1.5 Thiazolidinediones

A randomised controlled trial that compared pioglitazone 30 mg once daily with placebo in patients already taking other oral hypoglycaemic agents or alone, found no increase in hypoglycaemia during Ramadan fasting[70]. No studies have been reported on the use of rosiglitazone use during Ramadan. Continuing with thiazolidinediones during fasting is considered safe.

2.2.1.6 Dipeptidyl peptidase-4 inhibitors

A prospective non-interventional study conducted on Muslim patients with type 2 diabetes showed that adding vildagliptin to metformin treatment was associated with a reduced incidence of hypoglycaemic events and improved glucose control compared with patients treated with gliclazide and metformin during Ramadan[71]. This suggests that it may be safer to combine dipeptidyl peptidase-4 inhibitors, rather than sulphonylureas, with metformin in patients who are not well controlled when taking metformin alone and are planning to fast during Ramadan. The findings have since been confirmed in a randomised open-labelled study[72].

2.2.1.7 Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists are currently used in combination with other oral hypoglycaemic agents. In non-Ramadan studies, hypoglycaemic events associated with glucagon-like peptide-1 receptor agonists occurred primarily in patients taking a sulphonylurea[73]. Our findings (Chapter 5) suggested that its dosage does not need to be adjusted during Ramadan but that other agents, such as sulphonylureas, may need dose reductions when used as a combination treatment[74].

2.2.2 Patients taking insulin

2.2.2.1 Single basal insulin and oral combined treatment

A multicentre, prospective, observational study compared fasting patients taking metformin combined with glimepiride (n=21), repaglinide (n=18), or glargine (n=10)[27]. Although the rate of hypoglycaemia was higher in the glimepiride group (14.3%) than in the repaglinide (11%) and glargine (10%) groups, the increased rate was not significant. Glimepiride was given before iftar; repaglinide was given with both meals; and glargine at 10.00 pm. No studies have compared the incidence of hypoglycaemic events in patients taking insulin detemir or isophane insulin (NPH) (such as Insulatard or Humulin I).

In a small prospective non-randomised study of 19 patients who had type 2 diabetes, were at low risk of diabetic complications, and had a pre-Ramadan HbA1c concentration of less than 8% (64 mmol/mol), neither fasting (n=11) nor non-fasting (n=8) patients who were taking repaglinide three times a day and glargine experienced hypoglycaemic events, and both groups maintained stable glycaemic control[29]. Those who fasted took repaglinide at iftar, at midnight, and at suhur, and the doses of repaglinide and glargine remained unchanged throughout Ramadan. We advise patients who take long acting basal insulin, such as glargine, to reduce the dose by 20% to avoid hypoglycaemia. Patients taking repaglinide and single dose glargine may continue taking the same doses of repaglinide. The timing of repaglinide can be rearranged to coincide with suhur and iftar. Even though significant hypoglycaemia did not occur when the dose of basal insulin, glargine remained the same[29], a more cautious approach to avoid hypoglycaemia would be to consider reducing glargine by 20% during Ramadan. However, insulin dosage can

be highly variable in different individuals, therefore, the 20% reduction would only be a suggestion recommended by expert opinions.

2.2.2.2 Premixed insulins

A randomised, open labelled, crossover study comparing Humalog Mix25 (25% short acting insulin lispro and 75% intermediate acting neutral lispro protamine) and Humulin M3 (human insulin 30% soluble, 70% isophane) given in identical doses showed that the former offered better control of postprandial blood glucose after Iftar and a lower occurrence of hypoglycaemic events[75]. We performed an observational study (Chapter 6), which suggested that using Humalog Mix50 at Iftar instead of Mix30/70 reduced hypoglycaemia without compromising the overall blood glucose control[76]. Patients taking twice daily insulin may reduce the suhur dose by 30% if they are well controlled, and consider switching to a Mix50 preparation if their postprandial glucose remains elevated.

2.3 Fasting during pregnancy

Pregnant women with diabetes, including gestational diabetes, are exempted from fasting and are strongly cautioned against fasting because clear maternal and foetal risks are associated with poor glycaemic control in pregnancy[77]. However, no outcome study of women with diabetes specifically related to Ramadan fasting has been conducted. We conducted a survey to assess the habit of Ramadan fasting in pregnant women with diabetes (Chapter 3). Preconception counselling for diabetic Muslim women should include education about the substantial risks associated with poor glycaemic control to help to dissuade them from trying to fast.

2.4 Managing type 1 diabetes patients fasting for Ramadan

A small study examined the use of glargine and insulin lispro or aspart, divided in a 6:4 ratio of the total 24 hour insulin dose in nine patients with type 1 diabetes[78]. Of seven patients who started to fast, five continued for the whole month, and two broke the fast owing to hypoglycaemia. None of the patients had any episodes of severe hypoglycaemia or diabetic ketoacidosis requiring hospital admission, and the patients' HbA1c concentrations remained stable at the end of Ramadan. As the insulin requirement in this study group decreased by 28% from baseline (p=0.002), the authors suggested a reduced dose (70% of a patient's usual dose) during the fast.

An open label, comparative, crossover study of 64 patients with type 1 diabetes found significantly lower (p=0.026) two hour, postprandial glucose concentrations after iftar and fewer hypoglycaemic events with insulin lispro than with regular human insulin[79]. In both arms isophane insulin (Humulin I) was given as the basal insulin.

Most studies of patients with type 1 diabetes have comprised small numbers of patients and some have excluded adolescents, elderly patients, or patients with comorbidities such as renal impairment. Suggested treatments, therefore, may not be generalised to all fasting patients with type 1 diabetes, and no good evidence exists to allow us to give clear guidance for those who are not on a basal bolus regimen.

Patients with type 1 diabetes who are on a basal bolus regimen four times daily should be discouraged from fasting owing to the risks of poor glycaemic control[54]. If patients choose to fast despite medical advice, it will help if they are familiar with

carbohydrate counting. A suggested insulin reduction would be to decrease their total daily insulin by approximately 30% based on the above studies on Type 1 diabetes[78;79] and to omit the midday rapid acting insulin if their capillary blood glucose concentration is ≤7 mmol/l. If their blood glucose concentration is >7 mmol/l, patients will need to calculate their insulin correction dose as determined by their specialists.

In summary

Table 2.3 summarises the recommendations discussed, based on the best available and current evidence and on expert opinions in managing patients who fast during Ramadan.

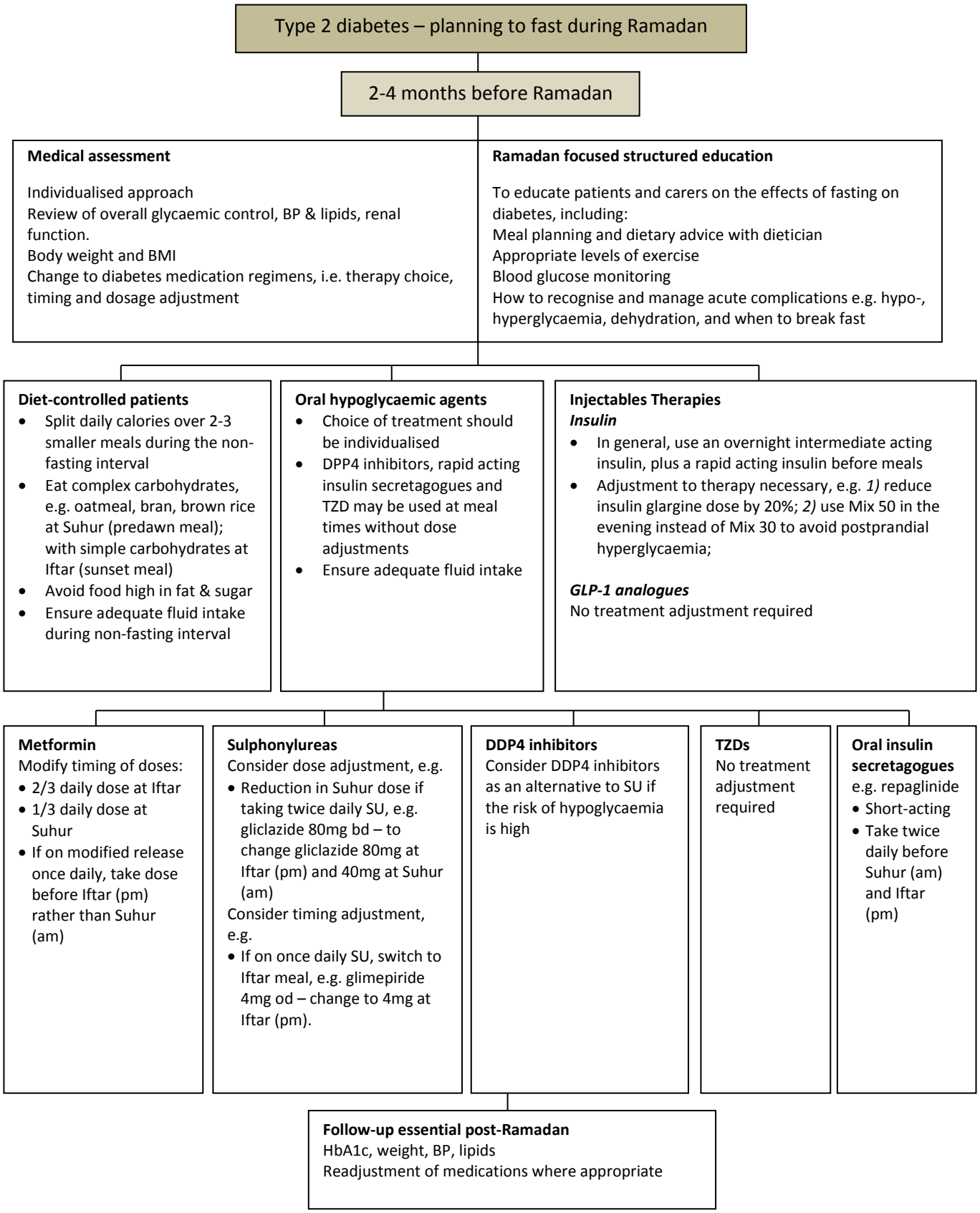


Table 2.3 An approach to oral treatment of type 2 diabetes in Ramadan

Chapter 3: Fasting among pregnant women with diabetes during Ramadan

3.1 Health beliefs of Muslim women about Ramadan fasting during pregnancy

Islamic law exempts menstruating, breastfeeding and pregnant women who are worried about their health, and/or pregnancy, from fasting during Ramadan[80]. Many Ramadan-related published sources also confirm the belief that Muslim women, who believed that fasting will endanger either their own or their foetuses/neonates' health, are exempted from fasting during pregnancy[81-84]. The Koran[14] states that "…fasting for a limited number of days. So whoever among you is ill, or on a journey, then an equal number of other days are to be made up. And upon those who are able to fast but with hardship, a ransom for substitute of feeding a poor person each day". It is believed that fasting during pregnancy causes hardship the same way as illness, hence, is exempted with a ransom for substitute or deferred, as illness and travelling do[80]. The Hadith Sharif, a collection of sayings of the Prophet Muhammad, also stated that "if a pregnant woman fears for herself or the breast-feeding women fears for her child in Ramadan, they should break their fast and feed a poor person for each day and they do not have to make up the fast"[85].

3.1.1 Fasting during Ramadan amongst healthy pregnant women

Although pregnant women are allowed to defer fasting until after the pregnancy, as compensational fasting 'qada' after pregnancy, pregnant women prefer to share the social and religious experience of Ramadan fasting with their families in Middle Eastern and African countries[86;87]. It was observed that 90% of pregnant women in a rural West African village fasted throughout the period of Ramadan[86].

A retrospective study on Muslim pregnant women in Singapore has shown that 87% of total respondents (n = 182) fasted during Ramadan[81]. Among the 158 women who fasted, 57% of women fasted more than 21 days, 17% fasted for 11 to 20 days, and 13% fasted for 1 to 10 days. About two-thirds of women believed that fasting during Ramadan is essential and compulsory in a healthy pregnancy and all women were aware that compensational fasting can be repaid after pregnancy. 55 out of 158 women experienced nausea and vomiting, giddiness during fasting but 80% overcame the adverse reactions and continued to fast. 30% of primagravidas did not fast at all, compared to only 3% of multigravidas. The Mufti, religious leaders in Singapore, agreed that if a pregnant woman is worried for her and her foetus' health, she is exempted from fasting. However, if a healthy pregnant woman does not feel any worry about her or her foetus and is capable to fast, she is required and expected to fast[81]. The latter is less clear in other Ramadan-related published sources but may explain the high prevalence of Ramadan fasting in some countries. The joint medical and religious guidance from the Islamic Organisation for Medical Sciences and the International Islamic Fiqh Academy agreed that patients with high risk of serious complications from fasting are exempted from Ramadan fasting. These patients include women with diabetes during pregnancy, patients with frequent hypoglycaemia or hypoglycaemic unawareness, and patients known to have difficulty in controlling diabetes. On the other hand, patients with low risk of complications of fasting are not permissible to break the fast. These include diabetic patients with stable situations and controlled by diet and/or the appropriate oral hypoglycaemic agents (sulphonylureas, metformin or thiazolidinediones)[88].

Figure 3.1 showed the percentage of healthy women that fasted during pregnancy in various countries. In Iran, 65% of pregnant Muslim women (n = 284) fasted for at

least 10 days for 13 daylight hours during Ramadan[89]. In southeast Michigan, United States, a total of 32 pregnant women, recruited by leaflet and word-of-mouth from Muslim communities, participated in a focus-group discussion about fasting during pregnancy. It showed that 28 of them fasted whilst pregnant for at least one day[90]. In United Kingdom, a small study of 44 women showed that 20 women (45%) fasted for 17 hours in 1987 during Ramadan[91].

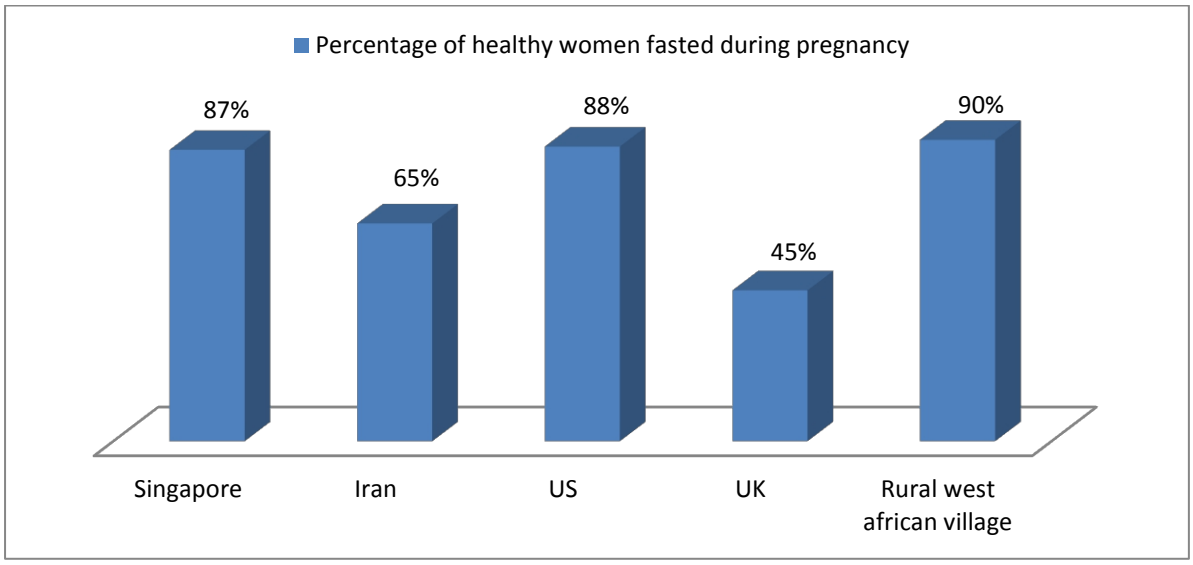


Figure 3.1 Percentage of healthy women fasted during pregnancy[81;86;89-91].

(The studies were conducted at different years and had different study protocols; therefore the diagram cannot be used as a direct comparison of the percentages).

3.2 Effects of fasting in pregnancy in the non-diabetic population

The physiology of fasting in normal pregnancy was studied in the setting of overnight fast. Plasma glucose levels were significantly lower in pregnant women in their third trimester after 12 hours of overnight fast (from 18:00 to 06:00 the next morning), equivalent to skipping breakfast. Glucose levels fell further during the subsequent 6 hours of fasting. Plasma alanine levels, one of the sources of circulating fuels, also declined significantly during the same time interval, with concurrent rises in plasma free fatty acids and beta-hydroxybutyrate and fall in plasma insulin level. In

comparison, the plasma levels of these gluco-regulatory hormones (insulin and glucagon) and food source (glucose, alanine, free fatty acids and beta-hydroxybutyrate) in non-pregnant women remained stable after 18 hours fast[92]. Hence, 'accelerated starvation' was noticed in pregnant women compared with non-pregnant women even with minor dietary deprivation in common clinical circumstances, such as omitting breakfast. Women who ate fewer than three meals and two snacks per day also had a 30% higher risk for delivering pre-term in comparison to pregnant women who had met the meal frequencies[93]. Prolonged periods without food lasting 13 hours or longer were associated with elevated maternal corticotropin-releasing hormone concentrations compared with those without food for periods less than 13 hours. Elevated maternal corticotropin-releasing hormone levels were associated with pre-term birth[94]. Skipping meals and sustaining periods without food may stimulate neuroendocrine hormones that lead to pre-term labour.

The question of whether Ramadan fasting is safe in healthy non-diabetic pregnant women remains unclear. Some studies on Ramadan fasting have found detrimental maternal and foetal effects in pregnant women who fasted. Excessive vomiting and hyperemesis gravidarum was found to be associated with fasting in the first month of pregnancy[95].

The frequency of foetal breathing movement was significantly less during fasting periods compared to post-prandial periods in healthy primagravidas of 30 weeks' gestation or more (n = 63). Foetal breathing movements comprised of normal foetal breathing activity and sporadic breathing patterns that resembled sighs, gasps, coughs and panting, can affect foetal circulation by influencing the rate of umbilical artery blood flow[96]. The time needed to detect breathing movements was also

significantly longer due to the low level of blood glucose concentration during fasting than post-prandial periods[97].

Foetal biophysical score is a standard method to assess foetal well-being and includes criteria for foetal breathing movements, foetal movements, foetal tone and amniotic fluid volume. More foetuses of fasting pregnant mothers (30 out of 81 foetuses) had a low foetal biophysical score of 6/8 compared with non-fasting controls (11 out of 81) matched for age, gestational age and parity (37% versus 13.6%, p = 0.001). Foetuses in both groups with a biophysical score of 6/8 showed no breathing movements[98]. Reduced foetal breathing movements in fasting pregnant women were related to low maternal glucose levels during fasting period. Following maternal ingestion of glucose, foetal movements were shown to be increased [99], with maximum movements one hour following the peak maternal plasma glucose concentration[100].

Despite significant difference in the foetal breathing movements between fasting and non-fasting pregnant women, other components of the foetal biophysical score, namely gross body movements, foetal tone and amniotic fluid volume remained similar between fasting and non-fasting groups[98]. Other foetal and maternal outcomes were not included in the study and it was unclear whether transient reduction in foetal breathing movements would have any long-term effects to the mother and child.

Other studies demonstrated that Ramadan fasting has no harmful effect on the unborn baby. In a case-control study comparing fasting (for at least 20 days during Ramadan) and non-fasting women, there were no significant differences between the two groups with regards to the intrauterine growth rate in the second trimester,

neonatal mean birth weight and the amniotic fluid volume[84]. There was also no significant effect of Ramadan fasting on maternal blood pressure and weight in the 101 women who fasted[84]. An analysis of twenty-year trends of birth weights of full-term babies (n = 13 351) to Asian Muslim women in comparison to non-Muslim Asian and Caucasian births showed that Ramadan had no effect on the birth weights of babies born at full-term in the United Kingdom. However, there was no indication of how many of the women included in the study adhered to Ramadan during pregnancy and the study did not take into account the difference in the length of time between sunrise and sunset in the twenty year period[101]. A retrospective cohort study from Iran showed that there was no significant difference in the birth weight of neonates from mothers with a history of Ramadan fasting during pregnancy compared to neonates of non-fasting women[89]. In a prospective study of 36 Turkish women with uncomplicated pregnancy, maternal fasting of 13 – 14 hour each day for at least 18 days during Ramadan did not lead to significant ketonaemia or ketonuria. The change in measurements of foetal biparietal diameter, foetal femur length, foetal biophysical profile, amniotic fluid index and umbilical artery systole/diastole ratio in the beginning and the end of Ramadan were not significantly different between the fasting and non-fasting women[102]. Transient ketonuria may occur during healthy pregnancy as a result of dehydration and caloric restriction or prolonged starvation. Ketones has been shown to alter the amniotic fluid volume in ewes in response to maternal dehydration[103]. The results indicated that fasting for about 13 -14 hours each day did not cause significant ketonaemia in the pregnant women[102], in contrast to the earlier studies[92;94]. Moreover, there was no difference in ketone levels between fasting and non-fasting women at more than 20 weeks gestation. The fasting pregnant women were given advice to drink at least two litres of water when

they ‘break’ fast after sunset, which may prevent the build-up of ketones in these fasting subjects.

Despite the short-term reduction on foetal breathing movements, Ramadan fasting did not appear to have any effects on intrauterine growth and neonatal birth weight at full term. It seems that the newborns of fasting women are able to withstand intermittent and short durations of hypoglycaemia without affecting its glycogen storage. Some authors have suggested that fasting for less than 15 hours may not be metabolically different from a physiological overnight fast during sleep for the healthy pregnant women[90]. Although the research to date is reassuring, there is still insufficient evidence to conclude that fasting during pregnancy is safe. Table 3.1 showed a summary of the studies on the effect of Ramadan fasting in healthy pregnant women and their neonates.

Study	Study Design	Gestation	Comparison	Neutral Outcomes	Detrimental Outcomes
Mirghani et al. 2007	Cross-sectional observational study	20-24 weeks	53 fasting vs. 53 non-fasting women	Similar uterine arterial blood flow velocity	
Mirghani et al. 2004	Cross-sectional observational study	30 weeks or more	81 fasting vs. 81 non-fasting women	Similar mean umbilical artery pulsatility index, vertical amniotic pool depth, and foetal bladder volume	Reduced foetal biophysical score in fasting women
Mirghani et al. 2003	Observational study	30 weeks or more	63 women during fasting and post-prandial periods		Reduced foetal breathing movement; Longer time needed to detect breathing movement
Cross et al. 1990	Retrospective study	n/a	13,351 babies to Asian Muslim mothers (assumed to be fasting during Ramadan) vs. 13,351 white and 5106 non-Muslim births from 1964 - 1984	Similar mean birth weight in Asian Muslim women	
Dikensoy et al. 2008	Prospective	20 weeks or more	36 fasting vs. 29 non-fasting women	Similar (the differences before and after Ramadan between groups) foetal biparietal diameter; foetal femur length; estimated foetal body weight; foetal biophysical profile; amniotic fluid index; and umbilical artery systole/ diastole ratio No change in urinary ketone concentration	
Kavehmanesh et al. 2004	Retrospective cohort study	n/a	Neonates of 284 women fasted during pregnancy vs. 255 women who did not fast	Similar neonatal birth weight, height and preterm delivery (adjusted for maternal body mass index)	
Naderi et al. 2004	Case-control study	18 to 28 weeks	51 fasting vs. 50 non-fasting women	Similar maternal weight increase, intrauterine growth (in terms of fundal height increase, amniotic fluid volume) during Ramadan Similar neonatal birth weights (matched)	

Table 3.1 A summary of the effect of Ramadan fasting in healthy pregnant women and their neonates.

3.3 Effects of fasting in pregnant population with diabetes

There is limited data on the effect of intermittent fasting in pregnant women with diabetes. In 10 insulin-dependent diabetic women (the type(s) of diabetes was not specified) of more than 5 years duration in their third trimester were consented and ethnically approved to undergo insulin-induced hypoglycaemia, achieved by lowering plasma glucose from 95 mg/dl (5.3 mmol/l) to 45 mg/dl (2.5 mmol/l) using insulin clamp technique at Yale Clinical Research Centre. The number of foetal limb and breathing movements, and foetal heart rate did not change significantly in spite of progressive lowering of blood glucose levels[104].

In the EPIDIAR study[15], the largest multi-centred epidemiological survey on the prevalence of fasting during Ramadan and its implications on people with diabetes, half of the respondents were women with the mean age of 31 ± 12.7 (standard deviation, SD) years for type 1 and 54.0 ± 11.0 (SD) years for type 2 diabetes. The majority of the patients fasted during Ramadan and had a significant increase in severe hypoglycaemic and hyperglycaemic complications during Ramadan. Although the study did not mention the specific population of pregnant women with diabetes, it was speculated that some pregnant women with diabetes also fasted during Ramadan.

3.4 The practice of Ramadan fasting in pregnant women with diabetes

The aims of this survey were to examine the practice of fasting among pregnant Muslim women with diabetes and to explore the factors that influenced the decision

to fast in London, the United Kingdom. The roles of healthcare professionals and Imams (Muslim religious leaders) in the decision to fast were also examined.

3.4.1 Methods

Standardised questionnaire-based one-to-one interviews were conducted on Muslim women with diabetes, who received antenatal care at 4 specialist antenatal centres in Northwest London from the start of Ramadan 2010 to the end of December 2010.

Setting

The survey was carried out in conjoint antenatal endocrine clinics run by obstetricians and diabetes specialist doctors in 4 London hospitals: Northwick Park Hospital, Central Middlesex Hospital, Hammersmith Hospital, and West Middlesex University Hospital. Patients attending the clinics were invited to participate in the survey if they had any type of diabetes mellitus, Muslim, and pregnant. The consulting specialist diabetes doctors or midwives identified the patients, obtained verbal consent and conducted the questionnaire survey during the clinic consultations. The doctors and midwives agreed to take part in the survey and were briefed about the questionnaire before the start of Ramadan 2010. The questionnaire served as part of the consultation to assist the doctors and midwives with issues regarding fasting during Ramadan.

Questionnaire

The participants were invited to fill in the standardised one-page questionnaire (Appendix 1) requiring mainly ‘yes’ or ‘no’ answers. The questionnaire covered the following topics:

1) Types of diabetes mellitus: type 1 (T1DM), type 2 (T2DM), gestational (GDM)

2) Prevalence of fasting for Ramadan during pregnancy
3) Discussion of fasting for Ramadan with healthcare professionals and/or Imams
4) Prevalence of glycaemic complications (hypo- and hyperglycaemia) associated with fasting during pregnancy

The questionnaire was developed following the questions asked in the EPIDIAR study[15]. The questionnaire was piloted on non-pregnant Muslim patients with diabetes at Central Middlesex Hospital and was reviewed by two consultant diabetologists. No changes were made to the questionnaire following the pilot.

Local National Health Service Trust Clinical Audit and Effectiveness committee approval to conduct the survey was sought before it was undertaken.

3.4.2 Results

A total of 48 women were invited and completed the questionnaire. Mean age (± SD) was 32 ± 5 years. 31 (65%) women had gestational diabetes (GDM), 15 (31%) had type 2 diabetes (T2DM), and 2 had type 1 diabetes (T1DM). 21 (44%) were diet-controlled, 12 (25%) were on oral hypoglycaemic agent(s), 10 (21%) on insulin, and 5 (10%) were taking insulin and metformin. Participant characteristics are shown in Table 3.2.

Characteristics	Number of patients	Percentage
Age (years)		
20 - 29	14	29%
30 - 39	21	44%
Not stated	13	27%
Type of Diabetes		
Type 1	2	4%
Type 2	15	31%
Gestational diabetes	31	65%
Diabetes treatment*		
Diet	21 (4 T2DM; 17 GDM)	44%
Metformin	12 (6 T2DM; 6 GDM)	25%
Insulin	10 (2 T1DM; 2 T2DM; 6 GDM)	21%
Insulin and metformin	5 (3 T2DM; 2 GDM)	10%

Table 3.2 Characteristics of the pregnant women with diabetes

* Diabetes treatment at the time of the questionnaire interview

Five out of forty eight pregnant women fasted during Ramadan. Three of the five women fasted for the entire month of Ramadan without experiencing hypoglycaemia. Two of them had gestational diabetes on insulin and/or metformin; the third patient had type 2 diabetes on diet-control at the time of interview. Table 3.3 showed the characteristics of women who fasted during pregnancy.

Patient	Type of diabetes	Diabetes treatment	Fasting whilst Pregnant previously	Number of days fasted during Ramadan	Discussion with healthcare professional	Discussion with Imam
1	T1DM	Insulin	N	14	Y	Y
2	T2DM	Diet	N	30	N	N
3	T2DM	Oral	Y	5	N	Y
4	GDM	Insulin + metformin	Y	30	N	Y
5	GDM	Insulin	Y	30	N	Y

Table 3.3 Characteristics of the women who fasted during pregnancy

One of the patients with type 2 diabetes (patient number 3) fasted for 5 days only as there was a history of hypoglycaemia before the month of Ramadan (Table 3.4). The patient was on oral medication(s). However, the type of oral hypoglycaemic agent(s) was not documented. She discussed the issue of fasting with an Imam but not a healthcare professional. Patient Number 2 also had type 2 diabetes, but diet-controlled. She did not have hypoglycaemic complications associated with fasting and completed a whole month of fasting. She did not seek medical or religious advice prior to fasting.

The patient with type 1 diabetes fasted for 14 days and experienced hypoglycaemia during the fast. She had not been pregnant during previous Ramadan periods but had discussed with both healthcare professionals and her community religious leaders whether it was safe to fast.

3 of these women had fasted previously whilst pregnant during Ramadan and had only consulted their Imams, but not healthcare professionals, regarding whether it was safe for them to fast.

Patient	Type of diabetes	History of hypoglycaemia before Ramadan	Hypoglycaemia during fasting periods of Ramadan	Frequency of hypoglycaemia during fasting hours	Hyperglycaemia during Ramadan: highest glucose readings* during Ramadan
1	T1DM	Y	Y	4	19
2	T2DM	N	N	0	Not recall high readings
3	T2DM	Y	N	0	13
4	GDM	N	N	0	Not recall high readings
5	GDM	N	N	0	11

Table 3.4 Glycaemic control in the women who fasted during pregnancy

*glucose readings indicated capillary blood glucose levels in mmol/l

The majority of pregnant women did not fast during Ramadan. Of the forty-three non-fasting pregnant women, ten (23%) had a history of hypoglycaemia during Ramadan. Seven of these women were on insulin treatment: five had type 2 diabetes, one had GDM, and one had type 1 diabetes. Their hypoglycaemic experiences were not specifically related to fasting whilst pregnant in previous Ramadan, as no non-fasting women who had hypoglycaemia had been pregnant whilst fasting during Ramadan (Table 3.5).

During previous Ramadan	No. of non-fasting women who had hypoglycaemia
pregnant and fasted	0
never pregnant and not fasted	1
fasted but never pregnant	2
pregnant but not fasted	1
not documented	6
total	10

Table 3.5 Experience of hypoglycaemia during previous Ramadan periods in non-fasting women

Among the 43 non-fasting women, 4 consulted both their Imam and healthcare professionals. 9 had consulted healthcare professionals only and 3 had discussed with their Imam only. Thirteen patients (33%) had consulted their doctors or nurses about the issue of fasting, and seven (18%) had discussed with their Imams (table 3.6).

	Fasting women No. (%)	Non-fasting women No. (%)
Glycaemic control during Ramadan:		
Hypoglycaemia	1	10
Hyperglycaemia	3	4
Ramadan discussions with:		
Healthcare professionals	0	9
Imams	3	3
Both	1	4

Table 3.6 Comparison between the pregnant women with diabetes who fasted and who did not fast during Ramadan

The majority of non-fasting women (39/43) did not recall any hyperglycaemia, whereas 3 of the 5 fasting women recorded hyperglycaemia during Ramadan period. The highest capillary blood glucose readings ranged from 11 – 19 mmol/l (Table 3.3).

3.4.3 Discussion

From our survey of pregnant women with diabetes, 10% fasted during Ramadan. This is in contrast to previous studies on healthy pregnant women who did not specifically have diabetes, where 45 – 90% of pregnant Muslim women fasted[81;89-91]. Moreover, 52 – 99% of non-diabetic Muslim adults in Asia, Africa and Europe observed fast. Although the specific proportion of non-diabetic Muslim women who fasted were not unknown, Muslim men and women were found to be equally committed to their religious belief[105]. The lower percentage of fasting in our group of high-risk women reflects the widely accepted belief that a women should not fast if it would hurt her or the baby. This was the sole reason for not fasting during pregnancy in a group of Muslim women in America[90]. Higher education level (English-speaking) and the urban background of these women may also have influenced their decision not to fast, as immigrant Muslims and women from rural areas tended to choose to fast[86;91]. Most of the women in the study (65%) had gestational diabetes which would be a new diagnosis in pregnancy. Women appeared to give up Ramadan fasting sooner after a diagnosis of diabetes than did men[106], suggesting that a new diagnosis of gestational diabetes may make these women give up fasting.

Twenty-three per cent of the women that did not fast had a history of hypoglycaemia. Seven out of ten women with a history of hypoglycaemia were on insulin treatment, which can be the cause of hypoglycaemia on prolonged fasting. One of the

limitations was that the questionnaire did not elaborate on previous experience of pregnancy and fasting, six of the ten women did not have documentation regarding previous history of pregnancy and fasting.

As mentioned, Muslim women who believed that fasting will endanger either their own, or their foetuses or neonates' health, are exempted from fasting during pregnancy. Having diabetes with the risk of hypoglycaemia may be the reason that these women did not fast during Ramadan, in comparison to healthy pregnant women who have been shown to be keen to fast despite adverse reaction[81]. The high incidence of hypoglycaemia (23%) in the population that did not fast may be the inhibiting factor towards fasting.

Even though 62% (27 out of 43 women) did not consult healthcare professionals or religious leaders for advice, they made conscious decisions themselves not to fast for Ramadan whilst pregnant. Women may consult other people apart from religious advisors and healthcare professionals, such as family members[107] and, in particularly, their husbands who tended to discourage fasting when they felt that the women were endangering themselves[90].

Three of the five women in the fasting group had fasted previously whilst pregnant and had only consulted their Imams, but not healthcare professionals. Two of these patients had gestational diabetes; and one had type 2 diabetes. These patients may not have diabetes prior to current pregnancy and may feel well enough to fast during previous pregnancy. None of the patients with type 2 diabetes or gestational diabetes had discussed the issue of fasting during pregnancy with healthcare professionals, as they may not be aware of the implications of diabetes in association with fasting during pregnancy.

For those who seek perinatal advice about fasting, more women in the non-fasting group discussed with their healthcare professionals than their Imams regarding fasting during Ramadan, whereas the fasting women mainly discussed Ramadan with their Imams. Overall, women were just as likely to discuss fasting with their Imams as they were with healthcare professionals (11 discussed with Imams and 14 discussed with healthcare professionals; within each group 5 discussed with both).

In comparison, a study in the south of France with large Muslim communities evaluated attitudes in hospital inpatients towards Ramadan fasting and diabetes (n=101). 65 patients had discussed the feasibility of fasting with their general practitioner (GP), and 25 patients sought advice from the local Imam. All the patients that had counselling from their Imam followed his advice, whereas more than half of those who were advised by their GPs not to fast did so anyway[107]. The role of religious advisors are as important, and sometimes, even more important, in deciding to fast or not. Some GPs may lack the specific medical knowledge and cultural competence to provide appropriate counselling to Muslim pregnant women regarding Ramadan fasting.

One of the limitations of the survey was that it relied on the retrospective recall of patients' past experience of Ramadan fasting. The small overall number of participants and the number of women with hyperglycaemia may represent under-reporting. This survey mainly focused on understanding the current practice of Ramadan fasting among pregnant women with diabetes in London. It would be useful to further extend the questions to directly include 'reasons for fasting or not fasting'. Information of the parity would also be helpful to delineate the factors that influence fasting, as more multiparous women has been shown to fast compared to primiparous women[81]. Information on the length of stay in London and U.K. would

also be helpful to assess the effect of different generations of immigrants on their commitment to fast. In addition, as London is the most ethnically diverse city in the UK[108], the sample may not be representative of all Muslim women with diabetes in other regions of the UK. Extending the survey beyond London, to other UK cities and other countries would provide a more comprehensive view of Muslim women with diabetes. Further research will be helpful to determine whether women in utero during Ramadan affect maternal and foetal outcomes.

As the questionnaire served as part of the antenatal clinic consultation, all of the women agreed to answer the questions. Appropriate advice and management plan were given accordingly by the consulting healthcare professionals. Although each clinic visit appeared to have a reasonable number of Muslim patients, these women were seen in the clinics frequently every 1 – 2 weeks. This may explain the small overall number of participants across the four clinics as each woman was only interviewed once even though they attended the clinic repeatedly during the studied period.

In conclusion, the majority of Muslim women, who were both pregnant and had diabetes during pregnancy, did not fast for Ramadan. A history of hypoglycaemia and the presence of medical illness, namely diabetes, were the deterrent factors for fasting. For those who planned to fast whilst pregnant, medical and religious advice are both important to ensure that the mother, pregnancy and foetus will not be compromised by the fast and that the mother is able to make an informed decision to fast.

Pre-Ramadan assessment and education about the potential complications of fasting is essential to stratify the risk of fasting and to provide adequate advice for people

with diabetes[109]. In this specific population of Muslim women with diabetes, pre-conception care should include education on the risks of fasting during Ramadan.

Further education for our healthcare professionals is important to understand the cultural behaviour and dilemmas faced by these Muslim women and to provide appropriate advice specific to Ramadan fasting. Further research is required to determine whether there are changes in the maternal and foetal complication rates, such as still birth rates, preterm delivery, macrosomia and other structural abnormalities, if the women are pregnant during Ramadan.

Chapter 4: Low glycaemic variability in type 2 diabetes subjects following pre-Ramadan assessment and adjustments for fasting during Ramadan

4.1 The role of continuous glucose monitoring for fasting people with diabetes

Ramadan is the ninth month of the Islamic Lunar calendar, during which Muslims abstain from food and fluid intake between dawn and sunset. Major changes to dietary patterns occur during Ramadan as meals are taken before dawn, known as Suhur, and immediately after sunset, known as Iftar. People with type 2 diabetes fasting during Ramadan have large increases in glycaemic excursions with a 7.5-fold increased frequency of severe hypoglycaemia and a 5-fold increase in severe hyperglycaemia[15].

During Ramadan, it is difficult to study glucose excursions using HbA1c as it does not reflect short-term glucose variations during the month of fasting. Even though studies did not demonstrate any significant changes in HbA1c[24] or fructosamine levels[110,37] during Ramadan in people with type 2 diabetes, it is the glycaemic variability leading to severe hypoglycaemia and hyperglycaemia that matters for these patients to fast safely for prolonged period. As diabetes patients undergo major changes in their dietary habits during Ramadan, continuous glucose monitoring (CGM) may be a better tool to examine the glycaemic variability in patients with diabetes who fast during Ramadan, particularly in patients with hypoglycaemia. CGM is helpful in detecting subclinical hypoglycaemic episodes[111] and provides additional indices for the assessment of GV that are not captured by HbA1c[112].

4.1.1 Glucose variability and diabetes complication risk

In patients with similar HbA1c values in the Diabetes Control and Complications trial (DCCT), the rates of retinopathy were significantly lower in the intensive cohort, suggesting that additional factors, such as glycaemic variations, may play a role in complication risk[113].

Glycaemic variability is implicated in the increased mortality risk amongst adults in the critical care setting[114], as is hypoglycaemia[115]. An increase in glycaemic variability probably also increases the risk of severe hypoglycaemia[116]. As both factors are closely related to the risk of mortality, it would be difficult to tease out either's contribution to mortality.

Excessive glycaemic excursions can induce oxidative stress leading to endothelial dysfunction[117,118]. Oscillating blood glucose concentrations have been shown in clamp studies to have a worse effect on endothelial function than stable hyperglycaemia[119] and endothelial dysfunction has been implicated in the preclinical stages of atherosclerosis[120].

In terms of microvascular endpoints, the fasting plasma glucose variation coefficient, as a measurement of glycaemic variability, was considered as a risk factor for diabetic retinopathy in patients with type 2 diabetes[121].

As for macrovascular complications, the Diabetes Interventional Study demonstrated, after an 11-year follow up of 1139 newly diagnosed type 2 diabetes individuals, that postprandial, but not fasting, hyperglycaemia was a significant predictor of myocardial infarction and mortality[122]. However, the trial was criticised for

calculating the prediction of myocardial infarction from the baseline plasma glucose rather than that during the time course of the trial.

On the other hand, the A1C-Derived Average Glucose (ADAG) study showed that indices of glycaemic variability, namely standard deviation, mean amplitude of glucose excursion (MAGE), and continuous overlapping net glycaemic action (CONGA), and 2-hour post-prandial hyperglycaemia, were not significantly associated with known cardiovascular risk factors (lipids, high-sensitivity C-reactive protein and blood pressure). In comparison, mean blood glucose and HbA1c were stronger associations with the cardiovascular risk factors in patients with type 1 or 2 diabetes[123]. Nonetheless, there are still no direct conclusions regarding the impact of postprandial glucose levels and glucose variability on actual cardiovascular events. Moreover, the aforementioned studies were performed in diabetes subjects on normal diet, rather than during prolonged fasting and feasting of Ramadan.

Whilst the relationship between glucose excursions and the aetiology of vascular complications in diabetes is complicated, severe hypoglycaemia and hyperglycaemia are associated with increased hospital admissions, reduced quality of life[124] and a decrease in the quality of glycaemic control[125] in people with type 2 diabetes. Therefore, targeting glycaemic variability is essential in the management of diabetes during Ramadan to empower people with diabetes to fast safely for prolonged periods.

The American Diabetes Association (ADA) has published recommendations on diabetes management during Ramadan, focusing on individualised care and pre-Ramadan structured education to minimise the risks of severe glycaemic excursions[109;126]. The objective of this study was to implement the ADA

recommendations for the management of diabetes during Ramadan, focusing on pre-Ramadan assessment, and to evaluate the impact of the guidelines on glycaemic variability using continuous glucose monitoring in fasting and non-fasting hours.

4.2 Impact of pre-Ramadan assessment on glycaemic variability: Methods

4.2.1 Subject characteristics

Muslim subjects over 18 years old with type 2 diabetes attending a specialist diabetes clinic in Brent, and planning to fast for Ramadan with a history of hypoglycaemia (symptomatic or documented capillary blood glucose (BG) $\leq$ 4.0 mmol/L), were invited to undergo a five-day glucose profile using the Abbott Freestyle Navigator (Abbot Diabetes, Alameda, CA) continuous glucose monitoring system as part of their clinical investigation. They were treated according to the American Diabetes Association's recommendations for management of diabetes during Ramadan[109]. Timing and dosage of diabetes medications were adjusted at their pre-Ramadan clinic visits when clinically indicated according to the ADA recommendations.

4.2.2 Study procedure and data collection

The continuous glucose monitoring (CGM) device was implanted for a random 5-day period during the month of Ramadan 2010 in the United Kingdom. Daily fasting duration ranged from 13 to 16 hours. Data from the CGM device were downloaded

using CoPilot® Healthcare Management System 4.0 (Abbot Diabetes, Alameda, CA).

4.2.3 Outcome measures

The following outcome measures were evaluated:

1) Glucose control: mean glucose, percentage of time in low (<4.4 mmol/L), normal (4.4 – 10.0 mmol/L) and high (>10.0 mmol/L) glucose ranges.

2) Glycaemic variability (GV): standard deviation of mean blood glucose (SD), M-value, mean amplitude of glycaemic excursion (MAGE), lability index (LI), J index, continuous overlapping net glycaemic action (CONGA), average daily risk ratio (ADRR), low blood glucose index (LBGI), high blood glucose index (HBGI). These indices were calculated using EasyGV software (available free at www.easygv.co.uk) and have been extensively reviewed[127].

As the continuous glucose monitoring was conducted as part of clinical service without reference to a standard. The choice of using the continuous glucose monitoring was that of the clinicians and the patients according to professional standards and patients' preference, central ethics committee approval was not sought for the study.

4.3 Results

4.3.1 Individual glycaemic variability

A total of nine subjects participated. 6 of them completed the 5-day monitoring. Three patients failed due to insufficient sensor data collections. Sensors/transmitters were detached from 2 subjects during the monitoring period without the participants' knowledge, and the remaining subject did not calibrate the sensor adequately. However, no adverse events related to the use of the CGM device were reported.

Mean age of the participants (n=6) was 53.7 ± 2.3 years, mean duration of diabetes 7.3 ± 2.8 years and HbA1c pre-Ramadan was 7.6 ± 1.1% (60 ± 1.1 mmol/mol) (Table 4.1). The presence of diabetic complications were documented in the diabetic patient database and updated during each clinic consultations. Retinopathy was assessed by community retinal screening programme; nephropathy was assessed using urinary albumin:creatinine ratio performed annually or as clinically required; painless and painful neuropathy was assessed during history taking and examination using the 10g monofilament test. All subjects fasted for more than fifteen days during Ramadan and fasted from dawn to sunset during the whole interval of their CGM.

Participant	HbA1c (%) pre-Ramadan	Age	Duration of diabetes (years)	BP (mm/Hg)	Retinopathy	Nephropathy	Neuropathy
1	6.3	53	10	138/74	N	N	N
2	9.2	53	9	120/79	Y	Y	N
3	8.4	57	6	126/72	N	N	N
4	7.4	50	10	130/80	N	N	N
5	7.7	55	6	135/82	N	N	N
6	6.8	54	3	126/75	N	N	N

Table 4.1 The baseline characteristics of the 6 participants who completed the continuous glucose monitoring during Ramadan.

All participants had pre-Ramadan assessments and 3 required dose and time adjustments of their diabetes medications (Table 4.2). Patient 2 decided to fast despite high pre-Ramadan HbA1c, therefore, he had insulin dose increase during Ramadan, instead of insulin reduction according to the ADA recommendations.

Participant	Doses and timing of medications before Ramadan	Doses and timing of medications during Ramadan	Time adjust-ment	Dose adjust-ment	Mean BG (mmol/L)
1	Metformin 500 mg od (lunchtime)	Metformin 500 mg od (Iftar)	Y	N	7.8
2	Humalog Mix 50 (19 and 25 units), Metformin 1g tds, Sitagliptin 100 mg od	Humalog Mix 50 (21 and 28 units) Metformin 1g bd Sitagliptin 100 mg od	Y	Y	13.6
3	Metformin 850 mg od Vildagliptin 50 mg bd	Metformin 850 mg od Vildagliptin 50 mg bd (Suhur and Iftar)	N	N	7.6
4	Metformin 850 mg tds Gliclazide 160 mg bd	Metformin 850 mg bd* (Suhur and Iftar) Gliclazide 160 mg bd	Y	Y	10.4
5	Metformin 500 mg (breakfast),1g (evening) Gliclazide 160 mg bd	Metformin 500 mg (Suhur), 1g (Iftar) Gliclazide 160 mg bd	N	N	6.8
6	Glimepiride 2 mg od (evening)	Glimepiride 2 mg (Iftar)	N	N	7.4

Table 4.2 The adjustments in timing and dosage of the participants' medications pre-Ramadan, and the mean tissue glucose (BG) during continuous glucose monitoring.

*Participant 4 had time and dose adjustments for metformin from thrice daily to twice daily.

4 participants had 84–95% of their glucose control within the target range (4.4 – 10.0 mmol/L). Participant 2, who was on premixed insulin, metformin and dipeptidyl peptidase IV inhibitor, had 93% of the glucose control in the high glucose range (> 10mmol/L), requiring insulin dose adjustments pre-Ramadan, as well as after CGM. Participant 4 spent 46% of the time in target and 54% above (Table 4.3).

No severe hypoglycaemia requiring third party assistance was reported during the 5-day monitoring period. Three subjects had documented glucose values of less than 4.4 mmol/L (i.e. below %, Table 4.3). However, two of these participants had glucose value < 4.4 mmol/L for only 1 - 2% of the total monitored period. The 1% Below target reading in participant 3 constituted to spurious sensing by the CGM device at the end of the monitoring period. The 2% Below target reading in participant 4 comprised of glucose levels between 4.1 – 4.3 mmol/L. They occurred during the first day of monitoring just before the breaking of fast at 17:40 – 18:50 in the evening. The patient was asymptomatic and did not require any intervention. There were no other clinically significant hypoglycaemic episodes of less than 4.4 mmol/L in subsequent days.

The hypoglycaemic episodes were clinically significant in participant 5 who spent 10% of their time with a tissue glucose value between 3.3 - 4.0 mmol/L, mainly less than an hour before Iftar (sunset meal) and before Suhur (sunrise meal). The gliclazide dose was halved to 80 mg bd after the CGM results were obtained and the patient continued to fast during the rest of the month without documented hypoglycaemia on capillary blood glucose monitoring.

Participant	Above %	Within %	Below %
1	8	92	0
2	77	23	0
3	9	90	1
4	52	46	2
5	6	84	10
6	5	95	0

Table 4.3 Percentage of time spent above (> 10.0 mmol/L), within (4.4 – 10.0 mmol/L) and below (< 4.4 mmol/L) target glucose range.

4.3.2 Glycaemic variability during fasting and non-fasting periods

Although the resulting measures of glycaemic variability, as indicated by mean amplitude of glycaemic variability (MAGE), lability index, J index, continuous overlapping net glycaemic action (CONGA), and M-value were higher during non-fasting hours when participants break their fast between sunset and dawn, there was no significant difference when compared to the fasting periods (Table 4.4).

The risk of hypoglycaemia as measured by low blood glucose index (LBGI) was not significantly different between the fasting hours compared with the non-fasting hours (9.45 ± 18.96 vs. 1.21 ± 1.12; p=0.35).

High blood glucose index (HBGI), an indicator of hyperglycaemic risk, was also similar across the two periods (6.41 ± 7.21 vs. 10.46 ± 10.99; p=0.15).

The average daily risk ratio (ADRR), a predictor of future hypoglycaemia (< 4.0mmol/L) and hyperglycaemia (> 10.0mmol/L), was 21.82 ± 12.53. An ADRR

between 20 and 40 is considered moderate risk for future low and high glucose excursions[128].

	Total periods	**Fasting periods**	**Non-fasting periods**	p-value
Mean tissue glucose	8.92 ± 2.76	8.56 ± 2.42	9.68 ± 3.46	0.17
Measures of glycaemic variability				
SD	2.07 ± 0.83	1.81 ± 0.47	2.10 ± 0.95	0.45
MAGE	4.47 ± 0.75	4.69 ± 1.47	4.82 ± 1.63	0.90
CONGA	8.01 ± 2.68	7.66 ± 2.34	8.29 ± 2.96	0.21
J-Index	42.25 ± 25.27	36.52 ± 19.18	49.42 ± 34.05	0.19
M-value	10.21 ± 13.96	7.34 ± 11.17	14.95 ± 19.53	0.17
Risk measures - Predictors of extreme hypoglycaemia and hyperglycaemia				
LBGI	9.44 ± 18.96	9.45 ± 18.96	1.22 ± 1.12	0.35
HBGI	7.91 ± 8.59	6.41 ± 7.21	10.46 ± 10.99	0.15
ADDR	21.82 ± 12.53			

Table 4.4 The parameters of blood glucose control and glycaemic variability of the participants during the fasting (daylight hours from sunrise to sunset) and non-fasting hours of Ramadan. Values are mean ± SD (mmol/L).

4.4 Discussion

A considerable amount of food rich in refined carbohydrate is traditionally prepared for Ramadan and taken during non-fasting hours, especially at the Iftar meal. Dietary fat consumption has been shown to be higher in type 2 diabetes subjects during Ramadan[35]. Despite these dietary changes and previous reports of hypoglycaemic and hyperglycaemic excursions in Ramadan, when pre-Ramadan assessment and adjustments are implemented, the difference compared with fasting hours is not significant.

Measures of GV calculated were measures of total variability (SD), within-day variability (MAGE), and between-day variability ($CONGA_{24}$[127]). Table 4.5 showed the interpretations of each measure of glycaemic variability.

Each measure was greater during the non-fasting hours, but was not statistically significant, which may, in part, be due to the small number of participants. However, despite the small sample size, the glycaemic variability assessed by MAGE during Ramadan (4.47 ± 0.75) is similar to the MAGE value in published series of non-fasting subjects with type 2 diabetes (4.8 ± 2.1)[129], suggesting a representative sample.

With regard to hypoglycaemia, the value of the low blood glucose index (LBGI), as a predictor of extreme hypoglycaemia was higher during fasting interval than in non-fasting interval. However, the difference was not significant (p=0.35). On an individual basis, CGM has identified hypoglycaemic episodes in participant 5. It is worth noting that this participant did not have any time or dosage adjustments before Ramadan and was taking a combination of metformin and sulphonylurea. This is consistent with the findings that hypoglycaemia is commoner in type 2 diabetes

Criterion	Definition	Advantages	Disadvantages
SD (Total)	SD of all glucose values	Simple Classical statistical method	Does not address skewed asymmetrical distribution
MAGE	Mean of glucose excursions from peak to nadir (or nadir to peak) where the difference is greater than 1 SD	- Assess intra-day glycaemic variability - Describes major fluctuations, e.g. due to meals - Directly proportional to and highly correlated with SD of all glucose values	- Inter-operator dependent - Potential bias towards hyper-glycaemic peaks and insensitive to hypo-glycaemic nadirs (as hypoglycaemic range is commonly narrower than hyperglycaemic range, i.e. < 1 SD)
CONGA$_n$	SD of the differences between any glucose value and another one exactly *n* hours ago (or later)	- Assess intra-day ($CONGA_{1-23}$) and inter-day ($CONGA_{24}$) GV - Specifically developed for CGM - Unaffected by the asymmetry of a glycaemic profile - Independent of peaks or nadirs according to arbitrary definitions	
J-index	Combination of information from mean and SD of all glucose values $J = 0.324 \times (mean+SD)^2$	- Measures mean glucose and variability in one formula - Independent of an arbitrarily selected ideal glucose value - highly correlated with percentage of time in target range	- Sensitive to hyperglycaemia but relatively insensitive to hypoglycaemia, similar to MAGE
M-value	Weighted average of transformed glucose values, using 1,000 x $\|\log_{10}(glucose/100)\|^3$ M(100) is M at glucose value 100mg/dL	- Measures glycaemic variability relative to an arbitrary 'ideal' value - highly correlated with percentage of time in target range	- Skewed emphasis on hypoglycaemic excursions than hyper-glycaemic excursions - Requires glycaemic reference points (i.e. arbitrary ideal values)

Table 4.5 The pros and cons of each measure of glycaemic variability[127;130]

subjects on sulphonylureas with or without metformin, fasting for Ramadan[131]. A preferable alternative would be the use of a DPP-4 inhibitor or GLP-1 agonist to those who do not have good glycaemic control on metformin alone; or to adjust the doses of the sulphonylurea during Ramadan[54].

Four of the participants (1, 3, 5 and 6) had 84% to 95% of their glucose values within 4.4 – 10.0 mmol/L. All of these patients found that the CGM was useful in their self-management of diabetes. They frequently checked their BG values and were more aware of their dietary intake in their Iftar (sunset meal). This may also be the reason why participant 4 had 2% of glucose values between 4.1 – 4.4 mmol/L on the first day of the monitoring period, who became more aware of projected low readings in subsequent days and thus, avoided more low CGM readings.

Given the high pre-Ramadan HbA1c, participant 2 would generally be advised not to fast during Ramadan. 95% of his CGM readings were higher than 10mmol/L. The use of continuous glucose sensor allowed the patient to understand that his glucose control was not as satisfactory as the patient believed and to intensify his insulin treatment without increasing the risk of hypoglycaemia in order to continue fasting safely.

The main limitations of the study are the small number of recruits and the lack of a control group. The lack of statistical significance may reflect the small number and high standard deviations in the parameters, particularly LBGI and HBGI. The trend towards higher variability in non-fasting in comparison to fasting periods may reflect insufficient power, leading to type 2 error. Recruitment of patients in a limited time can be challenging in Ramadan, particularly during a religious event of such importance, and further studies including a larger number and wider spectrum of

participants, are warranted. It would also be useful to compare the GV of these subjects in the non-fasting months with the GV in the month of Ramadan to assess the alterations in dietary and social habits during Ramadan, as compared to normal routine. However, the participants were not keen to have continuous glucose monitoring beyond the month of Ramadan. Further studies using other control groups of non-fasting diabetic patients and fasting non-diabetic people, as compared to fasting Muslim patients, would also be useful to assess the effects of fasting and diabetes on GV.

Pre-Ramadan assessment and educational advice regarding healthy diet, adequate exercise and awareness of the risks of hypoglycaemia and hyperglycaemia play an important role in eliminating the damaging GV previously demonstrated in the EPIDIAR study[15].

4.5 Conclusion

Continuous glucose monitoring is a useful tool for assessing glycaemic variability and risks of hypo- and hyperglycaemia during fasting for Ramadan. To individuals who have had pre-Ramadan assessment and adjustments in their diabetes regimens, the glycaemic variability is similar between fasting and non-fasting periods, the risk of severe hypoglycaemia is minimal and the risk of extreme glucose excursions as calculated by ADRR is also moderate. Our findings suggest that systematic pre-Ramadan assessment and appropriate therapeutic adjustment according to the ADA recommendations are important in negating the previously described glycaemic variability seen during Ramadan.

Chapter 5: Glucagon-like peptide-1 receptor agonist and Dipeptidyl peptidase-4 inhibitor therapies in type 2 diabetes patients during Ramadan

5.1 Incretin hormones: from physiology to therapeutic use during Ramadan

Glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are new anti-diabetic therapies acting via incretin receptor signalling. The two incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are gut hormones released from the intestinal L cells in the distal ileum and colon and the K cells in the duodenum and jejunum respectively[132]. The incretin hormones exert their actions via G-protein coupled receptors: 1) GIP receptors are expressed mainly on pancreatic islet β-cells, and to a lesser extent, in adipocytes and central nervous system; 2) GLP-1 receptors are expressed on islet α- and β-cells, in the heart, kidney, lungs, gastrointestinal tract, and peripheral and central nervous systems. Circulating incretin levels increase rapidly and transiently after food ingestion, activating the receptors on pancreatic β-cells which lead to increase in cyclic AMP and intracellular calcium and subsequent insulin exocytosis, in a glucose-dependent manner[133]. GLP-1 also inhibits glucose-dependent glucagon secretion from the α-cells, reducing hepatic glucose release. GLP-1 induces gene transcription and insulin biosynthesis to increase β-cell proliferation and decrease apoptosis. It slows gastric emptying, thereby promoting the feeling of satiety and reducing food intake. Animal studies have also showed that GLP-1 acts centrally to promote satiety[134].

Endogenous human incretins have short half-lives (in minutes) and are degraded by the enzyme, DPP-4. Exenatide, the synthetic GLP-1R agonist, is degradation-resistant and has a longer half-life (2.4 hours in humans)[135]. Selective DPP-4

inhibitors (such as sitagliptin, vildagliptin and saxagliptin) extend the half-life of native incretins, thereby prolonging their effects[136].

In type 2 diabetes, the incretin hormone response is impaired[137] and post-prandial glucagon secretion is not adequately suppressed[138]. Both GLP-1R agonists and DPP-4 inhibitors target the above mechanisms (Table 5.1), which depends on oral glucose intake to improve glycaemic control[139]. GLP-1R agonists achieve greater reduction in HbA1c than DPP-4 inhibitors and have additional effects on delaying gastric emptying, appetite suppression and weight loss[140].

Features in type 2 diabetes	**Actions of endogenous GLP-1 in type 2 diabetes**	**GLP-1R agonist (exenatide)**	**DPP-4 inhibitor**
Defective insulin-stimulated insulin secretion	Glucose-dependent stimulation of insulin secretion	Yes	Yes
Inability to suppress postprandial glucagon secretion	Suppression of glucagon secretion	Yes	Yes
Abnormally high β cell apoptosis rate	Inhibition of toxin-induced β-cell apoptosis	Yes	Probable
Decrease in β cell mass	Increase in β-cell mass	Yes	Yes
Normal, increase or decrease in gastric emptying	Decrease in gastric emptying	Yes	No
Hypercaloric energy intake and obesity	Suppression of appetite and induction of satiety	Yes	Weight neutral
Insulin resistance	No immediate effect	No	No

Table 5.1 Biological actions of endogenous GLP-1, GLP-1R agonist and DPP-4 inhibitor in relation to the pathophysiology of type 2 diabetes (adapted from Drucker *et al.*[132]).

These properties that GLP-1R agonists exhibit make them a suitable class to help moderate the changing dietary patterns during Ramadan. Its glucose-lowering effect is glucose-dependent, minimising hypoglycaemia both during prolonged fasting and irregular food intake in the month of Ramadan. Short-acting GLP-1R agonist, exenatide, can be taken before meals to reduce appetite; this would be useful at Suhur (pre-dawn meal) to promote satiety before the daylight fasting, and Iftar (post-sunset meal) to prevent excessive feasting in the evening. Its moderate weight-losing effect[141] may also be advantageous in combating potential weight gain from overeating in the evenings during Ramadan.

5.2 Glucagon-like peptide-1 receptor agonist and glycaemic control during Ramadan

There are currently no published studies on the use of glucagon-like peptide-1 receptor agonists during Ramadan. A retrospective evaluation was carried out on type 2 diabetes subjects taking exenatide, who fasted during Ramadan, to assess their HbA1c, weight and hypoglycaemic episodes.

5.2.1 GLP-1R agonist: Method

Muslim patients who fasted during Ramadan in 2009 were identified from the community diabetes clinic in Brent. All of the patients were treated with exenatide 10mcg twice daily. Aside from metformin, all patients on other oral hypoglycaemic agents and insulin were excluded. The primary endpoints were the mean weight change and hypoglycaemic episodes before and during Ramadan and the mean HbA1c change before and after the month of Ramadan. Each hypoglycaemic

episode was defined as a self-monitored capillary blood glucose < 3.5 mmol/L with or without symptoms and recorded by the patients during the month before Ramadan and the month of Ramadan.

A second group of type 2 diabetes Muslim subjects who fasted during Ramadan, but were taking gliclazide 80mg twice daily with or without metformin, acted as controls.

Statistical analysis was performed using GraphPad Prism 5.01. A paired t-test was used to analyse weight and HbA1c changes before and after the month of Ramadan.

5.2.2 GLP-1R agonist: Results

In the exenatide group, mean baseline HbA1c was 8.05% (± 0.69 SD), mean age was 53.2 years (± 9.7 SD) and the duration of diabetes was 8.3 years (± 2.5 SD). There was no significant different in weight between the exenatide group and the gliclazide group before Ramadan (Table 5.2).

Table 5.2 Baseline characteristics of the participants

	Group 1 (Exenatide)	Group 2 (Gliclazide)
Participants (n)	26	26
Men:Women [n (%)]	15(58%):11(42%)	8(31%):18(69%)
Age [years, mean ± SD (range)]	53.2 ± 9.7 (33-73)	62.3 ± 9.8 (45-77)
HbA_{1c} (%, mean ± SD)	8.05 ± 0.69	8.95 ± 1.28
Weight (kg, mean ± SD)	85.8 ± 7.2	89.4 ± 8.7*
Ethnicity (n)		
Pakistani [n (%)]	10	24
Middle Eastern [n (%)]	12	0
Other [n (%)]	4	2
Duration of diabetes [years, mean ± SD (range)]	8.3 ± 2.5 (4.5-15.3)	6.9 ± 1.4 (4.5-11.2)

*p > 0.05 between group 1 and 2. SD = standard deviation

In the exenatide group, the total number of hypoglycaemic events was 9 episodes before Ramadan and 7 episodes during Ramadan (p=0.43). There was a small but non-significant increase in mean weight of 0.11 kg before and after Ramadan (p=0.55) (Table 5.3).

In the gliclazide group, there was a significant increase in mean weight of 0.81 kg (p<0.001) before and after Ramadan (Table 5.3). There was also a significant increase in the total number of hypoglycaemic events from 7 to 24 (p<0.001).

Although the mean change in HbA1c was significantly better in the gliclazide group in comparison to the exenatide group (-0.05% versus -1.20%, p<0.001) (Figure 5.1), the gliclazide group had a significant increase in hypoglycaemic events whilst the exenatide group had no significant change in hypoglycaemic events before and during Ramadan (Table 5.3).

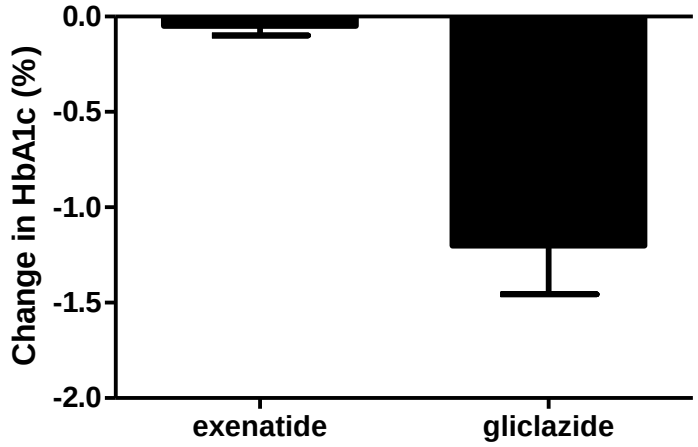


Figure 5.1 The mean changes in HbA1c before and after Ramadan between exenatide and gliclazide (p < 0.001).

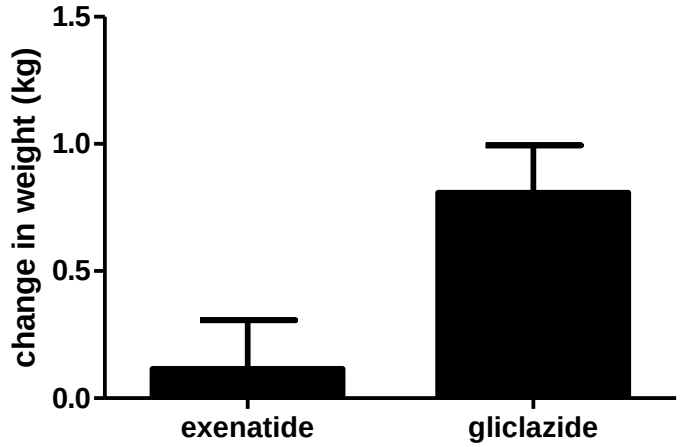


Figure 5.2 The mean changes in weight before and after Ramadan between exenatide and gliclazide (*p* = 0.013).

The mean increase in weight was significantly less in the exenatide group than the gliclazide group (0.11kg versus 0.81kg; *p*=0.013) (Figure 5.2).

Table 5.3 Change in outcome measures during Ramadan in participants taking exenatide (group 1) and gliclazide (group 2) with or without metformin

	Before Ramadan	After Ramadan	Mean change before and after Ramadan	Standard error of mean	p-value
Hypoglycaemic events (mean ± SD)					
Exenatide (n=26)	0.35 ± 0.49	0.27 ± 0.45	0.08		
Gliclazide (n=26)	0.27 ± 0.45	0.92 ± 0.94	0.65		
HbA1c (%, mean ± SD)					
Exenatide (n=26)	8.05 ± 0.69	8.00 ± 0.69	-0.05	1.304	P<0.001*
Gliclazide (n=26)	8.95 ± 1.28	7.75 ± 0.93	-1.20	0.256	
Weight (kg, mean ± SD)					
Exenatide (n=26)	85.82 ± 7.20	85.93 ± 7.55	0.11	0.191	P=0.013*
Gliclazide (n=26)	89.39 ± 8.69	90.20 ± 8.92	0.81	0.187	
*p-value for comparisons between the mean changes in group 1 and 2.					

5.2.3 GLP-1R agonist: Discussion

The number of hypoglycaemic events and mean weight remained stable before and during Ramadan in patients taking exenatide and metformin. In the gliclazide group, there was significant reduction in HbA1c, weight gain and an increase in hypoglycaemic events during Ramadan. The fall in HbA1c in the gliclazide group occurred in the expense of increased hypoglycaemia and weight gain. The reasons for such a large fall in HbA1c may be due to a combination of fasting, reduced meal frequencies, reduced caloric intake or food contents in the gliclazide group. However, details about food intake were not available for comparison.

In a randomised, triple-blind, placebo-controlled, 30-week non-Ramadan study, exenatide has been shown to reduce HbA1c with no weight gain or change in the incidence of hypoglycaemia in patients with type 2 diabetes inadequately controlled on metformin alone[141]. Reported rates of mild-to-moderate hypoglycaemia of 5.3% were the same in both the group that received exenatide 10mcg twice daily with metformin and metformin alone (with placebo).

Although this small audit lacked information regarding the duration of exenatide treatment, the length of fasting days and whether the timing of gliclazide or exenatide were altered during Ramadan, it corroborated the existing evidence that exenatide would be a safe addition, in terms of hypoglycaemic risk, for type 2 diabetes people fasting for Ramadan.

Exenatide also reduced the post-prandial glucose rise to a greater extent than insulin glargine in a comparative study[142]. As it stimulates insulin secretion following an oral glucose load with a dose-dependent blunting effect on the post-prandial rise of

plasma glucose[143], it provides possible benefits in moderating glucose excursions at Suhur and Iftar during Ramadan.

Apart from hypoglycaemia, dehydration is another risk of fasting in patients with diabetes during Ramadan[15]. As exenatide is cleared renally, it is not recommended for use in patients with severe renal impairment (Creatinine Clearance < 30 mL/min), and the U.S. food and drug administration recommended caution when starting or increasing the dose of exenatide from 5mcg to 10mcg in patients with moderate renal impairment (Creatinine Clearance 30 to 50 mL/min)[144]. Moreover, gastrointestinal (GI) adverse events (nausea, vomiting and diarrhoea) are commonly reported with highest incidence at initiation of the GLP-1R agonist therapy. Nausea was mostly mild-to-moderate in intensity in metformin-treated participants started on GLP-1R agonist[141], and generally subsided by 8 weeks after the initiation of exenatide treatment[141;145].

The potential impact of developing or worsening renal disease due to dehydration following prolonged fasting together with the known GLP-1R agonist-induced GI side effects should be considered when prescribing exenatide to the diabetic Muslim population, even in those with only mild renal impairment. The side effect profile would also indicate that exenatide should be initiated more than 8 weeks before Ramadan to allow potential GI symptoms to settle.

Alternatively, liraglutide, a once-daily GLP-1R agonist, is not primarily eliminated by the kidneys, but is metabolised by proteolysis[146]. Its extended activity is achieved by modifying the structure of the human GLP-1 peptide to increase the circulating half-life to 12 hours[135]. The GI side effects of liraglutide was also reported to be more

short-lived than exenatide, up to 4 weeks[147]. Therefore, it is a safe alternative for use in Ramadan.

Once-weekly formulations of GLP-1R agonists, such as exenatide LAR and taspoglutide[148] are being developed and further studies of these agents during periods of fasting with respect to their tolerability and efficacy will be eagerly anticipated.

5.3 Dipeptidyl peptidase-4 inhibitor and glycaemic control during Ramadan

5.3.1 Hypoglycaemia

The addition of a DPP-4 inhibitor to metformin therapy during Ramadan in fasting Muslim patients with type 2 diabetes offers advantages over gliclazide primarily in the reduction in the incidence of hypoglycaemia[71;72]. One of the commonest causes of hypoglycaemia is diabetes medication, especially where the goal of treatment is intensive glucose control[8] involving insulin therapy or insulin secretagogues, such as sulphonylureas, particularly in patients with irregular eating patterns or who miss meals (such as during Ramadan fast). In view of this, the American Diabetes Association recommends caution in the use of sulphonylureas during Ramadan[126].

DPP-4 inhibitor is associated with minimal risk of hypoglycaemia in combination with metformin, sulphonylurea or a thiazolidinedione[149;150]. In a 52-week non-Ramadan study, when added to metformin, vildagliptin significantly lowered the incidence and severity of hypoglycaemic episodes compared with glimepiride[151].

This low hypoglycaemic risk may be because GLP-1 enhanced insulin secretion and inhibition of glucagon secretion are glucose-dependent[152]. Vildagliptin, a DPP-4 inhibitor, prevents the rapid degradation of endogenous GLP-1 and glucose-dependent insulinotropic peptide and increases plasma levels of their intact, active form. It acts by an enhancement of pancreatic islet function, with improved β- and α-cell sensitivity to glucose[153]. The action of potassium channel-based insulin secretagogues, such as sulphonylureas, is non-glucose-dependent, which explained the higher hypoglycaemic risk during fasting.

A prospective study comparing vildagliptin and gliclazide as an add-on to metformin during Ramadan showed that there was no hypoglycaemia in the vildagliptin group (n = 23), compared with 34 hypoglycaemic events (41.7%) in the gliclazide group (n = 36)[71].

A large randomised open-labelled study comparing sitagliptin and sulphonylureas (glibenclamide, gliclazide, and glimepiride) in type 2 diabetes Muslims who were treated with or without metformin, and fasted for Ramadan, also demonstrated that fewer patients experienced hypoglycaemic events in the sitagliptin group (n = 507) relative to the sulphonylurea group (n = 514) (6.7% versus 13.2%, respectively). And the risk of symptomatic hypoglycaemia was significantly lower with sitagliptin relative to sulphonylurea (Mentel-Haenszel relative risk ratio = 0.51; 95% CI, 0.34 - 0.75; p<0.001).

The findings of these prospective observational and randomised studies[71;72] indicate that these newer anti-diabetic agents have a beneficial role in the management of patients during Ramadan, particularly to reduce their risk of hypoglycaemia during the long daytime fasting periods.

5.3.2 Safety and adverse events

The primary concern regarding these new therapies centres on their long-term safety profiles. Safety outcomes on these incretin-based therapies were reported in non-Ramadan randomised control trials for a duration up to 52 weeks[147;154;155]. DPP-4 is a cell-membrane protein expressed in many tissues, including lymphocytes. This raised concerns about its long-term effect on the immune system. Upper respiratory tract infection and urinary tract infection have been reported as adverse events in patients treated with DPP-4 inhibitors[156]. Meta-analysis of clinical trials has found a significant increase in all-cause infection associated with sitagliptin but not with vildagliptin[157]. Although the relative risk is low (relative risk = 1.15; 95% CI, 1.02 – 1.31; p=0.03), the clinical implication is still significant in millions of Muslim diabetes patients who are prone to urinary tract infection due to diabetes or dehydration associated with fasting.

Moreover, during post-marketing surveillance, acute pancreatitis and severe allergic reaction were reported in 88 patients taking DPP-4 inhibitors[158] and 6 reported cases of necrotising and haemorrhagic pancreatitis in patients taking exenatide[159]. Other factors can also predispose the individuals to pancreatitis, such as obesity and hypertriglyceridaemia, and the presence of type 2 diabetes. Analysis of pancreatitis in U.S. healthcare claims database of individuals with type 2 diabetes suggested that their risks were increased threefold over non-diabetic individuals[160].

With reference to Ramadan, there has been a case report of massive gastric dilatation and acute pancreatitis following ‘breaking’ the Ramadan fast at Iftar meal[161], similar to that of acute pancreatitis associated with re-feeding syndrome in anorexia nervosa[162]. This case merely represents a single incident as there is

currently no evidence causally linking Ramadan fasting and acute pancreatitis-associated refeeding syndrome. Nonetheless, Ramadan-focused education on a healthy balanced diet is essential to minimise overeating.

5.3.3 Recommendations during Ramadan

The National institute for clinical excellence (NICE) recommended exenatide as a third line agent following metformin and sulphonylurea when blood glucose control is inadequate [HbA1c $\geq$ 7.5% (58 mmol/mol)][55]. Our findings suggest that exenatide would be more suitable than gliclazide when considering an add-on to metformin for type 2 diabetes patients planning to fast for Ramadan.

DPP-4 inhibitors are recommended by NICE as second-line therapy to first-line metformin or sulphonylurea when blood glucose control is inadequate [HbA1c $\geq$ 6.5% (48 mmol/mol)][55]. This would also be an appropriate choice in people with type 2 diabetes who are planning to fast for Ramadan.

In the context of moderate to severe renal impairment, DPP-4 inhibitors are safe in reduced doses[163] and provide a better alternative to GLP-1R agonists in patients with diabetic nephropathy.

Chapter 6: Insulin regimens in type 2 diabetes patients during Ramadan

6.1 Different options of insulin regimens during Ramadan

For people already on insulin, Ramadan fasting can represent a challenge to their glycaemic control. As mentioned in Chapter two, patients with well-controlled diabetes on insulin are considered as moderate risk to fast during Ramadan[54;126]. The EPIDIAR study primarily observed the effects of fasting in diabetes subjects without any intervention and reported that insulin dose was unchanged in more than 64% of patients. The survey also reported increased risks of severe hypoglycaemia and hyperglycaemia associated with fasting, which may have contributed to their insulin dosage not being adjusted[15]. A recent study using continuous glucose monitoring reported no symptomatic hypoglycaemia when 20 – 30% of insulin requirement was reduced during Ramadan[164]. It is therefore important for these moderate-risk patients to have pre-Ramadan medical assessment to adjust their insulin treatment appropriately.

6.1.1 Switching insulin doses Suhur to Iftar, and vice versa

The Ramadan Prospective Diabetes Study initially suggested switching the full pre-Ramadan morning dose of insulin to Iftar (sunset meal) and taking half of the pre-Ramadan evening dose at Suhur (pre-dawn) (Table 6.1). However, the highest frequency of hyperglycaemic episodes (defined as > 11.11 mmol/l) with this regimen was seen at pre-dawn, followed by post-dusk, whilst most of the hypoglycaemic events also occurred at pre-dawn, followed by midday. Following this, the authors suggested further reduction in the pre-dawn insulin dose by 75%, rather than only 50%, to help minimise the pre-dawn and midday hypoglycaemia[165].

Table 6.1 Suggested changes in insulin regimens during Ramadan.

	Pre-Ramadan				**During Ramadan**				
Authors	Breakfast	Lunch	Dinner	Bedtime	Suhur	Fasting Period	Iftar	Bedtime	Midnight
Ahmedani et al. 2012[165]	Morning insulin *(e.g. 20 units Novomix 30)*		Evening insulin *(e.g. 30 units Novomix 30)*		25% of evening insulin *(e.g. 7.5 units Novomix 30)*		Morning insulin *(e.g. 20 units Novomix 30)*		
Salti et al. 2009[166]	Glimepiride			Glargine			Glimepiride	Glargine	
Bakiner et al. 2009[29]	Repaglinide	Repaglinide	Repaglinide	Glargine	Repaglinide		Repaglinide	Glargine	Repaglinide
Mattoo et al. 2003[75]	Humulin 30/70		Humulin 30/70		Lispro Mix25/75		Lispro Mix25/75		
Hui et al. 2010[76]	Human Mixtard 30/70		Human Mixtard 30/70		Human Mixtard 30/70		Humalog Mix 50/50		

6.1.2 Long-acting insulin and oral hypoglycaemic agents

In an open, multi-centre, prospective study, glimepiride (given at Iftar, mean dose 4.3mg ± 1.0mg SD per day) in combination with glargine (given any time before bedtime, but at the same time every day, mean dose 29.2 ± 16.1 SD units/day) conferred a significant increase in the total number of hypoglycaemic episodes during Ramadan, as compared to pre- and post-Ramadan periods, despite a stable HbA1c and mean fasting blood glucose during the fasting periods[166]. Whilst a shorter acting sulphonylurea, such as gliclazide, with glargine may help ameliorate part of the hypoglycaemia risk[7], alternative regimens should be considered[67;167].

In a small prospective study (n = 19), repaglinide (taken at suhur, iftar and midnight meals) plus single-dose glargine (at bedtime) (Table 6.1) has been shown to be safe in well-controlled type 2 diabetic patients when compared to non-fasting controls (repaglinide taken with regular meals three times a day and glargine at bedtime). Fructosamine, fasting and post-prandial glucose levels were similar between fasting and control group, with no reported hypoglycaemia[29]. However, this regimen required taking an extra meal at midnight and may not be ideal for patients with suboptimal HbA1c. Similarly, for patients on maximally tolerated doses of metformin and sulphonylurea, the addition of a single basal analogue insulin, detemir, was not sufficient to achieve an HbA1c of < 6.5% (48 mmol/mol) in as many patients when compared to the addition of a biphasic or prandial analogue insulin aspart[168].

Other possibilities include a DPP-4 inhibitor and glargine or DPP-4 and detemir or using exenatide at suhur and iftar meals and glargine at bedtime; however, further research is necessary before these combinations can be fully endorsed.

6.1.3 Once or twice daily neutral protamine hagedorn (NPH) insulin

Intermediate-acting NPH insulin has an onset of action within 1.5 hours and a maximum duration of 12 hours. In one of the earliest Ramadan studies, patients on once or twice daily NPH insulin tried a variety of ways to self-manage their glycaemia whilst fasting. These options included either omitting the morning dose or evening dose when taking twice daily regimen, or switching the once-daily dose from morning to evening. The outcomes of these measures were not clearly reported[169].

More recently, pregnant women with diabetes (all types) treated with NPH insulin whilst fasting for Ramadan had stable fructosamine and HbA1c before and after Ramadan[170]. Unfortunately, insulin requirements in pregnant diabetic women are very different and the findings cannot be extrapolated to non-pregnant diabetes subjects.

Nonetheless, NPH insulin is cheaper compared to basal analogues, such as glargine and detemir. This approach may be more practical and sustainable in developing countries. Indeed, NICE guidance stated that the first insulin treatment for type 2 diabetes should be NPH insulin at bedtime or twice daily[55].

6.1.4 Basal Bolus regimen

Studies on Ramadan fasting using basal bolus regimens were primarily performed on type 1 diabetes subjects[78;171;172]. The sample sizes were small and the selected patients in these studies were usually well controlled [HbA1c < 7.5% (58 mmol/mol)], with no history of hypoglycaemia or diabetic ketoacidosis. Although the use of glargine was found to be safe and maintained sufficient plasma insulin levels over the fasting periods, this was achieved via a strict regimen of meticulously adjusted

insulin dosage and close monitoring of blood glucose levels[171;172] that may be difficult to realise in practice. Children with type 1 diabetes who chose to fast during Ramadan were liable to hypoglycaemia during fasting unless the dose of basal insulin was reduced by 10 – 20%[173].

For people with type 2 diabetes, it would seem reasonable that basal bolus regimen would provide the flexibility during Ramadan. Reduction of the basal insulin dose will probably be necessary, but further studies will be needed to quantify that.

6.1.5 Mixed insulin regimens

For patients already on twice daily mixed insulin before Ramadan, omitting lunchtime meals during Ramadan can result in low glucose levels at midday and postprandial glucose rises pre-dawn and after sunset.

In a randomised, open-label, crossover study, patients initially taking human insulin 30/70 (Humulin® 30/70) pre-Ramadan instead received insulin lispro Mix 25 at Suhur and Iftar for the first two weeks during Ramadan and then switched back to Humulin® 30/70 for the remaining 2 weeks, and vice versa. The insulin doses were not changed. There was a small, but significant improvement in 2-hour post-prandial mean blood glucose in the Mix 25 group compared to the human insulin 30/70 group at iftar[75]. It was attributed to the rapid peak concentration following subcutaneous administration of the analogue insulin (C_{max} 90 minutes) compared to the human Mix 30/70 (C_{max} 130 minutes).

6.1.6 Proposed Insulin regimen – Mixtard 30 at suhur, Humalog Mix 50 at iftar

For patients who cannot achieve good glycaemic control with twice daily human Mixtard 30 insulin, the evening dose at Iftar is switched from Mixtard 30 to Humalog Mix 50. The greatest variability with nadir and peak glucose occurred before and after Iftar, respectively[164]. Hence, the rationale for the switch is to provide patients with a more rapid-acting insulin that has shorter time of onset and peak time for the large meal in the evening, to improve the post-prandial glucose control without increasing the risk of hypoglycaemia. Since a smaller proportion of the daily caloric intake is usually consumed at suhur (pre-dawn meal), the morning insulin is kept with Mixtard 30 before the daylight fasting begins.

6.2 Comparison of Humalog Mix 50 with human insulin Mix 30 in type 2 diabetes patients during Ramadan

6.2.1 Aim

We undertook an observational study to evaluate hypoglycaemic events (defined as a blood glucose < 3.5 mmol／l with or without symptoms), HbA1c and weight change in Muslim patients with type 2 diabetes who fasted and whose HbA1c was insufficiently controlled with twice daily Mix 30 insulin regimen (Human Mixtard 30/70) before Ramadan. The evening dose was therefore changed to Mix 50 (Humalog Mix 50/50) based on clinical judgement.

The aim is to compare the effect of Mix 30 and Mix 50 insulin regimes on HbA1c, weight and hypoglycaemic events in type 2 diabetes patients who fasted during the month of Ramadan.

6.2.2 Methods

Participants

This was an observational study of Muslim patients with type 2 diabetes treated in accordance with the American Diabetes Association's recommendations for the management of diabetes during Ramadan[126]. Participants who were 18 years or over and fasted for more than 15 days were included. Patients attended six primary care practices in the London boroughs of Brent, Ealing and Harrow, which had taken part in a workshop to educate healthcare professionals on issues surrounding diabetes and fasting. All participants received Ramadan-focused education about the management of their diabetes and the identification and management of hypoglycaemia. Patients were already on Mix 30 insulin twice daily before attending the education. They either continued on Mix 30 insulin twice daily or their evening insulin dose was changed to Mix 50 two weeks before Ramadan. Patients who continued on Mix 30 used their usual pre-study injection-to-meal time interval. Patients who had Mix 50 insulin in the evening were advised to inject immediately before meals. Allocation to treatments was based on clinical judgement prior to inclusion and was not randomised. Indications for changing to Mix 50 included an elevated 2-hour postprandial capillary blood glucose greater than 10mmol/l in the evenings.

Assessments

All participants were seen two weeks before the start of Ramadan and seen again ten days after the last day of Ramadan. All participants were instructed to monitor their symptoms closely and record daily pre-prandial and 2-hour postprandial blood glucose, hypoglycaemic events and weight. An Ascensia Contour glucose meter (Bayer Healthcare, U.K.) was provided to participants. Before Ramadan, participants were asked to provide any documentation of hypoglycaemia from either a blood glucose meter or glucose diary records. During Ramadan, participants were asked to check their blood glucose levels if they had any symptoms of dizziness, visual blurring, palpitations, nausea, sweating, confusion, tremor or intense hunger. Both the blood glucose diary and the blood glucose meter were analysed for episodes of hypoglycaemia. Patients were also asked to notify their general practitioner if they had any episodes of hypoglycaemia, and they were told to attend the daily rapid access clinics in Brent if they had any concerns about their diabetes. Severe hypoglycaemia was defined as a low blood sugar (< 3.5 mmol/l) requiring assistance to treat the hypoglycaemic event. In addition, participants were asked to document the total number of days they had fasted.

Statistical Analysis

Changes between pre- and post-fasting HbA1c and weight were analysed using analysis of covariance (ANCOVA) models to adjust for the effects of age, gender, and ethnicity, duration of diabetes and baseline values. ANOVA can firstly be used to add precision in comparisons between datasets by accounting for the variability (i.e. how scatter the data points around the mean) on prognostic variables. Secondly, the purpose of using ANOVA in this context was to ‘adjust’ comparisons between the

groups for imbalances in the prognostic variables (referred to as covariates) between these groups, e.g. to determine whether there was a difference between the pre- and post-fasting HbA1c, independent of any age or gender differences between the groups. The ‘adjustment’ was made based on fitting a particular kind of regression line. By doing so, it eliminates variation due to each covariate and therefore provides a more precise analysis.

Patients were asked to record the total number of hypoglycaemic events 4 weeks prior to the start of Ramadan and subsequently asked to record hypoglycaemic events during the month of Ramadan. Least squared (adjusted) means (LSM) were presented for treatment differences. For hypoglycaemic events, in addition to the total number per patient, the data were also dichotomised into groups of patients who experienced no events during fasting and those who experienced at least one event during fasting.

As a result of the non-interventional nature of this study according to the Medicines and Healthcare products Regulatory Agency guidance on what constitutes a clinical trial, central ethics committee approval was not sought for the observational study.

6.2.3 Results

Fifty-two patients were included. The Mix 50 group (n=26 patients) received Mix 30 at the meal before sunrise and Mix 50 after sunset. The Mix 30 group (n=26 patients) received Mix 30 twice daily. The baseline demographics of the two groups are shown in Table 6.2. The mean age was 62.3 ± 9.8 years in Mix 50 group and 61.9 ± 9.2 years in Mix 30 group (p=0.90). The mean duration of diabetes was approximately 9.5 years in each group. The mean baseline HbA1c values were similar between the

two groups (9.05 ± 0.43% versus 8.98 ± 0.37%; *p*=0.22). ANCOVA models were used to adjust for baseline imbalances due to the non-randomised allocation to treatment.

Mix 50 was associated with a small reduction of 0.04 (*p*=0.81) in the mean number of hypoglycaemic events during Ramadan compared with before Ramadan (Table 6.3a), whereas Mix 30 was associated with an increase of 0.15 (*p*=0.43) (Table 6.3b). These differences between the groups were not statistically significant following adjustment for baseline factors [LSM difference between groups = 0.135, *p*=0.36, 95% confidence limits (-0.16, 0.43)].

The Mix 50 group had a mean HbA1c reduction of 0.48% (*p*=0.0001) (Table 6.3a) whereas the Mix 30 group had a mean HbA1c increase of 0.28% (*p*=0.007) (Table 6.3b). These differences, adjusting for baseline factors, were statistically significant [LSM difference 0.40%, *p*=0.0004, 95% confidence limits (0.19%, 0.62%)].

In the Mix 50 group, there was a significant increase in mean body weight before and after Ramadan (mean weight change = 0.81kg, *p*=0.0002) (Table 6.3a). There was a small, but non-significant increase in mean weight in the Mix 30 group of 0.33kg (*p*=0.082) after Ramadan (Table 6.3b). These differences however, adjusting for baseline imbalances, were not statistically significant [LSM difference -0.09, *p*=0.62, 95% confidence limits (-0.47, 0.28)].

However, direct comparison between the groups can be biased due to the non-randomised nature of the groups in that patients with higher post-prandial glucose values were pre-selected to the Mix 50 group. In summary, the Mix 50 group had no significant change in hypoglycaemic events, but had a significant reduction in mean

HbA1c (Figure 6.1) and an increase in mean body weight (Figure 6.2) before and after Ramadan. In the Mix 30 group, there were no significant changes in hypoglycaemic events and mean body weight (Figure 6.4), but a significant increase in mean HbA1c (Figure 6.3) before and after Ramadan.

Table 6.2 Baseline characteristics of the participants		
	Group 1 (Mix 50)	Group 2 (Mix 30)
Participants (n)	26	26
Men:Women [n (%)]	8 (30.8%):18 (69.2%)	10 (38.5%):16 (61.5%)
Age [years, mean ± SD (range)]	62.3 ± 9.8 (45-77)	61.9 ± 9.2 (44-77)*
HbA_{1c} (%, mean ± SD)	9.05 ± 0.43	8.98 ± 0.37*
Weight (kg, mean ± SD)	89.4 ± 8.7	85.8 ± 7.2*
Ethnicity (n)		
Pakistani [n (%)]	24 (92.3%)	10 (38.46%)
Middle Eastern [n (%)]	0 (0%)	12 (46.15%)
Other [n (%)]	2 (7.7%)	4 (15.4%)
Duration of diabetes [years, mean ± SD (range)]	9.8 ± 2.8 (4.6-16.5)	9.5 ± 3.3 (4.5-16.5)*

*p > 0.05 between group 1 and 2. SD = standard deviation

Table 6.3a Change in outcome measures during Ramadan in participants receiving Mix 30 before sunrise and Mix 50 after sunset (the Mix 50 group)			
	Before Ramadan	After Ramadan	Least squares mean change
Hypoglycaemic events (n ± SD)			
Mix 50	0.46 ± 0.65	0.42 ± 0.58	0.058
HbA1c (%, mean ± SD)			
Mix 50	9.05 ± 0.43	8.56 ± 0.62	-0.100
Body weight (kg, mean ± SD)			
Mix 50	89. 4 ± 8.7	90.2 ± 8.9	0.57
Analysis of covariance (ANCOVA) including terms for treatment group, gender and ethnicity as factors and age and duration of diabetes and baseline values for weight, HbA1c and hypoglycaemic events. SD = standard deviation, SEM = standard error.			

Table 6.3b Change in outcome measures during Ramadan in participants receiving Mix 30 twice daily (the Mix 30 group)			
	Before Ramadan	After Ramadan	Least squares mean change
Hypoglycaemic events (n ± SD)			
Mix 30	0.42 ± 0.58	0.58 ± 0.81	0.193
HbA1c (%, mean ± SD)			
Mix 30	8.98 ± 0.37	9.27 ± 0.59	0.303
Body weight (kg, mean ± SD)			
Mix 30	85.8 ± 7.2	86.1 ± 7.7	0.47
Analysis of covariance (ANCOVA) including terms for treatment group, gender and ethnicity as factors and age and duration of diabetes and baseline values for weight, HbA1c and hypoglycaemic events. SD = standard deviation, SEM = standard error.			

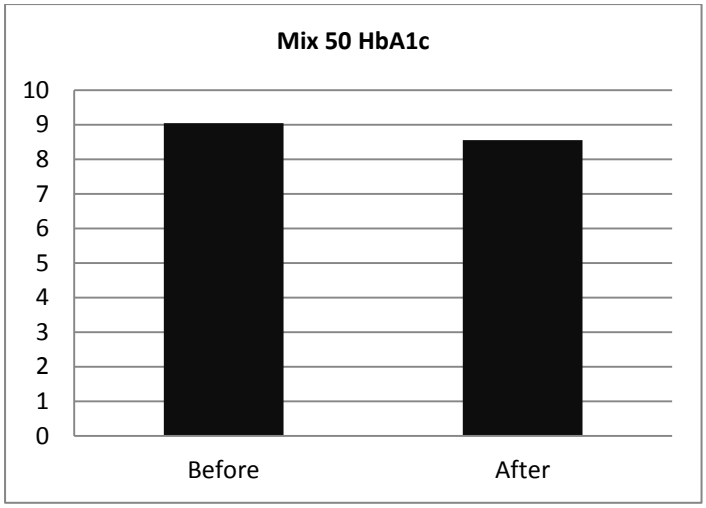


Figure 6.1 HbA1c (%) of the Mix 50 group before and after Ramadan (9.05 ± 0.43 vs. 8.56 ± 0.62; p = 0.0001).

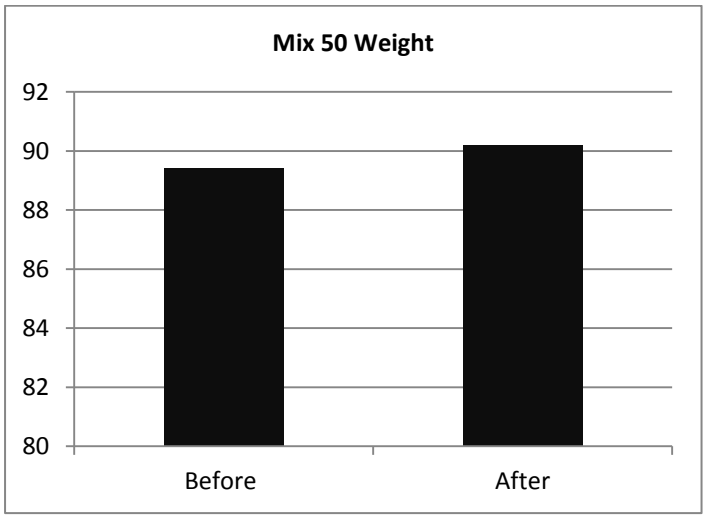


Figure 6.2 Weight (kg) of the Mix 50 group before and after Ramadan (89.4 ± 8.7 vs. 90.2 ± 8.9; p = 0.0002).

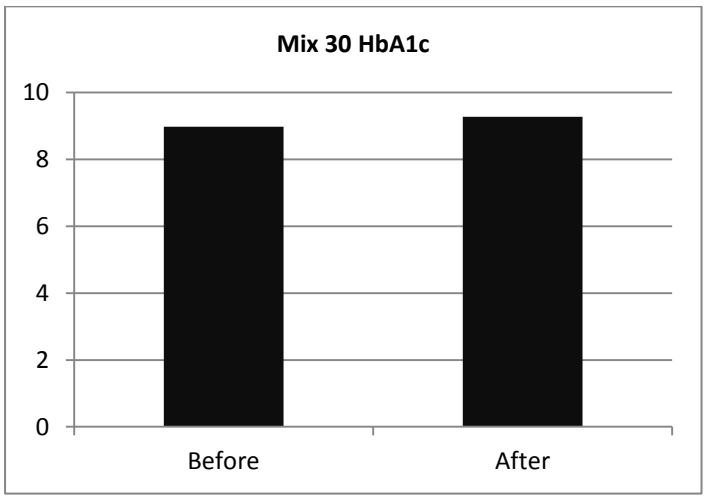


Figure 6.3 HbA1c (%) of the Mix 30 group before and after Ramadan (8.98 ± 0.37 vs. 9.27 ± 0.59; p = 0.007).

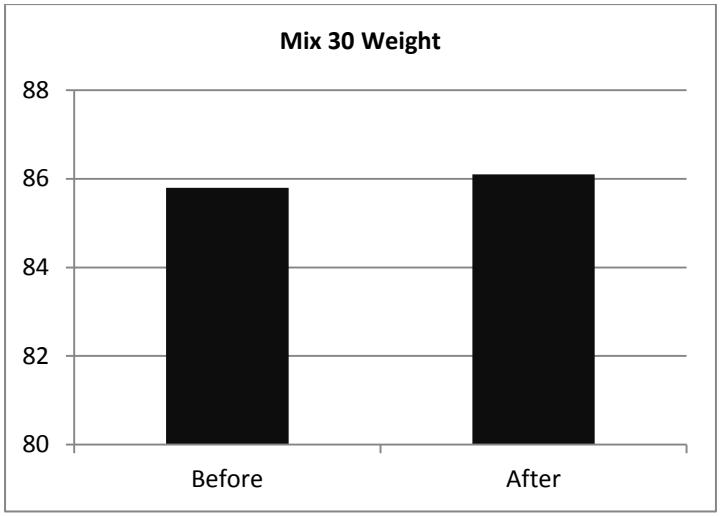


Figure 6.4 Weight (kg) of the Mix 30 group before and after Ramadan (85.8 ± 7.2 vs. 86.1 ± 7.7; p = 0.082).

6.2.4 Discussion

Humalog Mix 50 is a premixed insulin analogue containing 50% of lispro and 50% neutral protamine lispro (NPL, an intermediate-acting insulin), whereas human Mixtard 30 is a mixture of 30% dissolved human insulin (rDNA) and 70% isophane insulin (NPH) (Table 6.4). The pharmacokinetics of analogue premixed insulin is considered to be more akin to the normal pattern of insulin secretion than premixed human insulin[174]. The former has a quicker time to onset of 5-15 minutes versus 30-60 minutes and a shorter time to peak (Tmax) of 115 minutes versus 173 minutes in premixed human insulin.

6.2.4.1 Hypoglycaemia

Although hypoglycaemia tends to be less frequent in type 2 compared to type 1 diabetes, it remains a considerable risk, particularly in patients treated with insulin for years and in those who have significant beta-cell failure and insulin deficiency[126]. Hypoglycaemia may be exacerbated by the inappropriate response of counter-

regulatory hormones and the defect in epinephrine secretion due to autonomic neuropathy[171].

In this report, there were no significant differences in the mean number of hypoglycaemic episodes before and during Ramadan in both Mix 50 and Mix 30 groups. In the crossover, comparative trial, Mattoo et al.[75] have also shown no change in the mean number of hypoglycaemic episodes in patients on Humalog Mix 25/75 and human insulin Mix 30/70. These four regimens are tolerated during Ramadan in their risk of hypoglycaemia.

The focus of both studies was mainly on the change in the type and composition of the premixed insulins, rather than on dosage adjustments, which can also affect hypoglycaemic rate, weight and overall glycaemic control. There were only a few studies during Ramadan focusing on the appropriate dose adjustments, mainly on type 1 diabetes. Further studies taking into account the amount of food intake, titration regimens and total insulin requirements would guide clinicians on appropriate insulin adjustments of the commonly used premixed insulins, such as Novomix 30, in type 2 diabetes patients during Ramadan.

6.2.4.2 Weight change

Previous studies have shown no change in body mass index or weight during the fasting period in type 2 diabetes patients treated with once daily insulin compared to controls that were on repaglinide or sulphonylureas[27;29]. In the crossover study with Humalog Mix 25/75 and human insulin Mix 30/70, there was also no significant change in body weight for all patients for the duration of the study (mean 0.08, SD 1.5, p=0.607). Information about calorie intake and exercise are not available in this

study. These would be important factors that may have contributed to the weight increase in the Mix 50 group.

6.2.4.3 Glycaemic control

Changing to Humalog Mix 50 in the evening during Ramadan resulted in an improvement in glycaemic control without increasing the incidence of hypoglycaemia. In reviews of comparative trials, premixed insulin analogues and premixed human insulin provided similar glycaemic control in terms of decreasing HbA1c, fasting blood glucose and hypoglycaemia[175;176]. Therefore, the main advantage of using analogue insulin during Ramadan is to provide a more physiologic and predictable time-action profile. Premixed insulin analogues, such as Humalog Mix 50, have quicker onset and peak shorter than human Mixtard 30 (Table 6.4). It produces greater reductions in the magnitude of postprandial glucose excursions than human insulin 30/70[177], helping to tackle the large meal at Iftar.

The predawn meals are usually smaller. Keeping the morning insulin to Human Mixtard 30 has not resulted in a higher incidence of hypoglycaemia, which can be expected with the slower onset of action of the human premixed insulin. As Human Mixtard 30 is no longer available in the U.K., future studies will be useful to explore other viable options including Humalog Mix 50 or Novomix 30 twice daily, and other treatment approaches, such as basal analogues at bedtime and bolus insulin at iftar and suhur. As the duration of action of glargine is longer than detemir (median duration of action for glargine = 24 hours; median for detemir = dose-dependent: 12 hours for 0.2 units/kg, 20 hours for 0.4 units/kg)[178;179], using detemir as the basal insulin during Ramadan may have lower risk of hypoglycaemia, particularly just

before breaking the fast (before Iftar in the afternoon or early evening depending on seasonal changes).

The duration of the study (7.5 weeks) was too short to firmly conclude that the groups achieved their maximum HbA1c. An alternative measurement for glycaemic control, such as serum fructosamine, would have been useful in this study as a more appropriate marker to evaluate the glycaemic control during this short interval. Due to the observational nature of the study, patients were not randomised. Further studies with ethics approval in which patients were randomised to different groups of insulin treatments with a crossover design after 2 weeks during Ramadan would be preferable. An additional limitation of the study is that complete post-prandial glucose measurements were not available from the participants, which would have been useful in evaluating the contribution of HbA1c in the Mix 50 group.

In conclusion, our findings demonstrated that switching to analogue Mix 50 insulin in the evening has a role in the management of type 2 diabetes patients already on twice daily mixed insulin in order to improve their glycaemic control without compromising their risk of hypoglycaemia during Ramadan.

Table 6.4 The onset and duration of different insulins (adapted from Diabetes UK insulin wall chart)[180].

NAME	SOURCE	TAKEN	ONSET, PEAK AND DURATION
			0 2 4 6 8 10 12 14 16 18 20 22 24
RAPID ACTING ANALOGUE			
NovoRapid	Analogue	Just before / with / just after food	
Humalog	Analogue	Just before / with / just after food	
SHORT-ACTING INSULINS/NEUTRAL INSULIN			
Actrapid	Human	30 mins before food	
Humulin S	Human	20-45 mins before food	
MEDIUM AND LONG-ACTING INSULINS			
Insulatard	Human	About 30 mins before food or bed	
Humulin I	Human	About 30 mins before food or bed	
MIXED INSULINS			
Mixtard 30	Human	30 mins before food	
Humulin M3	Human	20-45 mins before food	
ANALOGUE MIXTURE			
Humalog Mix 25	Analogue	Just before / with / just after food	
Humalog Mix 50	Analogue	Just before / with / just after food	
NovoMix 30	Analogue	Just before / with / just after food	
LONG-ACTING ANALOGUE			
Lantus	Analogue	Once a day, anytime (but at same time each day)	
Levemir	Analogue	Once or twice daily	

Chapter 7: Advances, Challenges and future directions in Ramadan research

7.1 Advances in research on Ramadan

7.1.1 Increasing awareness of Ramadan in medical conditions

There has been an exponential increase in the number of studies based on fasting during Ramadan in the last few years. Using 'Ramadan' as a title or abstract search term on PubMed revealed 43 articles published from 1960 – 1990. From 1991 – 2000, there were 90 published articles and since 2001, there were about 330 Ramadan-related articles with diabetes being the focus in the majority. However, in recent years, there has been a growing interest in the effects of Ramadan on health as global awareness of fasting for Ramadan increases. In both Muslim and non-Muslim countries, there is now increasing awareness of the influence of Ramadan not only on healthy individuals or people with diabetes, but also on people with other illnesses. Recent research on other conditions have centred on cancer[181], multiple sclerosis (MS)[182], asthma[183] and psychiatric disorders[184;185]. Consequently, clinicians are starting to address issues such as adherence to medications and potential exacerbations of these conditions. Prospective studies have not shown any rise in MS relapse rate or deterioration in the lung function of asthmatics during the month of fasting when compared to non-fasting months[182;186]. Changes in the sleep/wake cycle and social routine during Ramadan can precipitate relapses in manic disorder[184]. One group were able to minimise the chance of relapses in bipolar affective disorder using measures such as giving advice about adequate sleep, assessment of mood at least 3 months before Ramadan, and careful monitoring of lithium levels, electrolyte and fluid balance during Ramadan[185].

We predict that research on other medical conditions and public health efforts will increase in the near future.

7.1.2 Increasing awareness in Muslim and non-Muslim countries

In countries with a Muslim majority, the normal routine of an entire nation changes during Ramadan: working hours are from 8 am to 3 pm; nocturnal sleep is shortened[187]; and daytime sleeping hours increase during Ramadan[188]. The effect of such social and behavioural modifications during Ramadan were assessed in recent studies from Morocco, United Arab Emirates, Turkey, Pakistan and other Muslim countries[34;165;189-191]. Collectively, three themes have emerged: 1) the need for pre-Ramadan assessment for patients intending to fast for Ramadan; 2) the need to support clinicians with both medical and religious knowledge of Ramadan; 3) demonstration that Ramadan is safe in various patient groups, e.g. cardiac, renal, and obese and diabetes patients. Raising the awareness of Ramadan helps clinicians to understand the act of fasting and to avoid medically unjustified negative advice for fasting to patients.

Addressing ethnic populations on their religious practices can be a challenge in countries with a Muslim minority for healthcare professionals, who often have different religious and language backgrounds. For that reason, interview-based studies from Sweden, France, Belgium, and Canada were carried out to evaluate the attitudes of Turkish, Somali and Bangladeshi Muslims and their physicians towards Ramadan fasting and diabetes care[107;192-194]. Many healthcare professionals in these countries were not familiar with the fasting practices, whilst more than half of the Muslim patients in France disagreed with the advice given by their physicians[107].

We have shown that, in a specific sub-group of pregnant women with diabetes, fasting during Ramadan was rare and the influence of religious leaders was as important as medical advice[195]. In overall, women were just as likely to discuss fasting with their Imams as they were with healthcare professionals. Pre-conception care in Muslim women with diabetes should include education on the potential risks of fasting during Ramadan and healthcare professionals should work together with Imams to address the medical and religious aspects of fasting.

The updated ADA recommendations for management of diabetes during Ramadan[109] also recognised the importance of global awareness of Ramadan in educating healthcare professionals and including religious and community leaders when providing guidance on health maintenance during fasting. The challenge now is for healthcare and faith communities to engage patients together both on an individual and population level.

Adolescents, pregnant women, patients who have had bariatric surgery, geographically isolated patients of low socioeconomic background, and immigrants with language difficulty all deserve more attention.

7.1.3 Advances in diabetes research

7.1.3.1 Structured education for both healthcare professionals and patients

We have demonstrated that Ramadan-focused structured education on Muslim diabetes patients minimised hypoglycaemic risk and weight gain during Ramadan[56]. A number of studies have also shown the benefits of structured patient education to empower people with diabetes to improve their health during Ramadan[34;165;196]. In Pakistan, pre-Ramadan assessment, education and adjustment of dietary control

and diabetes medications prepared type 2 diabetes patients on all treatment groups (oral agents and insulin) to fast safely during Ramadan, resulting in a reduction in hypoglycaemic events over the course of the month and no major hyperglycaemic complications, such as diabetes ketoacidosis and hyperglycaemic hyperosmolar state[165].

The ADA recommended that Muslim patients with diabetes intending to fast should have structured education, preferably in patients' own languages, from well-informed healthcare professionals[109]. Accordingly, healthcare professionals are now seeking to understand more about the religious perspective of fasting and the medical options to fast safely, as demonstrated by an increase in the BMJ article usage meter (in blue squares) of a review about diabetes management during Ramadan around the months leading up to Ramadan[54] (Table 7.1).

Month	Abstract	Full	PDF
May 2012	86	126	0
April 2012	138	181	0
March 2012	161	113	0
February 2012	159	90	0
January 2012	179	91	0
December 2011	54	191	0
November 2011	33	140	0
October 2011	69	137	0
September 2011	48	77	0
August 2011	187	354	0
July 2011	239	472	0
June 2011	121	229	0
May 2011	102	224	0
April 2011	86	158	0
March 2011	111	123	0
February 2011	119	214	0
January 2011	134	112	0
December 2010	95	121	0
November 2010	117	163	15
October 2010	113	129	51
September 2010	142	328	35
August 2010	248	713	0
July 2010	478	1155	0
June 2010	1329	1311	0

Table 7.1 Article metrics: an indication of how often the Ramadan review article has been accessed month by month[197].

By following the ADA recommendations for pre-Ramadan assessment and therapeutic adjustments, we showed that the glycaemic variability between fasting and non-fasting periods during Ramadan were similar[198]. Even though each measure of glycaemic variability was non-significantly higher during the non-fasting hours, which may be due to the small number of participants, the glycaemic variability assessed by mean amplitude of glycaemic excursion (MAGE) during Ramadan was similar to the MAGE value in published series of non-fasting subjects with type 2 diabetes[129], suggesting a representative sample.

7.1.3.2 Evidence-based recommendations to Muslims with diabetes

Our findings suggested that exenatide, the GLP-1R agonist, is safe during Ramadan by minimising hypoglycaemia and significant weight gain. From the observational study, Humalog Mix 50 injection at Iftar in addition to Human Mixtard 30 at Suhur is as good as twice-daily Human Mixtard 30 in achieving stable weight with no significant differences in the mean number of hypoglycaemic events before and during Ramadan. Changing to Humalog Mix 50 in the evening during Ramadan resulted in a modest but significant improvement in glycaemic control without increasing the incidence of hypoglycaemia.

Large multicentre studies have provided more answers regarding optimal diabetes treatment during Ramadan. A five-country observational study showed that nearly 20% of sulphonylurea-treated Muslims with type 2 diabetes had symptomatic hypoglycaemia during the month of fasting. Among all the sulphonylurea medications, gliclazide had the least incidence of hypoglycaemia[67]. A randomised, multicentre open-label study revealed that sitagliptin reduced the risk of

hypoglycaemia compared with a sulphonylurea in patients who were fasting during Ramadan[72].

There are no further randomised controlled trials on premixed insulins in recent years. Earlier, crossover studies comparing analogue insulins (Humalog Mix 25 and Humalog) and human insulins (human insulin 30/70 and human soluble insulin Humulin I) suggested that analogue insulins were better in lowering post-prandial hyperglycaemia following the sunset meal[75;199]. However, the debate of analogue versus human insulin is not resolved. A randomised trial has been proposed to compare once-daily detemir and NovoMix 30/70 to standard patient care. Further randomised controlled studies on commonly used insulin regimens, such as basal bolus regimes, are warranted.

7.2 Challenges in Ramadan studies

7.2.1 Geographical and cultural differences

There is a vast amount of work on the effects of fasting during Ramadan in relation to anthropometric indices, including weight and body mass index; metabolic markers, such as lipid profile, high-sensitivity CRP (hs-CRP), HbA1c, glucose; and dietary intake with respect to protein, carbohydrate and fat. The findings often varied from one study of practising Muslim populations to another. For instance, studies on healthy Muslims in Turkey and Morocco demonstrated an increase in total energy intake[200;201], whilst Jordanian and Emirati Muslims had no change in total energy consumption before and during Ramadan[202;203]. These differences have been partly attributed to the unique food habits of different Islamic countries, and also due to the

differing beliefs and practices among the various denominations in Islam[204]. For instance, Sunni Muslims are allowed to eat shellfish but some Shiite sects are not. We have not taken into account the different sects of Islam in our study but the information will be helpful in future works.

Moreover, the daylight hours and the length of daily fast vary depending on the month Ramadan falls on and the geographical location. It is, therefore, important to bear in mind these changing variables when conducting multicentre trials on Ramadan.

7.2.2 Physiological adaption during the month of fasting

Another variable that is not usually accounted for in Ramadan studies is that people fasting for the whole month undergo physiological and psychological adaptations. Changes experienced at the start of Ramadan may be different to the end of the month. By completing an appetite rating questionnaire every week throughout Ramadan, the average fasting levels of hunger was higher for women than men during the early days of Ramadan. As the month progressed, the women showed a decline in hunger and the average levels of hunger became similar for both sexes[205]. Interestingly, the women were often involved in preparing food before sunset, whilst the men were usually at work, away from this external cue of hunger. There may be changes in food consumption patterns throughout Ramadan[35]. Alternatively, unreinforced exposure to food cues during intermittent daily fasting may have led to a progressive decrease in the capacity of these cues to stimulate hunger[205].

We demonstrated that one participant ‘corrected’ his low glucose readings (4.1 – 4.4 mmol/L) during days of continuous glucose monitoring[198], and Muslim students also

adapted during Ramadan to avoid daytime somnolence by increasing daytime sleep hours[188]. To account for these variations, assessments should be performed throughout the month of Ramadan when evaluating the effects of medical treatment.

7.2.3 Limitations and Bias

Limitations in our research include: 1) selection bias of the study participants (mainly from diabetes community clinics and specialist clinics in North West London) and small sample sizes, which may not be representative to the whole Muslim type 2 diabetes population in the U.K. We intended to include other parts of London with high proportion of Muslims. Unfortunately, the plan was abandoned due to the inability to arrange Bangladeshi interpreters; 2) reporting bias of the hypo- and hyperglycaemic events by the participants. Downloading data from glucometers would minimise recall bias of symptomatic events. More studies using continuous glucose monitoring would be helpful to capture the temporal differences of glycaemic control; 3) assessment of glycaemic variability – we have used a range of measures to assess glycaemic variability. Each of them has its own advantages and disadvantages. As there is currently no consensus as to the best method for assessing glycaemic variability from continuous glucose monitoring data[206], we aimed to display a comprehensive assessment using the currently available measures.

7.3 Future directions in Ramadan research

7.3.1 The 'Ramadan-model': initiation of lifestyle modification

Globally, an estimated 50 million people with diabetes fast during Ramadan each year[109]. The ability to suppress hunger daily for long periods and subsequent weight loss in some Muslim populations[35;202;207] are fascinating topics that are worth exploring. Fasting and reduced meal frequency during Ramadan resulted in a 3.7% weight loss in obese women with diabetes (before versus mid-Ramadan, 84.26 ± 8.84kg vs. 81.14 ± 6.34kg respectively; $p<0.01$)[35]. Fasting during Ramadan serves as a great opportunity to initiate healthy lifestyle changes and to lose weight, especially in obese people with diabetes.

Maintaining weight loss after Ramadan is equally important. The obese women regained their weight after Ramadan as they returned to their pre-Ramadan lifestyle[35]. The goal of pre-Ramadan assessment with dietary and therapeutic adjustments should not only be restricted to the Ramadan period, but should ideally provide a sustainable weight and lifestyle modification, and improvement in glycaemic control beyond Ramadan.

Further research on the physiology of fasting and the role of gut hormones is needed to help understand the complex hormonal and metabolic changes that occur during Ramadan, which may help to provide novel solutions to maintain weight loss after Ramadan.

7.3.2 Ramadan and other diabetes complications

We have primarily focused on the short-term effects of Ramadan fasting, namely hypo- and hyperglycaemia, glycaemic variability, HbA1c and weight change to ensure safety during Ramadan. The impact of fasting on other diabetes complications also needs attention:

1) Nephropathy: The risk of dehydration, particularly when Ramadan occurs during summer months in the Northern hemisphere with long daylight hours, is potentially high. Kidney-transplant recipients, with or without diabetes, had stable estimated glomerular filtration rate and urinary protein excretion before and after Ramadan in the Middle East where the duration of fasting was shorter ; however, the sample size of the studies were small[52;208;209].

Current evidence revealed that hospital admissions for urolithiasis in a Saudi hospital did not increase during the months of Ramadan in three consecutive years[210]. Further studies will be helpful to address whether Ramadan is safe in patients with moderate to severe nephropathy and in patients on dialysis, and whether Ramadan fasting has an effect on the prevalence of urinary tract infections. Randomised controlled studies on therapeutic regimens or adjustments, such as GLP-1R agonist and insulin, is greatly needed to risk-stratify patients with diabetic nephropathy who choose to fast.

2) Neuropathy: About a quarter of the EPIDIAR population (n=12,243) of type 1 and 2 diabetes patients had pre-existing neuropathy[15]. Hypoglycaemic unawareness and gastroparesis associated with autonomic neuropathy and acute hyperglycaemia are likely to produce grave consequences for those who are keen to fast. Continuous

glucose monitoring would be useful in this group of patients with hypoglycaemic unawareness. Continuous glucose monitoring also demonstrated that glucose excursions occurred more frequently and glycaemic control, as indicated by M-value and mean glucose, was worse in patients with painful neuropathy compared to those with painless neuropathy[211]. Glycaemic variability with multiple glucose excursions may have a biochemical effect on nociceptive afferent fibres and exacerbate painful symptoms. Studies to assess its prevalence are greatly needed and fasting in these patients should not be recommended and should be assessed on an individual basis.

Apart from Ramadan, diabetes and its complications can also affect other aspects of Islamic practice. For instance, diabetic neuropathy may affect Muslims who travel to Hajj, the pilgrimage to Mecca. In a large population-based study in Northwest England, painful neuropathy symptoms were greater in South Asians compared with other ethnic groups, even in the absence of clinical neuropathy[212]. This would have an impact on the South Asians in the U.K., which comprised of the largest group of British Muslims predominantly of Pakistani and Bangladeshi origins[213].

3) Retinopathy: Apart from a report on the increased incidence of retinal vein occlusion during Ramadan due to dehydration in Saudi Arabia[214], there are currently no published data about the effects of Ramadan on diabetic retinopathy. Preliminary evidence has shown that acute hyperglycaemia increased blood flow to the retina associated with the progression of retinopathy[215]. The link between retinopathy and acute hyperglycaemia associated with fasting and feasting has yet to be established.

7.3.3 Ramadan and cardiovascular outcomes

By reviewing the hospital admissions of ACS to a district general hospital in Brent during the month of Ramadan in 2009, we observed that only one patient, out of a total of 30 patients admitted with ACS, was fasting. The patient did not have diabetes and had a normal fasting glucose during the hospital stay[216]. Two patients with diabetes were admitted with ACS during the month, but they did not fast. From this small single-centred study, hospital admissions for acute coronary syndrome did not appear to be a major problem in Muslims with diabetes who fasted in the London borough of Brent. Larger studies are needed to determine the incidence of ACS during Ramadan in the U.K, including centres with facilities for primary angioplasty to capture the incidences of both ST-elevation and non-ST elevation myocardial infarctions.

Retrospective reviews of hospital admissions over 10 years showed no increase in the incidences of acute coronary syndrome (ACS) in Qatar[217], congestive heart failure[218] or stroke[219] during Ramadan. A prospective study on stable cardiac outpatients with no or mild symptoms classified as congestive heart failure with New York Heart Association class I and II, patients with stable angina, atrial fibrillation or prosthetic valves concluded that these patients were safe to fast[53].

Serum leptin and hs-CRP, biomarkers of vascular inflammation, were also unchanged in stable cardiac patients who fasted. Twenty-nine per cent of these patients felt that their symptoms improved and none of them felt worse during Ramadan[189].

Spiritually, Ramadan is the month of self-purification. From a medical point of view, Ramadan may have a cardioprotective effect on certain patients. Additional research is needed to clarify the safety profile of fasting in patients with multiple comorbidities or those with coronary artery disease.

7.4 Summary and Conclusion

- 10% of pregnant women with diabetes fasted during Ramadan in our survey. Both Imams and healthcare professionals were important to these women in making the decision to fast.
- Therapeutic adjustments in relation to the type of insulins, timing and/or dosage of medications, as well as education focused on Ramadan issues in the period preceding Ramadan, are beneficial in minimising large glycaemic excursions during fasting and non-fasting intervals of Ramadan.
- New therapeutic strategies, including glucagon-like peptide-1 receptor agonists, for patients with type 2 diabetes should incur less hypoglycaemia and weight gain during Ramadan fasting.
- Global awareness on the impact of religious fasting would bridge the gap in the cultural differences between the patients and their healthcare providers.

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Chapter 8: Appendix 1

Ramadan & Diabetes Questionnaire (delete when appropriate)	
Age:	
What type of diabetes do you have?	Type 1/Type 2/gestational
How long have you had diabetes?	……months…….years
Do you take tablets or insulin or both for your diabetes?	
Please write down the names of your diabetes medications:	
Were you pregnant during any previous Ramadan periods?	Yes/No
Did you fast during Ramadan?	Yes/No
- If yes, how many days (of the month of Ramadan)?	
Are you taking your tablets/insulin at different times or different doses during Ramadan, when compared to other months?	Yes/No
- if yes, is your tablets/insulin:	increased/ decreased/ maintained/ stopped
Have you ever discussed with a health care professional (doctor/nurse) if it is safe to fast?	Yes/No
Did you consult with an Imam or representative from the Mosque regarding whether to fast or not?	Yes/No
Did you check your blood sugars during Ramadan?	Yes/No
Did you have any low blood sugars (BM less than 4) during Ramadan or experienced symptoms of low blood sugars – e.g. feeling faint, dizziness, palpitations, sweating, hunger pains, disorientated?	Yes/No
How many times did you have low blood sugars (BM less than 4) during Ramadan?	
Did the low blood sugars occur during fasting time?	Yes/No
When your sugars are low, did you stop fasting?	Yes/No
- If not, what happened?	
Did you have low blood sugars BEFORE Ramadan?	Yes/No
- if Yes, how many times a month?	
What was your highest blood sugar reading during Ramadan?	Yes/No
What did you do when the blood sugar was high?	
Were you admitted to hospital because of diabetes during Ramadan?	Yes/No
- if Yes, what was the cause(s)?	

Appendix 2

Appendix 2.1 Declaration of Originality

I wrote Chapter 1 and Chapter 2. The authors listed in Appendix 2.3 (Chapter 2) critically commented and redrafted the article. I conceived, designed, recruited and analysed the data in Chapter 3 and 4. The list of authors in Appendix 2.3 (Chapter 3) helped recruit and interpret the data in Chapter 3. Dr. Nick Oliver helped with the analysis and interpretation of the data in Chapter 4. Dr. Devasenan Devendra and Dr. Mohammed Hassanein conceived and designed the studies in Chapter 5 and 6. The list of authors in Appendix 2.3 (Chapter 6) helped with patient recruitment, data capture and statistical analysis in Chapter 6. I was responsible for analysis and writing of Chapter 5 and 6 with Dr. Devendra. I wrote Chapter 7 and my supervisors reviewed all the Chapters.

Appendix 2.2 Supervision

My supervisors for this research was Professor Azeem Majeed, department of Primary Care and Public Health, Imperial College London; and Dr. Devasenan Devendra, department of Investigative Medicine, Imperial College London.

Appendix 2.3 Authors

Chapter 2: Dr. Vassiliki Bravis, Dr. Mohammed Hassanein, Dr. Wasim Hanif, Professor Rayaz Malik, Dr. Tahseem Chowdhury, Dr. Mohamed Suliman, Dr. Devasenan Devendra

Chapter 3: Dr. Monika Reddy, Dr. Vassiliki Bravis, Dr. Mushtaq Rahman, Dr. Daniel Darko

Chapter 6: Mr Sali Salih, Dr. Vassiliki Bravis, Statistical analysis supported by Lilly UK

Chapter 9

Publications arising from this work:

Papers:

(1) Hui E, Reddy M, Bravis V, Rahman M, Darko D, Hassanein M. Fasting among pregnant women with diabetes during Ramadan. *International journal of clinical practice* 2012;66(9):910-911.

(2) Hui E, Oliver N. Low Glycaemic Variability in Subjects with Type 2 Diabetes following pre-Ramadan Assessment and Adjustments for Fasting. *Diabetes Medicine* 2012; 29(6):828-829.

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Reviews:

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Abstracts (Poster presentations):

(1) Bravis V, Hui E, Salih S, Hassanein M, Devendra D. A comparative analysis of exenatide and gliclazide during the month of Ramadan. *Diabetes Medicine* 2010; 27(Supplement 1):130.

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LETTER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

QRisk superior in diverse South Asian groups - response to Robson *et al.*

To the Editor:
We thank Robson et al., for their comments (1). We agree that the differences in calculated vascular risk that we documented are relevant to patient management. Also, it is very likely that *QRisk2* is a better predictor of risk in Caucasians and/or South Indian Asians (1).

Because South Indian Asians have a greater risk of vascular events (2), it is imperative to validate a risk engine specifically aimed at this population living in India and in other countries where substantial migration has occurred (e.g. UK, USA). It is also possible that risk calculations will differ between South Asian populations (e.g. Pakistanis, Bangladeshis, Sri Lankans and even in Indians with different dietary habits, faiths and geographical origins within India).

In this context, it is of interest that we found that the estimated glomerular filtration rate (eGFR) calculated using different equations varies substantially in South Indian Asians (3). These equations have not been validated in South Asian populations despite the fact that a low eGFR is a predictor of vascular risk (4). This situation is similar to that discussed above regarding the need for validated risk engines specifically designed for South Asians.

A. Jain,[1] N. Rao,[1] D. P. Mikhailidis,[2] D. R. Nair[1]
[1]Department of Clinical Biochemistry, Royal Free Hospital, Pond Street, London, UK
[2]Department of Clinical Biochemistry, Royal Free Hospital Campus, UCL Medical School, Pond Street, London, UK
Email: mikhailidis@aol.com

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Disclosure

DRN has received grants from Pfizer (Pfizer Foundation award 2008), Abbott, Merck Sharp & Dohme, and Astra Zeneca for this service. DRN has advisory board membership for Merck Sharp & Dohme and Roche. DRN is a speaker for Merck Sharp & Dohme, Abbott and Pfizer. DPM has advisory board membership and is a speaker for Merck Sharp & Dohme, Abbott and Genzyme. AJ, NR has no competing interests to disclose.

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LETTER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Fasting among pregnant women with diabetes during Ramadan

To the Editor:
Islamic law exempts pregnant women from fasting during Ramadan [1,2]. Although women can defer fasting until after pregnancy, they prefer to share the experience during Ramadan. A total of 45–90% of healthy pregnant women fasted during Ramadan [3–5]. Our aims were to examine the practice of fasting among pregnant Muslim women with diabetes and to explore the roles of healthcare professionals and Imams in the decision to fast.

Standardised questionnaire-based interviews, based on questions in the EPIDIAR study [6], were conducted at four specialist antenatal centres in London. Forty-eight women completed the questionnaire. Mean age (± SD) was 32 ± 5 years. Sixty-five per cent had gestational diabetes, 31% had type 2 and the remainder had type 1 diabetes. Forty-four per cent were diet-controlled, 25% on oral hypoglycaemic agent(s), 21% on insulin and 10% on insulin and metformin.

Table 1 Characteristics of the five women (n = 48) who fasted during pregnancy

Patient	Type of diabetes	Diabetes treatment	Fasting whilst Pregnant previously	Number of days fasted during Ramadan	Discussion with healthcare professional	Discussion with Imam
1	T1DM	Insulin	N	14	Y	Y
2	T2DM	Diet	N	30	N	N
3	T2DM	Oral	Y	5	N	Y
4	GDM	Insulin + metformin	Y	30	N	Y
5	GDM	Insulin	Y	30	N	Y

Ten per cent of women fasted during pregnancy (Table 1). Twenty-three per cent of women who did not fast, had a history of hypoglycaemia. Having diabetes with risk of hypoglycaemia may be why these women did not fast, compared with healthy pregnant women who were keen to fast despite adverse reaction [2]. Urban background may have influenced their decision not to fast, as immigrants and women from rural areas tended to fast [3,5]. Family members may have been consulted instead, as 63% did not consult healthcare professionals or religious leaders for advice [7]. Husbands tended to discourage fasting when they felt that the women were endangering themselves [4].

In overall, women were just as likely to discuss fasting with their Imams as they were with healthcare professionals (Table 2). Preconception care in Muslim women with diabetes should include education on the risks of fasting during Ramadan and healthcare professionals should work together with Imams to address the medical and religious aspects of fasting.

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Table 2 Comparison between the pregnant women with diabetes who fasted and who did not fast during Ramadan

	Fasting women No.	Non-fasting women No.
Glycaemic control during Ramadan:		
Hypoglycaemia	1	10
Hyperglycaemia	3	4
Ramadan discussions with:		
Healthcare professionals	0	9
Imams	3	3
Both	1	4

Extending the survey beyond London would provide a more comprehensive view of Muslim women with diabetes. Further research is needed to determine whether fasting during Ramadan affect maternal and foetal outcomes.

E. Hui,[1] M. Reddy,[1] V. Bravis,[1] M. Rahman,[2] D. Darko,[2] M. Hassanein[3]
[1]Imperial College London, United Kingdom
[2]Northwest London Hospitals NHS Trust, United Kingdom
[3]Glan Clwyd Hospital, Wales, United Kingdom
Email: eyh09@imperial.ac.uk

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Author contributions

EH contributed to the concept and design, data collections and preparation of this manuscript; MR,VB, DD and MR are the clinicians responsible for patient follow-up; MR and VB performed data collections; DD and MR helped in critical revision of the article; MH revised and corrected the final version of the manuscript.

Disclosures

No competing interest.

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Low glycaemic variability in subjects with Type 2 diabetes following pre-Ramadan assessment and adjustments for fasting

Diabet. Med. 29, 828–829 (2012)

Ramadan is the 9th month of the Islamic lunar calendar, during which Muslims abstain from food intake between sunrise and sunset. Major changes to dietary patterns occur during Ramadan as meals are taken before dawn and immediately after sunset. People with Type 2 diabetes fasting during Ramadan have large increases in glycaemic excursions, with a 7.5-fold increased frequency of severe hypoglycaemia and a 5-fold increase in severe hyperglycaemia [1]. Glycaemic excursions are disruptive to the individual and measures of variability are associated with subsequent hypoglycaemia [2]. Therefore, diabetes management in Ramadan should target glycaemic variability to empower people with diabetes to fast safely for prolonged periods.

The American Diabetes Association has published recommendations on diabetes management during Ramadan, focusing on individualized care and pre-Ramadan structured education [3]. Our objective was to implement the American Diabetes Association recommendations for the management of diabetes during Ramadan, focusing on pre-Ramadan assessment, and to evaluate the impact of the guidelines on glycaemic variability using continuous glucose monitoring in fasting and non-fasting hours.

Muslim subjects over 18 years old with Type 2 diabetes attending a specialist diabetes clinic, and planning to fast for Ramadan, with a history of hypoglycemia (symptomatic or documented capillary blood glucose ≤ 4.0 mmol/l) were invited to undergo a 5-day glucose profile using the Abbott Freestyle Navigator (Abbot Diabetes, Alameda, CA, USA) continuous glucose monitoring system as part of their clinical investigation during Ramadan. Data from the continuous glucose monitoring device were downloaded using the CoPilot® Healthcare Management System 4.0 (Abbott Diabetes Care Inc, Alameda, CA, USA). Timing and dosage of diabetes medications were adjusted at the patients' pre-Ramadan clinic visits when clinically indicated according to the American Diabetes Association recommendations.

The following outcome measures of glycaemic variability were evaluated: standard deviation of mean blood glucose, M-value, mean amplitude of glycaemic variability (MAGE), lability index, J-index, continuous overlapping net glycaemic action (CONGA), average daily risk ratio, low blood glucose index, high blood glucose index. These indices were calculated using EasyGV software (available free at http://www.easygv.co.uk) and have been extensively reviewed [4].

Mean age of the participants (n = 6) was 53.7 ± 2.3 years, mean duration of diabetes 7.3 ± 2.8 years and HbA_{1c} pre-Ramadan was 60 ± 1.1 mmol/mol (7.6 ± 1.1%). Daily fasting duration ranged from 13 to 16 h. All participants had pre-Ramadan assessments and three patients required dose and time adjustments of their diabetes medications in line with American Diabetes Association recommendations. Although the resulting measures of glycaemic variability, as indicated by MAGE, lability index, J-index, CONGA and M-value, were higher during non-fasting hours when participants break their fast between sunset and dawn, there was no significant difference when compared with the fasting periods (Table 1).

The risk of hypoglycaemia as measured by low blood glucose index was not significantly different between the fasting hours compared with the non-fasting hours (9.45 ± 18.96 vs. 1.21 ± 1.12; P = 0.35) and high blood glucose index, an indicator of hyperglycaemic risk, was the same across the two periods (6.41 ± 7.21 vs. 10.46 ± 10.99; P = 0.15).

The average daily risk ratio, a predictor of future hypoglycaemia (< 4 mmol/l) and hyperglycaemia (> 10 mmol/l), was 21.82 ± 12.53. An average daily risk ratio between 20 and 40 is considered moderate risk for future low and high glucose excursions [5]. No severe hypoglycaemia requiring third-party assistance was reported for any of the participants.

A considerable amount of food rich in refined carbohydrate is traditionally prepared for Ramadan and taken during non-fasting hours. Despite dietary changes and previous reports of hypo- and hyperglycaemic excursions in Ramadan, when pre-Ramadan assessment and adjustments are implemented, the difference compared with fasting hours is not significant. Measures of glycaemic variability calculated were measures of total variability (SD), within-day variability (MAGE) and between-day variability (CONGA). Each measure was greater during the non-fasting hours, but was not statistically significant,

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Table 1 The parameters of blood glucose control and glycaemic variability of the participants during the fasting (daylight hours from sunrise to sunset) and non-fasting hours of Ramadan

	Total periods	Fasting periods	Non-fasting periods	*P*-value
Mean tissue glucose	8.92 ± 2.76	8.56 ± 2.42	9.68 ± 3.46	0.17
Measures of glycaemic variability				
Standard deviation (SD)	2.07 ± 0.83	1.81 ± 0.47	2.10 ± 0.95	0.45
Mean amplitude of glycaemic variability (MAGE)	4.47 ± 0.75	4.69 ± 1.47	4.82 ± 1.63	0.90
Continuous overlapping net glycaemic action (CONGA)	8.01 ± 2.68	7.66 ± 2.34	8.29 ± 2.96	0.21
Lability index	2.90 ± 1.09	2.39 ± 0.79	5.38 ± 4.54	0.17
J-index	42.25 ± 25.27	36.52 ± 19.18	49.42 ± 34.05	0.19
M-value	10.21 ± 13.96	7.34 ± 11.17	14.95 ± 19.53	0.17
Risk measures—predictors of extreme hypoglycaemia and hyperglycaemia				
Low blood glucose index	9.44 ± 18.96	9.45 ± 18.96	1.22 ± 1.12	0.35
High blood glucose index	7.91 ± 8.59	6.41 ± 7.21	10.46 ± 10.99	0.15
Average daily risk ratio	21.82 ± 12.53			

Values are mean ± SD (mmol/l)

which may, in part, be attributable to the small number of participants. However, despite the small sample size, the glycaemic variability assessed by MAGE during Ramadan (4.47 ± 0.75) is similar to the MAGE value in published series of non-fasting subjects with Type 2 diabetes (4.8 ± 2.1) [6], suggesting a representative sample. Recruitment of subjects in a limited time can be challenging in Ramadan, particularly during a religious event of such importance, and further studies including a larger number and wider spectrum of participants are warranted. It would also be useful to compare the glycaemic variability of these subjects in the non-fasting months with that in the month of Ramadan to assess the alterations in dietary and social habits during Ramadan, as compared with normal routine. We acknowledged that the lack of such a control group and that the continuous glucose monitoring was not blinded may have reduced the glycaemic variability.

In conclusion, our findings suggest that systematic pre-Ramadan assessment with appropriate therapeutic adjustments and educational advice regarding healthy diet, adequate exercise and awareness of the risks of hypo- and hyperglycaemia are important in negating the previously described glycaemic variability seen during Ramadan [1].

Competing interests

Nothing to declare.

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E. Hui[1] and N. Oliver[2]

[1]Department of Medicine, Imperial College London and [2]Department of Medicine, Imperial College Hospitals NHS Trust, London, UK

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Death rate of residents with diabetes in nursing homes

Diabet. Med. 28, 829–830 (2011)

In our paper published in *Diabetic Medicine* in July 2011 [1] entitled 'People living with diabetes resident in nursing homes—assessing levels of disability and nursing needs', we made the assertion that it was likely that the majority of individuals described in this study could be classified as terminally ill. This assertion came from the definition of terminal illness that is based on a negative answer to the question, 'would I be surprised if my patient were to die in the next 12 months?'.

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ORIGINAL PAPER

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Comparison of Humalog Mix 50 with human insulin Mix 30 in type 2 diabetes patients during Ramadan

E. Hui,[1] V. Bravis,[1,2] S. Salih,[3] M. Hassanein,[4] D. Devendra[1,2,3]

SUMMARY

Aims: To compare hypoglycaemic events, glycated haemoglobin (HbA1c) and changes in body weight in Muslim patients with Type 2 diabetes receiving Humalog Mix 50 and human Mixtard 30 twice daily during Ramadan fasting. **Methods:** Data were collected from Muslim patients with Type 2 diabetes attending primary care practices in North-West London, who were on Mixtard 30 insulin twice daily before Ramadan. Group 1 had their evening insulin changed to Humalog Mix 50 ($n = 26$) 2 weeks before Ramadan, i.e. taking Mixtard 30 at predawn meal and Humalog Mix 50 at the sunset meal during Ramadan. As the major proportion of the daily caloric intake was consumed at the sunset meal, the rationale of switching the evening dose from human Mixtard 30 to Humalog Mix 50 was to provide more rapid-acting insulin that has shorter time of onset and peak time for the large evening meal to improve the postprandial glucose control without increasing the risk of hypoglycaemia. Group 2 continued on Mixtard 30 twice daily ($n = 26$). All patients received structured education about how to identify and manage hypoglycaemia during Ramadan. **Results:** Group 1 had a mean HbA1c reduction of 0.48% ($p = 0.0001$) before and after Ramadan, whereas group 2 had a mean HbA1c increase of 0.28% ($p = 0.007$). Group 1 was associated with a small reduction of 0.04 ($p = 0.81$) in the mean number of hypoglycaemic events during Ramadan compared with before Ramadan, whereas group 2 was associated with an increase of 0.15 ($p = 0.43$), although these differences between the groups were not statistically significant following adjustment for baseline factors [LSM difference between groups = 0.135, $p = 0.36$, 95% confidence limits (−0.16, 0.43)]. **Conclusion:** Changing to humalog Mix 50 during Ramadan resulted in improvement in glycaemic control without increasing the incidence of hypoglycaemia.

What's known

- There are risks, such as hypoglycaemia, in patients who choose to fast during Ramadan, especially for those taking insulin.
- There are only a few studies about the use of premixed insulin regimens during Ramadan fast:
  - Short-acting analogue insulin lispro has been shown to have less hypoglycaemic episodes during Ramadan compared with soluble human insulin, when both given with NPH (neutral protamine Hagedorn). Humalog Mix 25, given twice daily, has been shown to have less postprandial glucose excursion than human insulin Mix 30/70.

What's new

- Muslims fast between sunrise and sunset during the month of Ramadan, which varies according to the lunar calendar. The long daylight hours in countries in the Northern hemisphere will have large implications, e.g. hypoglycaemia, on diabetes patients who wish to fast during Ramadan.
- This is the first study looking at the risks of hypoglycaemia and glycaemic control of twice daily premixed insulin regimens in the UK during Ramadan.

[1]Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, London, UK
[2]Department of Investigative Science, Imperial College London, London, UK
[3]Brent Integrated Diabetes Pathway, NHS Brent, London, UK
[4]Department of Diabetes, Glan Clwyd Hospital, North Wales, UK

Correspondence to:
Dr Devasenan Devendra, Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, Acton Lane, Park Royal, London NW10 7NS, UK
Tel.: + 44 208 4532401
Fax: + 44 208 4532415
Email: d.devendra@imperial.ac.uk

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Introduction

Ramadan is the ninth month of the Islamic lunar calendar. Healthy Muslims are obliged to abstain from all food and drink during daylight hours throughout this month and can do so with little long-term impact on their health (1). As the lunar year rotates from season to season, Ramadan can occur in any month. Its duration varies between 29 and 30 days and the hours spent in fasting range from only a few hours to more than 20 h per day depending on season and geographical location (2).

The EPIDIAR study showed that 78.7% of patients with Type 2 diabetes chose to fast for at least 15 days during Ramadan (3). Although several studies have shown that Ramadan fasting did not affect overall glycaemia in balanced Type 2 patients treated with diet and oral hypoglycaemic agents (4–6), acute metabolic complications are thought to be important concerns for patients with diabetes during Ramadan. Increased frequencies of hypoglycaemia have been reported during Ramadan fasting (3,7,8). There was a 7.5-fold increased risk of hypoglycaemia in Type 2 diabetes patients (3).

There is no consensus regarding the most appropriate insulin therapy for Muslim diabetes patients during Ramadan. Risk of hypoglycaemia did not differ significantly during Ramadan in patients treated with either repaglinide, glimepiride or insulin glargine (9). Repaglinide plus single-dose insulin glargine regimen has been shown to be safe in low-risk Type 2 diabetic patients as compared with non-fasting controls. There

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were no reported hypoglycaemic events and no significant differences in metabolic parameters including fasting and postprandial blood glucose and fructosamine levels before and after Ramadan (10). However, changes in dietary habits during Ramadan can result in extreme postprandial glucose rises and difficulty in maintaining glycaemic control in patients taking twice daily insulin.

As part of a larger programme of diabetes-focused education and interventions during Ramadan in North-west London, we undertook an observational study to evaluate hypoglycaemic events (defined as blood glucose < 3.5 mmol/l with or without symptoms), glycated haemoglobin (HbA1c) and weight change in Muslim patients with Type 2 diabetes who fasted and whose HbA1c was insufficiently controlled with twice daily Mix 30 insulin regimen (Human Mixtard 30/70) before Ramadan. As a larger proportion of the daily caloric intake was usually consumed at the evening meal (at sunset, *Iftar*) (11), the evening dose was therefore changed to Mix 50 (Humalog Mix 50/50) based on clinical judgement.

In this study, we aimed to compare the effect of Mix 30 and Mix 50 insulin regimes on HbA1c, weight and hypoglycaemic events in Type 2 patients who fasted during the month of Ramadan.

Patients and methods

Participants

This was an observational study of Muslim patients with Type 2 diabetes treated in accordance with the American Diabetes Association's recommendations for the management of diabetes during Ramadan (2). Participants who were 18 years or over and fasted for ≥ 15 days were included. Patients attended six primary care practices in the London boroughs of Brent, Ealing and Harrow, who had taken part in a workshop to educate healthcare professionals on issues surrounding diabetes and fasting. All participants received Ramadan-focused education about the management of their diabetes and the identification and management of hypoglycaemia. Patients were already on Mix 30 insulin twice daily before attending the education. They either continued on Mix 30 insulin twice daily or changed their evening insulin dose to Mix 50 2 weeks before Ramadan. Patients who continued on Mix 30 used their usual prestudy injection-to-meal time interval. Patients who had Mix 50 insulin in the evening were advised to inject immediately before meals. Allocation to treatments was based on clinical judgement prior to inclusion and was not randomised. Indication for changing to Mix 50 includes elevated 2-h postprandial capillary blood glucose > 10 mmol/l in the evenings.

Assessments

All participants were seen 2 weeks before the start of Ramadan and seen again 10 days after the last day of Ramadan. All participants were instructed to monitor their symptoms closely and record daily preprandial and 2-h postprandial blood glucose, hypoglycaemic events and weight. An Ascensia Contour glucose meter (Bayer Healthcare, UK) was provided to participants. Before Ramadan, participants were asked to provide any documentation of hypoglycaemia from either a blood glucose meter or glucose diary records. During Ramadan, participants were asked to check their blood glucose levels if they had any symptoms of dizziness, visual blurring, palpitations, nausea, sweating, confusion, tremor or intense hunger. Both the blood glucose diary and the blood glucose meter were analysed for episodes of hypoglycaemia. Patients were also asked to notify their general practitioner if they had any episodes of hypoglycaemia, and they were told to attend the daily rapid access clinics in Brent if they had any concerns about their diabetes. Severe hypoglycaemia was defined as a low blood sugar (< 3.5 mmol/l) needing assistance to treat the hypoglycaemic event. In addition, participants were asked to document the total number of days they had fasted.

Changes between prefasting and postfasting HbA1c and weight were analysed using analysis of covariance (ANCOVA) models to adjust for the effects of age, gender, ethnicity, duration of diabetes and baseline values. Patients were asked to record the total number of hypoglycaemic events 4 weeks prior to the start of Ramadan and subsequently asked to record hypoglycaemic events during the month of Ramadan. Changes between prefasting and intra-fasting occurrence of hypoglycaemic events were also analysed using ANCOVA models to adjust for the effects of age, gender, ethnicity, duration of diabetes and baseline values. Least squares (adjusted) means (LSM) are presented for treatment differences. For hypoglycaemic events, in addition to the total number per patient, the data were also dichotomised into groups of patients who experienced no events during fasting and those who experienced at least one event during fasting.

As a result of the non-interventional nature of this study according to the Medicines and Healthcare products Regulatory Agency guidance on what constitutes a clinical trial, central ethics committee approval was not sought for the observational study. However, local National Health Service Trust Research and Development committee approval to conduct the study was sought before the study was undertaken.

Results

Fifty-two patients were included in this observational study. The Mix 50 group (n = 26 patients) received Mix 30 at the meal before sunrise and Mix 50 after sunset. The Mix 30 group (n = 26 patients) received Mix 30 twice daily. The baseline demographics of the two groups are shown in Table 1. The mean age was 62.3 ± 9.8 years in Mix 50 group and 61.9 ± 9.2 years in Mix 30 group (p = 0.90). The mean duration of diabetes was approximately 9.5 years in each group. The mean baseline HbA1c values were similar between the two groups (9.05 ± 0.43 vs. 8.98 ± 0.37; p = 0.22). ANCOVA models were used to adjust for baseline imbalances because of the non-randomised allocation to treatment.

Table 2 shows the difference in outcome measures (hypoglycaemic events, HbA1c and weight) between the start and end of Ramadan and between the two treatment groups.

Mix 50 was associated with a small reduction of 0.04 (p = 0.81) in the mean number of hypoglycaemic events during Ramadan compared with before Ramadan, whereas Mix 30 was associated with an increase of 0.15 (p = 0.43), although these differences between the groups were not statistically significant following adjustment for baseline factors [LSM difference between groups = 0.135, p = 0.36, 95% confidence limits (−0.16, 0.43)].

The Mix 50 group had a mean HbA1c reduction of 0.48% (p = 0.0001), whereas group 2 had a mean HbA1c increase of 0.28% (p = 0.007). These differences, adjusting for baseline factors, were statistically significant [LSM difference 0.40%, p = 0.0004, 95% confidence limits (0.19%, 0.62%)].

In the Mix 50 group, there was a significant increase in mean body weight before and after Ramadan (mean weight change = 0.81 kg, p = 0.0002). There was a small but non-significant increase in mean weight in the Mix 30 group of 0.33 kg (p = 0.082) after Ramadan. These differences, however, adjusting for baseline imbalances, were not statistically significant [LSM difference −0.09, p = 0.62, 95% confidence limits (−0.47, 0.28)].

Discussion

Ramadan represents a period when there is a major change in dietary patterns. People take considerable quantities of sweet foods specially prepared for Ramadan and carbohydrate rich meals during non-fasting hours (12). A considerable proportion of food intake usually occurs at the meal after sunset. In healthy subjects, 65% of the daily caloric intake was observed after this meal (11).

Humalog Mix 50 is a premixed insulin analogue containing 50% of lispro and 50% neutral protamine lispro (NPL, an intermediate-acting insulin), whereas human Mixtard 30 is a mixture of 30% dissolved human insulin (rDNA) and 70% isophane insulin (NPH). The pharmacokinetics of analogue premixed insulin was more akin to the normal pattern of insulin secretion than premixed human insulin (13). The former has a quicker time to onset of 5–15 min vs. 30–60 min and a shorter time to peak (Tmax) of 115 min vs. 173 min in premixed human insulin. The rationale of switching the evening dose from human Mixtard 30 to Humalog Mix 50 was to provide patients with more rapid-acting insulin that has shorter time of onset and peak time for the large meal in the evening to improve the postprandial glucose control without increasing the risk of hypoglycaemia. Although hypoglycaemia tends to be less frequent in Type 2 than in Type 1 diabetes, it is still a considerable risk, particularly in patients who

Table 1 Baseline characteristics of the participants

	Group 1 (Mix 50)	Group 2 (Mix 30)
Participants (n)	26	26
Men:women [n (%)]	8 (30.8%):18 (69.2%)	10 (38.5%):16 (61.5%)
Age [years, mean ± SD (range)]	62.3 ± 9.8 (45–77)	61.9 ± 9.2 (44–77)*
HbA1c (%, mean ± SD)	9.05 ± 0.43	8.98 ± 0.37*
Weight (kg, mean ± SD)	89.4 ± 8.7	85.8 ± 7.2*
Ethnicity (n)		
Pakistani [n (%)]	24 (92.3%)	10 (38.46%)
Middle-Eastern [n (%)]	0 (0%)	12 (46.15%)
Other [n (%)]	2 (7.7%)	4 (15.4%)
Duration of diabetes [years, mean ± SD (range)]	9.8 ± 2.8 (4.6–16.5)	9.5 ± 3.3 (4.5–16.5)*

*p > 0.05 between groups 1 and 2. SD, standard deviation.

Table 2 Change in outcome measures during Ramadan in participants receiving Mix 30 before sunrise and Mix 50 after sunset (group 1) and Mix 30 twice daily (group 2)

	Before Ramadan	After Ramadan	Least squares mean change	Mean (SEM) difference between groups	95% confidence limits	p-Value
Hypoglycaemic events (n ± SD)						
Mix 50 (n = 26)	0.46 ± 0.65	0.42 ± 0.58	0.058	0.135 (0.146)	(−0.160, 0.429)	0.36
Mix 30 (n = 26)	0.42 ± 0.58	0.58 ± 0.81	0.193			
Glycated haemoglobin (%, mean ± SD)						
Mix 50 (n = 26)	9.05 ± 0.43	8.56 ± 0.62	−0.100	0.403 (0.105)	(0.190, 0.617)	0.0004
Mix 30 (n = 26)	8.98 ± 0.37	9.27 ± 0.59	0.303			
Body weight (kg, mean ± SD)						
Mix 50 (n = 26)	89. 4 ± 8.7	90.2 ± 8.9	0.57	−0.09 (0.19)	(−0.47, 0.28)	0.62
Mix 30 (n = 26)	85.8 ± 7.2	86.1 ± 7.7	0.47			

Analysis of covariance (ANCOVA) including terms for treatment group, gender and ethnicity as factors and age and duration of diabetes and baseline values for weight, HbA1c and hypoglycaemic events. SD, standard deviation; SEM, standard error.

required insulin for years and had significant beta-cell failure and insulin deficiency (2). Hypoglycaemia may be exacerbated by the inappropriate response of counter-regulatory hormones and the defect in epinephrine secretion caused by autonomic neuropathy (14). In this report, there were no significant differences in the mean number of hypoglycaemic episodes before and during Ramadan in the Mix 50 and the Mix 30 groups after adjusting for baseline factors. In a crossover, comparative trial, Mattoo et al. (15) has also shown no change in the mean number of hypoglycaemic episodes in patients on Humalog Mix 25/75 and human insulin Mix 30/70.

Previous studies have shown no change in body mass index or weight during the fasting period in Type 2 diabetes patients treated with once daily insulin compared with controls who were on repaglinide or sulphonylureas (9,10). Information about calorie intake and exercise is not available in this study. These would be important factors that may contribute to the weight increase in the Mix 50 group, which is not significant after adjusting for baseline imbalance.

Changing to humalog Mix 50 during Ramadan resulted in an improvement in glycaemic control without increasing the incidence of hypoglycaemia. However, the duration of the study (7.5 weeks) is rather short to conclude firmly that the groups achieved their maximum HbA1c. Alternative measurement for glycaemic control, such as serum fructosamine, would be useful in this study, as serum fructosamine would be more appropriate to evaluate the glycaemic control of this short interval. Additional limitation of the study is that complete postprandial glucose measurements were not available from the participants, which would be useful in evaluating the contribution of HbA1c in the Mix 50 group. This was an observational study of a relatively small number of Muslim patients with Type 2 diabetes in North-west London. There is a need for larger, prospective studies to investigate the appropriate insulin regimens that may enable patients with Type 2, and even Type 1, diabetes who wish to fast with minimal complications.

If a person with diabetes chooses to fast during Ramadan, his or her decision needs to be respected and an appropriate care plan needs to be devised, taking into account the individual dietary and sleeping patterns during the month and any treatment modifications that may be needed. It is critical that patients with diabetes should be counselled about the need to adjust their insulin regimen before the start of Ramadan as part of a focused education on meal planning, glucose monitoring and dietary requirements (2). In an audit of 123 Muslim patients with diabetes, patients who fasted without attending a structured education session (n = 54) had a fourfold increase in hypoglycaemia ($p < 0.001$), whereas those who attended the Ramadan-focused education programme had a significant decrease in hypoglycaemic events (16).

Switching to analogue Mix 50 insulin in the evening may have a role in the management of Type 2 diabetes patients during Ramadan, particularly to minimise their risk of hypoglycaemia without compromising their glycaemic control and weight.

Author contributions

D. Devendra was responsible for the concept and design of the study and contributor to the writing of the manuscript. E. Hui was responsible for data

capture, statistical analysis and was a contributor to the writing of the manuscript. V. Bravis helped with data capture and statistical analysis. S. Salih helped with patient recruitment for the study. M. Hassanein was involved in the concept of the study and reviewed the manuscript.

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REVIEW ARTICLE

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Diabetes and fasting during Ramadan

Elaine Hui[1]
Devasenan Devendra[1,2]*

[1]*Department of Investigative Sciences, Imperial College London, London, UK*

[2]*Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, London, UK*

*Correspondence to:
Devasenan Devendra, Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, London NW10 7NS, UK.
E-mail: d.devendra@imperial.ac.uk

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Summary

Abstinence from food and liquid during daylight hours is observed by Muslim individuals during the month of Ramadan. Even though the Koran exempts the sick from fasting, many people with diabetes still fast during this religious period. It is essential for patients, family and healthcare professionals to be aware of the religious attitude to and health implications of fasting. Major changes in dietary habits, daily physical activities and sleeping patterns during Ramadan have significant impact on the glycaemic control, lipid profile, weight and dietary intake. Hence, the patient is encouraged to have appropriate pre-Ramadan assessment and education in order to stratify and modify his or her risk with fasting. Dose and timing adjustments to insulin and to some oral hypoglycaemic agents, especially sulphonylureas, may well be necessary during Ramadan. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords diabetes; Ramadan; fasting; hypoglycaemia

Introduction

Ramadan is the ninth month of the Islamic calendar, when Muslims fast during daylight hours. It is based on a lunar calendar; therefore, the duration of daily fast and the overall period of the month of Ramadan vary each year depending on the geographical location and season. Two main meals are usually consumed during Ramadan, before sunrise, known in Arabic as 'Sohur', and after sunset, known as 'Iftar'. Changes in meal frequency, daily physical activities and sleeping patterns during Ramadan may influence the glycaemic and other biochemical parameters in patients with diabetes [1–3]. Although the Koran exempts sick people from fasting, many Muslims with diabetes may not perceive themselves as sick and choose to fast, despite medical advice to the contrary.

Effects of fasting on lipid profile and weight

Caloric intake

Even though people abstain from any oral intake from sunrise to sunset, they eat considerable amounts of sweet and fried foods traditionally prepared for Ramadan during non-fasting hours, especially at the Iftar meal. An increase in daily caloric intake during Ramadan has been shown in healthy subjects [1,4]. However, some studies reported a decrease in daily caloric and carbohydrate intake in patients with type 1 and type 2 diabetes [5,6].

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Weight and body mass index

Weight and body mass index did not change before and 15 days after Ramadan in 120 patients with type 2 diabetes well controlled on diet or oral hypoglycaemic medications after receiving dietary advice and adjustment of the timing of their medications [7]. In women with type 2 diabetes and a high body mass index (34.63 ± 3.29 kg/m^2), fasting during Ramadan resulted in significant weight loss (-3.12 kg; $p < 0.01$), a decrease in meal frequency (2.2 ± 0.3 *versus* 4.3 ± 0.4) as well as in energy intake (1488 ± 118 *versus* 1823 ± 262 kcal/day) [8].

Lipid profile

It was postulated that physiological adaptations during the month of fasting lead to an increase in reliance on fat as a source of fuel during daytime fasting [9]. In obese patients with type 2 diabetes, dietary fat consumption increased (35.84 *versus* 25.36%), especially the saturated fats (231 kcal/day or 43.25% of total fat [8]). Total cholesterol intake, as well as total and low-density lipoprotein cholesterol concentrations, increased significantly in non-obese patients with type 2 ($n = 57$) ($p < 0.03$) [10] and in type 2 patients with hyperlipidaemia on diet, fibrates or statins [11].

Effects of fasting on cardiovascular endpoints

A large population-based study conducted in Qatar, where 95% of the adult population fast for Ramadan, has shown no significant difference in hospital admissions for acute coronary syndrome between Ramadan and non-fasting months ($p < 0.05$) [12]. A 13-year review of a stroke database also showed no significant difference in the number of hospitalizations for stroke during the fasting month of Ramadan as compared to other months ($p < 0.05$) [13].

Effects of fasting on glycaemic control

Several studies have demonstrated no change in haemoglobin A_{1c} [14] or fructosamine levels [10,15] during Ramadan. However, it is the variation in glycaemia leading to severe hypo- and hyperglycaemia that is the main issue for patients with diabetes fasting for prolonged periods during Ramadan. A large epidemiological study, the Epidemiology of Diabetes and Ramadan study, showed that daytime fasting during Ramadan increased the risk of severe hypoglycaemia by 4.7-fold (from 3 to 14 events/100 people/month) in type 1 diabetes and 7.5-fold (from 0.4 to 3 events/100 people/month) in type 2 diabetes. The incidence of severe hyperglycaemia in patients with type 2 diabetes also increased fivefold [16]. In a multicentre observational study ($n = 1374$), symptomatic hypoglycaemia occurred in about 20% of diabetic patients on sulphonylurea with or without metformin who fast during Ramadan [17], whilst other studies have not shown a significant increase in the risk of hypoglycaemia during Ramadan in patients treated with oral diabetic medications or insulin [18,19].

Management of diabetes during Ramadan

Blood glucose monitoring and the potential role of continuous glucose monitoring

Blood glucose monitoring does not constitute a break of fast [20]. All patients who fast should be provided with the means to monitor their blood glucose [21].

Continuous glucose monitoring has been shown to improve overall mean glucose, reduce glycaemic excursions and reduce time spent in hyperglycaemia in non-fasting type 2 diabetes subjects [22]. Although it has not been studied, continuous glucose monitoring may be a useful tool in studying the glycaemic variability during Ramadan in patients with a history of hypoglycaemia and in raising an alarm if there is rapid decrease in glucose or pending hypoglycaemia.

Pre-Ramadan assessment

A pre-Ramadan assessment of patients who wish to fast during Ramadan is recommended to assess whether their health risk increases by doing so [23]. Other opportunities for discussions about fasting during Ramadan can be at the time of diagnosis and at an annual diabetes review. Consensus guidelines have categorized patients according to their health risks [23,24]. Patients in the high-risk category should be advised not to fast while those in the low risk can be allowed to fast. Those in the medium category should discuss with healthcare professionals their management of Ramadan several months before Ramadan to reduce their risks.

Muslim religious leaders also play an important role in the education regarding religious fasting, especially for patients with diabetes who are keen to fast but overlook the risks involved, and also for patients who do not wish to fast but do so in order not to alienate themselves from the rest of the Muslim community [25]. Both religious leaders and healthcare professionals are crucial in providing education and support for safer fasting during Ramadan.

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Structured education

In a systematic review of randomized controlled trials of the effectiveness of self-management training in people with type 2 diabetes, educational interventions that involved patient collaboration were more effective than didactic interventions in improving glycaemic control (<6 months), weight and lipid profiles [26].

Structured educational sessions specific to Ramadan have been shown to be effective. In an observational study, patients who fasted without attending a structured education session had a fourfold increase in hypoglycaemic events, whereas those who attended a Ramadan-focused education programme had a significant decrease in hypoglycaemic events [27]. Patients, as well as their family, are encouraged to attend so that awareness of hypo- and hyperglycaemic symptoms, planning of meals, blood glucose monitoring, administration of medications, physical activity and management of acute complications such as when to break the fast, are provided to the family as a whole. It is also a good opportunity to encourage healthy living advice, such as smoking cessation. It has been shown that Ramadan fasting has a positive impact in that it helps Muslim adults to quit smoking [28].

Management of type 1 diabetes during Ramadan

Patients with poorly controlled type 1 diabetes should not fast during Ramadan. If patients choose to fast against medical advice, it is advantageous if they are on a basal bolus regime and are familiar with carbohydrate counting [24]. A small study ($n = 9$) of patients with type 1 diabetes using insulin glargine and insulin lispro or aspart, divided in a 6 : 4 ratio of the total 24-h insulin dose, reported no episodes of severe hypoglycaemia or diabetic ketoacidosis requiring hospitalization, and the haemoglobin A_{1c} remained stable at the end of Ramadan. As the insulin requirement decreased by 28% from baseline ($p = 0.002$), it has been suggested that insulin should be reduced by 70% of the pre-Ramadan doses during the fast [29].

Insulin lispro, as a short-acting component of the basal bolus regimen, has been found to have a lower 2-h post-prandial glucose level after the sunset meal ($p = 0.026$), with less hypoglycaemia ($p < 0.01$), as compared to regular human insulin when given with neutral protamine hagedorn insulin in an open-label crossover study ($n = 64$) [30].

Insulin pump therapy (using a Medtronic MiniMed 722 model) was observed in 49 type 1 patients who fasted during Ramadan. Seventeen patients had hypoglycaemia requiring breaking the fast but no severe hypoglycaemia was reported. Usual hyperglycaemia was reported in nine patients, with one patient needing hospital admission due to a disconnected pump. The authors concluded that fasting during Ramadan is feasible in patients with type 1 diabetes using an insulin pump, provided that adequate counselling and support are available [31].

Management of type 2 diabetes during Ramadan

Oral hypoglycaemic drugs

For patients taking once-daily oral hypoglycaemic drugs (OHDs), particularly sulphonylureas in the morning during non-fasting times, it has been recommended that the usual morning dose be moved to the evening [32]. However, a large prospective observational study ($n = 332$) demonstrated that the hypoglycaemic rates and overall glycaemic control did not change when once-daily glimepiride taken with breakfast before Ramadan was switched to an evening dose taken at Iftar during Ramadan [32].

Once-daily pioglitazone 30 mg has been considered safe with no increase in hypoglycaemia during Ramadan in patients already taking other OHDs or pioglitazone alone [33].

For patients taking twice- or thrice-daily doses of OHDs, most Ramadan studies have suggested adjusting to two doses during Ramadan, one dose at Sohur and one at Iftar [24,34,35]. As Iftar is usually the larger meal during Ramadan, expert consensus suggested that the OHD dose should be split such that two thirds of the dose is taken at Iftar and one third at Sohur (as the lunchtime dose during the daytime fast is not allowed). For instance, for a regimen of metformin 500 mg three times a day, the adjusted regimen during Ramadan would be 500 mg at Sohur and 1000 mg at Iftar.

For patients who are not well controlled on metformin alone and are planning to fast during Ramadan, there is evidence showing that combining a dipeptidyl peptidase-4 inhibitor, rather than a sulphonylurea, with metformin led to less incidence of hypoglycaemia and better glycaemic control [36].

Thiazolidenediones and incretin-based therapies, such as dipeptidyl peptidase-4 inhibitors (e.g. sitagliptin and saxagliptin) and glucagon-like peptide-1 analogues (e.g. exenatide), may not need dose adjustment during Ramadan. However, other agents, such as sulphonylureas, may need dose reductions when used as a combination treatment.

Insulin treatment

Long-acting insulin, such as glargine, should be given at Iftar to avoid potential hypoglycaemia during daytime fasting [19]. A dose reduction of 20% has been suggested in type 2 diabetic patients with a pre-Ramadan haemoglobin $A_{1c} < 8\%$ [18].

A randomized, open-labelled, crossover study comparing Humalog Mix 25 and Humulin M3 showed that the former offered better postprandial blood glucose control after Iftar and a lower incidence of hypoglycaemia [37]. It has also been suggested that patients taking twice-daily insulin should reduce the Sohur dose by 30% if they

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are well controlled, and consider switching to a Mix 50 preparation if their postprandial glucose remains raised [38].

Special circumstances

Pregnancy

Even though fasting during Ramadan in women without diabetes and with uncomplicated pregnancies has been shown to result in no significant change in maternal ketonaemia or adverse effect on intrauterine development [39], pregnant women with diabetes have been strongly advised against fasting due to the potential maternal and foetal risks associated with poor glycaemic control in pregnancy [23,24]. Therefore, pregnant women with diabetes should be made aware that they are exempted from fasting and that fasting during pregnancy may be associated with risks to the mother and foetus.

Bariatric surgery

Bariatric surgery is increasingly being performed for the correction of morbid obesity in patients with diabetes. As bariatric surgery limits the amount of food and fluid that can be consumed in one sitting, patients who underwent bariatric procedures who fast may encounter problems with dehydration, vomiting and poor nutritional intake as prolonged fasting can lead to the desire to consume larger amounts quickly upon breaking the fast. It has been advised that patients should avoid total fasts in the first 12–18 months after bariatric surgery when new dietary habits are being established [40].

Conclusion

We have summarized (Figure 1) the recommendations for people with diabetes who fast during the month of Ramadan. There is an overwhelming need for better-designed clinical trials, which could provide us with evidence-based information and guidance in the management of patients with diabetes who wish to fast during Ramadan. Currently, we advocate a thorough assessment of a patient's individual risk and modifying the treatment accordingly, so as to reduce the risk of hypoglycaemia or hyperglycaemia. One effective way of managing patients would be by offering group education classes to enable patients to be empowered to manage their condition themselves during Ramadan.

Conflict of interest

None declared.

Recommended 2 – 4 months before Ramadan	**Medical assessment** Tailored to individual needs Review of overall glycaemic control, BP & lipids, renal function, weight and BMI. Review of diabetes medications, i.e. therapy options, timing and dosage adjustment **Ramadan focused structured education** To educate patients, family and carers on the effects of fasting on diabetes, including: Meal planning and dietary advice with dietician Appropriate exercise Blood glucose monitoring Recognition and management of acute complications e.g. hypo-, hyperglycaemia, dehydration, and when to break fast
During Ramadan	**Oral hypoglycaemic agents** Metformin suggested modification: 2/3 daily dose at Iftar; 1/3 daily dose at Suhur Sulphonylureas (SU) suggested dose adjustment: Reduce Suhur dose if taking twice daily SU, e.g. gliclazide 80mg bid pre-Ramadan to gliclazide 80mg at Iftar (pm) and 40mg at Suhur (am) during Ramadan DPP4 inhibitors, rapid acting insulin secretagogues and thiazolenediones may be used at meal times without dose adjustments
	Insulin In general, use an overnight intermediate acting insulin, plus a rapid acting insulin before meals Dose and type of insulin may need adjustments, e.g. 1) reduce insulin glargine dose by 20% 2) use Mix 50 in the evening instead of Mix 30 to avoid postprandial hyperglycaemia **GLP-1 analogues** No treatment adjustment required, but concomitant use of SU may need dose reduction
Follow-up post-Ramadan	HbA1c, weight, BP, lipids Readjustment of medications where appropriate Other opportunities for discussion of Ramadan issues with patients, include: Pre-pregnancy counseling, at diagnosis, at annual diabetic review

Figure 1. The recommendations for people with diabetes who fast during the month of Ramadan

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CLINICAL REVIEW

Management of people with diabetes wanting to fast during Ramadan

E Hui,[1] V Bravis,[1] M Hassanein,[2] W Hanif,[3] R Malik,[4] T A Chowdhury,[5] M Suliman,[6] D Devendra[17]

[1]Department of Investigative Science, Imperial College London, London
[2]Department of Diabetes, Glan Clwyd Hospital, Rhyl
[3]Department of Diabetes and Endocrinology, University Hospital Birmingham, Birmingham
[4]Cardiovascular Research Group, University of Manchester, Manchester
[5]Department of Diabetes, Barts and the London NHS Trust, London
[6]Department of Medicine, Royal Preston Hospital, Preston
[7]Northwest London NHS Trust and Brent Community Services, London

Correspondence to: D Devendra, Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, London NW10 7NS
d.devendra@imperial.ac.uk

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The holy month of Ramadan is one of five main pillars of being a Muslim. Most Muslims are passionate about fasting during this month. Although the Koran exempts sick people from the duty of fasting,[1 2] many Muslims with diabetes may not perceive themselves as sick and are keen to fast. A large epidemiological study of Muslims with diabetes in 13 Muslim countries (n=12 914)—the EPIDIAR study—showed that 43% of patients with type 1 and 79% of those with type 2 diabetes fasted during Ramadan.[3]

As the month of Ramadan follows the lunar calendar, the fasting month is brought forward by about 10 days each year, which means that over time the season in which Ramadan falls changes. For the next decade Ramadan will fall in the summer in the northern hemisphere. As daylight hours vary considerably between summer and winter months in non-equatorial countries, the length of the fast (which lasts from dawn to sunset) increases in the summer (to about 16-20 hours). People with diabetes who fast are at risk of adverse events, and the risks may increase with longer fasting periods. We review the evidence for optimum management of diabetic patients who wish to fast during Ramadan, drawing on a small evidence base comprising randomised trials, non-randomised comparison studies, and observational studies. We combine this with recommendations based on expert consensus. To reduce complications experienced by diabetic patients who fast during Ramadan, health professionals should aim to educate Muslim patients about safe fasting, not only before Ramadan but also at their annual diabetic review and at diagnosis.

SUMMARY POINTS

- Ramadan is one of the five main pillars of Islam
- Muslims are obliged to abstain from food and drink from dawn to sunset during the month of Ramadan
- Muslims with diabetes may be exempted from fasting during Ramadan, although a high proportion fast
- Patients with diabetes who fast risk hypoglycaemia, hyperglycaemia, and dehydration
- Guidelines from the National Institute for Health and Clinical Excellence emphasise the importance of individualising care on the basis of patients' social, cultural, and religious needs
- Diabetic patients who want to fast need an assessment before Ramadan and education to increase their awareness of the risks of fasting

SOURCES AND SELECTION CRITERIA

We searched Embase, Medline, and the Cochrane Library from January 1970 to May 2010 for systematic reviews, randomised trials, large population based studies, case-control studies, observational studies, and published consensus statements. We used the search terms "Ramadan", "fasting", and "diabetes mellitus".

What does fasting during Ramadan involve?

Fasting during Ramadan involves abstaining from food and drink from dawn to sunset for about 30 days. Most people take two meals a day during Ramadan—suhur (the meal before dawn and iftar (the meal after sunset).

What are the risks of fasting for people with diabetes?

Most Muslim religious authorities accept that if a person is advised by a trusted health professional (such as a doctor or nurse) that fasting is harmful to his or her health, then that person is exempted from fasting.[4] The risks of fasting include hypoglycaemia, hyperglycaemia, and dehydration. The EPIDIAR study found that the change in eating patterns during Ramadan increased the risk of severe hypoglycaemia 4.7-fold (from 3 to 14 events per 100 people per month) in type 1 diabetes and 7.5-fold (from 0.4 to 3 events per 100 people per month) in type 2 diabetes. It also found a five-fold increase in the incidence of severe hyperglycaemia in patients with type 2 diabetes during Ramadan. A small observational study (n=41) conducted in 1998 found an increase in symptomatic hypoglycaemia,[5] but other studies have not found a significant increase in the risk of hypoglycaemia during Ramadan in patients treated with oral hypoglycaemic medications or insulin.[6 7] One explanation for different findings among studies is that because Ramadan occurs in a different season every nine years, and the duration and temperature of fasting days change, rates of hypoglycaemia may vary according to the year in which the study was performed. The differences in methods and the small number of patients included in these studies would also explain the disparity of the results.

Over the coming decade, the number of fasting hours will progressively increase in the northern hemisphere as Ramadan falls in the summer months. This will have important implications for Muslims with diabetes who wish to fast.

How should patients with diabetes who fast for Ramadan be managed?

Assessment before Ramadan

Expert opinion recommends that if a patient has made it

clear that they wish to fast during Ramadan their primary physicians and/or diabetes care specialists should assess whether they increase their health risk by doing so.[8] Box 1 outlines how patients planning to fast during Ramadan may be categorised as either high, moderate, or low risk of adverse events. Patients classed as high risk are advised not to fast as it can lead to worsening diabetes control, resulting in, for example, severe hypoglycaemia and diabetes ketoacidosis. Patients at moderate risk can reduce their level of risk if they see a healthcare professional several months before Ramadan and make necessary changes to their diabetes treatment. Those at low risk can fast without healthcare advice. Patients who choose to fast despite advice not to do so need support to help them fast as safely as possible.

In case patients miss the opportunity for assessment before Ramadan, discussion with patients and provision of information packs (see the "Additional educational resources" box) that include advice on Ramadan fasting can be made available at diagnosis and also at annual diabetic review.

Box 1 | Expert recommendations for risk stratification in patients with type 1 or type 2 diabetes who fast during Ramadan[8]

Patients at high risk
- Those with severe and recurrent episodes of hypoglycaemia and unawareness
- Those with poor glycaemic control
- Those with ketoacidosis in the three months before Ramadan
- Those who experience hyperosmolar hyperglycaemic coma within the three months before Ramadan
- Those with acute illness
- Those who perform intense physical labour
- Pregnant women
- Those with comorbidities such as advanced macrovascular complications, renal disease on dialysis, cognitive dysfunction, uncontrolled epilepsy (particularly precipitated by hypoglycaemia)

Moderate risk
- Well controlled patients treated with short acting insulin secretogogue, sulphonylurea, insulin, or taking combination oral or oral plus insulin treatment

Low risk
- Well controlled patients treated with diet alone, monotherapy with metformin, dipeptidyl peptidase-4 inhibitors, or thiazolidinediones who are otherwise healthy

Box 2 | Four key areas in Ramadan focused education[9]

Meal planning and dietary advice
- The diet during Ramadan should be a healthy balanced diet
- Slow energy release foods (such as wheat, semolina, beans, rice) should be taken before and after fasting, whereas foods high in saturated fat (such as ghee, samosas, and pakoras) should be minimised[10]
- Advise patients to use only a small amount of monounsaturated oils (such as rapeseed or olive oil) in cooking
- Before and after fasting include high fibre foods such as wholegrain cereals, granary bread, brown rice; beans and pulses; fruit, vegetables, and salads

Exercise
- Regular light and moderate exercise is safe in type 2 diabetes patients[11]
- Rigorous exercise is not recommended as the risk of hypoglycaemia may be increased, particularly in patients taking sulphonylureas or insulin
- Encourage patients to continue their usual physical activity, especially during non-fasting periods
- Tarawaih prayers (a series of prayers after the sunset meal) should be considered as part of the daily exercise regimen as they involve standing, bowing, prostrating, and sitting

Blood glucose monitoring
- Blood glucose monitoring does not constitute the break of fast[12]
- All patients who fast should be provided with the means to monitor their blood glucose[13]
- Capillary blood glucose testing should be done when:
  -The patient suspects they have symptoms of hypoglycaemia (subjective to the individual). Patients should be advised to break their fast if hypoglycaemia is confirmed on blood glucose testing
  -The patient is unwell (eg, has a fever)
- Testing at other times may be useful only if patients are able and willing to adjust their diabetes treatment regimens, such as insulin dosage titration

Recognising and managing complications
- Patients should be aware of the warning symptoms of dehydration, hypoglycaemia, and hyperglycaemia and should stop the fast as soon as any complications or acute illness occur

Ramadan focused education

Structured education interventions have been endorsed by the National Institute for Health and Clinical Excellence as important in empowering patients to improve their journey with diabetes. In a large observational study, patients who fasted during Ramadan without attending a structured education session had a fourfold increase in hypoglycaemic events, whereas those who attended an education programme focusing on Ramadan had a significant decrease in hypoglycaemic events.[9] We therefore recommend that Muslim patients with diabetes attend some form of structured education intervention to increase their chance of being well when fasting during Ramadan. Patients at high risk who plan to fast despite medical advice not to are also invited to attend structured education to support their self management and decision to fast. Box 2 outlines suggested content of Ramadan focused education.

How should fasting patients with type 2 diabetes be managed?

Patients taking oral hypoglycaemic agents

Metformin

Hypoglycaemia occurs in patients with type 2 diabetes taking metformin who are not fasting.[14] A systematic review reported that levels of risk for hypoglycaemia among people taking metformin who are not fasting range from 0% to 21%.[15] No data exist for the incidence of hypoglycaemia in people who fast for prolonged periods and take only metformin.

As iftar is usually the largest meal during Ramadan, expert consensus suggests that the metformin dose should be split such that two thirds of the dose is taken at iftar and one third at suhur (as the lunchtime dose during the daytime fast is not allowed). So for a regimen of, for example, metformin 500 mg three times a day, we recommend 500 mg at suhur and 1000 mg at iftar.

Acarbose

Acarbose inhibits the action of intestinal brush border alpha-glucosidases, which retards glucose absorption and modifies the secretion of insulin.[16] A randomised double blind study showed that the risk of hypoglycaemia is low with this class of drugs,[17] although we could not find any evidence that this is so during Ramadan. We suggest that it is acceptable to continue with the prescribed dose(s) of acarbose taken only with meals during fasting.

ADDITIONAL EDUCATIONAL RESOURCES

For healthcare professionals

- Al-Arouj M, Bouguerra R, Buse J, Hafez S, Hassanein M, Ibrahim MA, et al. American Diabetes Association recommendations for management of diabetes during Ramadan. *Diabetes Care* 2005;28:2305-11
- Karamat MA, Syed A, Hanif W. Review of diabetes management and guidelines during Ramadan. *J R Soc Med* 2010;103:139-47.
- Benaji B, Mounib N, Roky R, Aadil N, Houti IE, Moussamih S, et al. Diabetes and Ramadan: review of the literature. *Diabetes Res Clin Pract* 2006;73:117-25.
- Ramadan health factsheet 2009 (from Muslim Spiritual Care Provision in the NHS, PO box 57330, London E1 2WJ; nhsspiritualcare@mcb.org.uk)—Provides a brief summary of issues for doctors, healthcare staff, and patients

For patients

- LeicestershireDiabetes (www.leicestershirediabetes.org.uk)—Website with information on fasting and insulin treatment during Ramadan
- United Kingdom Ramadan Diabetes Network (www.ukRamadandiabetes.net)—Has a useful publication on diabetes and fasting
- Ramadan health guide: a guide to healthy fasting. 2007. www.ramadan.co.uk/RamadhanHealth_Guide.pdf. (Useful Department of Health document on healthy fasting, but not specifically about diabetes)

Rapid acting insulin secretogogues

An open label, multicentre, randomised study showed that repaglinide, a rapid acting insulin secretogogue, contributed to improved glycaemic control, with a lower number of hypoglycaemic events among fasting patients during Ramadan when compared with glibenclamide. Patients taking repaglinide lowered their fructosamine levels from baseline, and there were 0.03 hypoglycaemic events per patient per month in this group versus 0.05 events per patient per month in the glibenclamide group.[18]

A small study compared repaglinide (n=27) with a group of patients taking a sulphonylurea (glimepiride (n=23) or gliclazide (n=17)). Fructosamine, HbA_{1c}, and body weight did not change significantly in either group from before to after Ramadan. Hypoglycaemia was documented in only one patient who took glimepiride during Ramadan.[19] The evidence cited suggests that rapid acting insulin secretogogues taken at suhur and iftar are a safer alternative than glibenclamide for patients who fast.

Sulphonylureas

Early studies examined the use of glibenclamide or glimepiride during Ramadan.[20] A more recent, large prospective observational study (n=332) showed that changing once daily glimepiride from a morning dose taken with breakfast before Ramadan to an evening dose taken at iftar during Ramadan did not alter rates of hypoglycaemia or glycaemic control.[21] However, the rate of hypoglycaemia in patients taking glimepiride in the mornings during Ramadan was not studied, so whether that rate is higher than the rate in those taking glimepiride in the evenings is unknown. The incidence of hypoglycaemic events did not differ between a group of patients taking once daily glimepiride (n=21) and a group taking twice daily repaglinide (n=20) (taken at suhur and iftar).[22] More recently, gliclazide has been compared with newer agents, such as dipeptidyl peptidase-4 inhibitors.[23]

On the basis of the prospective study by the GLIRA study group[21] we recommend that during Ramadan clinicians change the timing of the once daily dose of sulphonylurea (such as glimepiride) from the usual morning dose to the evening (at iftar). With regard to gliclazide, we recommend that patients take a larger dose at iftar than at suhur and that clinicians consider reducing the prescribed dose for suhur if the patient's glycaemic control before Ramadan is stable (for example, change gliclazide 160 mg twice daily to 80 mg in the morning and 160 mg in the evening).

Thiazolidenediones

A randomised controlled trial that compared pioglitazone 30 mg once daily with placebo in patients already taking other oral hypoglycaemic agents or alone, found no increase in hypoglycaemia during Ramadan fasting.[24] No studies have been reported on the use of rosiglitazone use during Ramadan. Continuing with thiazolidenediones during fasting is considered safe.

Dipeptidyl peptidase-4 inhibitors

A retrospective audit of Muslim patients with type 2 diabetes showed that adding vildagliptin to metformin treatment was associated with a reduced incidence of hypoglycaemic events and improved glucose control compared with patients treated with gliclazide and metformin during Ramadan.[23] This low grade evidence suggests that it may be safer to combine dipeptidyl peptidase-4 inhibitors, rather than sulphonylureas, with metformin in patients who are not well controlled when taking metformin alone and are planning to fast during Ramadan.

Glucagon-like peptide-1 mimetics

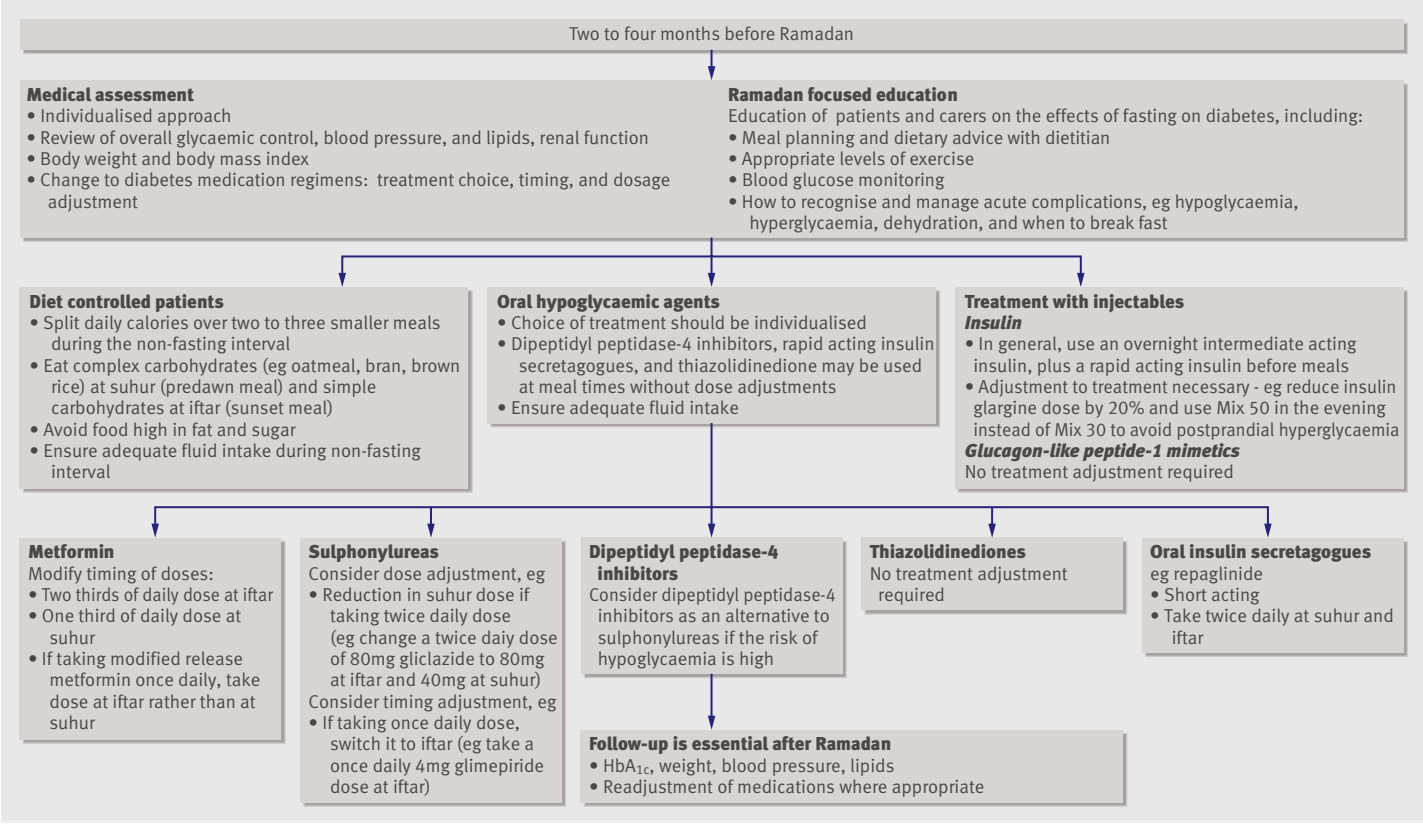
Glucagon-like peptide-1 mimetics are currently used in combination with other oral hypoglycaemic agents. In non-Ramadan studies, hypoglycaemic events associated with glucagon-like peptide-1 mimetics occurred primarily in patients taking a sulphonylurea.[25] The findings of an audit suggested that its dosage does not need to be adjusted during Ramadan but that other agents, such as sulphonylureas, may need dose reductions when used as a combination treatment.[26]

Patients taking insulin

Single basal insulin and oral combined treatment

A multicentre, prospective, observational study compared fasting patients taking metformin combined with glimepiride (n=21), repaglinide (n=18), or glargine (n=10).[7] Although the rate of hypoglycaemia was higher in the glimepiride group (14.3%) than in the repaglinide (11%) and glargine (10%) groups, the increased rate was not significant. Glimepiride was given before iftar; repaglinide was given with both meals; and glargine at 10.00 pm. No studies have compared the incidence of hypoglycaemic events in patients taking insulin detemir or isophane insulin (NPH) (such as Insulatard, Novo Nordisk; or Humulin I, Lilly).

In a small prospective non-randomised study of 19 patients who had type 2 diabetes, were at low risk of diabetic complications, and had a pre-Ramadan HbA_{1c} concentration of <8%, neither fasting (n=11) nor non-fasting (n=8) patients who were taking repaglinide three times a day and glargine experienced hypoglycaemic events,



An approach to oral treatment of type 2 diabetes during Ramadan for patients planning to fast

and both groups maintained stable glycaemic control.[6] Those who fasted took repaglinide at iftar, at midnight, and at suhur, and the doses of repaglinide and glargine remained unchanged throughout Ramadan. We advise patients who take long acting basal insulin, such as glargine, to reduce the dose by 20% to avoid hypoglycaemia. Patients taking repaglinide and single dose glargine may continue taking the same doses of repaglinide but to be safer should consider reducing glargine by 20%. The timing of repaglinide can be rearranged to coincide with suhur and iftar.

Premixed insulins

A randomised, open labelled, crossover study comparing Humalog Mix25 (Lilly) (25% short acting insulin lispro and 75% intermediate acting neutral lispro protamine) and Humulin M3 (Lilly) (human insulin 30% soluble, 70% isophane) given in identical doses showed that the former offered better control of postprandial blood glucose after iftar and a lower occurrence of hypoglycaemic events.[27] However, the findings of an observational study suggested that using Humalog Mix50 (Lilly) at ifta instead of Mix30 reduced postprandial glucose excursions and reduced hypoglycaemia.[28] We suggest that patients taking twice daily insulin should reduce the suhur dose by 30% if they are well controlled, and consider switching to a Mix 50 preparation if their postprandial glucose remains raised.

Is fasting safe for pregnant women with diabetes?

Pregnant women with diabetes, including gestational diabetes, are exempted from fasting and are strongly cautioned against fasting because clear maternal and fetal risks are associated with poor glycaemic control in pregnancy.[29] However, no outcome study of women with diabetes specifically related to Ramadan fasting has been conducted. Preconception counselling for diabetic Muslim women must include education about the substantial risks associated with poor glycaemic control to help to dissuade them from trying to fast.

How should fasting patients with type 1 diabetes be managed?

A small study examined the use of glargine and insulin lispro or aspart, divided in a 6:4 ratio of the total 24 hour insulin dose in nine patients with type 1 diabetes.[30] Of seven patients who started to fast, five continued for the whole month, and two broke the fast owing to hypoglycaemia. None of the patients had any episodes of severe hypoglycaemia or diabetic ketoacidosis requiring admission to hospital, and the patients' HbA_{1c} concentrations remained stable at the end of Ramadan. As the insulin requirement in this study group decreased by 28% from baseline (P=0.002), the authors suggested a reduced dose (70% of a patient's usual dose) during the fast.

An open label, comparative, crossover study of 64 patients with type 1 diabetes found significantly lower (P=0.026) two hour, postprandial glucose concentrations after iftar and fewer hypoglycaemic events with insulin lispro than with regular human insulin.[31] In both arms isophane insulin (Humulin I) was given as the basal insulin.

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Most studies of patients with type 1 diabetes have comprised small numbers of patients and some have excluded adolescents, elderly patients, or patients with comorbidities such as renal impairment. Suggested treatments, therefore, may not be generalised to all fasting patients with type 1 diabetes, and no good evidence exists to allow us to give clear guidance for those who are not on a basal bolus regimen (basal insulins are intermediate or long acting insulins; bolus is rapid acting insulin taken with meals).

We suggest that patients with type 1 diabetes who are on a basal bolus regimen four times daily should be discouraged from fasting owing to the risks of poor glycaemic control. If patients choose to fast despite medical advice, it will help if they are familiar with carbohydrate counting. We suggest they reduce their background insulin by 20% and omit the midday rapid acting insulin if their capillary blood glucose concentration is ≤7 mmol/l. If their blood glucose concentration is >7 mmol/l, patients will need to calculate their insulin correction dose as determined by their specialists.

Conclusion

The figure summarises the recommendations given in this article, based on the best available and most current evidence and on our collective experience in managing patients who fast during Ramadan. Overall, the evidence available for guiding management of patients with diabetes who wish to fast during Ramadan is poor, and well designed studies are lacking. An assessment of a patient's individual risk and a tailored approach to treatment seems to be the best management strategy. Offering structured education to enable patients to manage their condition better themselves during Ramadan is essential.

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DIABETES AND RAMADAN

Elaine Hui, Vassiliki Bravis, Margaret Devereux and Devasenan Devendra



Diabetes and Ramadan.
Patient Management.

The following case highlights the potential risks of both hypoglycaemia and renal impairment in Muslim patients with type 2 diabetes who fast during the lunar month of Ramadan from sunrise to sunset. A 66-year-old Muslim man with type 2 diabetes treated with metformin and gliclazide, was fasting during the daylight hours of Ramadan. He was admitted with symptomatic hypoglycaemia and acute renal impairment following a short history of diarrhoea. A diagnosis of viral gastroenteritis and dehydration secondary to prolonged fasting was made. The hypoglycaemia was precipitated by a combination of fasting, gliclazide use and acute renal impairment. Although the choice of fasting rests with an individual, the risks could be minimised through patient education and medical assessment before Ramadan. It is also important for all healthcare professionals to be aware of and respect this religious obligation in order to provide appropriate care for patients with diabetes who choose to fast during Ramadan.

Case History

A 66-year-old Muslim gentleman presented unresponsive on the sofa, following two days of loose watery diarrhoea. His capillary blood glucose measured 2.9mmol/L and he was given an intramuscular injection of 1mg glucagon followed by an intravenous bolus of 25ml of 50% dextrose solution to treat the hypoglycaemia. He had a 5-year history of type 2 diabetes treated with metformin 850mg and Gliclazide 80mg twice daily. Apart from retinopathy, there was no history of nephropathy or neuropathy; Background essential hypertension was controlled on Losartan 50mg daily. Following initial treatment, he was alert with a GCS 15/15; abdominal and neurological examinations were normal. Laboratory investigations identified a serum glucose of 12.0mmol/l and creatinine of 235µmol/L with a previously normal eGFR and creatinine level. Further history revealed that he had been fasting for Ramadan, 10 days prior to hospital admission. Stool culture was negative for infection and renal ultrasound demonstrated normal size kidneys.

There was no recent antibiotic use, foreign travel or known contacts, and the acute episode of diarrhoea was likely secondary to viral gastroenteritis. He was rehydrated with intravenous fluids and was commenced on an insulin sliding scale. His oral medications were stopped for 2 days while the diarrhoea settled and was discharged from hospital when his renal function normalised after 3 days. He was recommended to consult medical advice if he decided to fast during the next Ramadan to assess his risks of fasting and whether his diabetes medications require adjustment prior to fasting.

Discussion

This case highlights the potential risks of fasting during Ramadan in a type 2 diabetes patient treated with metformin and gliclazide. Ramadan is the ninth month of the Islamic lunar calendar and healthy Muslims are obliged to abstain from eating and drinking from sunrise to sunset during this month. Most people take two meals a day during the month, one before sunrise and one after sunset. The Koran exempts the sick from fasting[1], but some diabetes patients may not perceive themselves as "sick" and instead choose to fast during Ramadan. Studies have shown that the pattern of daytime fasting and night-time meals during Ramadan can increase the rate of severe hypoglycaemia in type 2 diabetes 7.5-fold (from 0.4 to 3 events per 100 people per month)[2]. Other risks include dehydration and hyperglycaemia[3], due to the change in the dietary pattern during Ramadan, when the main meal is consumed in the evening.

The duration of the Ramadan month varies between 29 and 30 days and the hours spent fasting can range from only a few hours to more than 20 hours per day, depending on season and geographical location. The month of Ramadan will occur during summer in the Northern hemisphere in the next few years as the lunar year rotates from season to season, and the number of fasting hours will be progressively longer. Hence, it is important for healthcare professionals in the United Kingdom to be aware of this issue for Muslim patients with diabetes who intend to fast during Ramadan.

The combination of diarrhoea and fasting may have contributed to the acute renal impairment secondary to pre-renal causes, which was corrected with supportive measures of fluid resuscitation, careful monitoring and replacement of any electrolyte disturbance, and adequate glycaemic control. Patients on sulphonylurea drugs, such as gliclazide, may be more prone to hypoglycaemia during the Ramadan fast. Changes to the timing and dosages of sulphonylureas may be needed during Ramadan. As patients tend to eat their main meal after sunset, it has been suggested that switching the usual evening dose of sulphonylurea to before dawn and the usual morning dose (together with any midday dose) to the evening may result in better glycaemic control4. In the case of this patient, an alternative solution would be to half the morning dose of sulphonylurea (taken with their sunrise meal) and combine the other half of the morning dose with his regular evening dose (taken with the sunset meal)5. He would thus be taking 40mg gliclazide in the morning and 120mg in the evening during Ramadan.

DIABETES AND RAMADAN

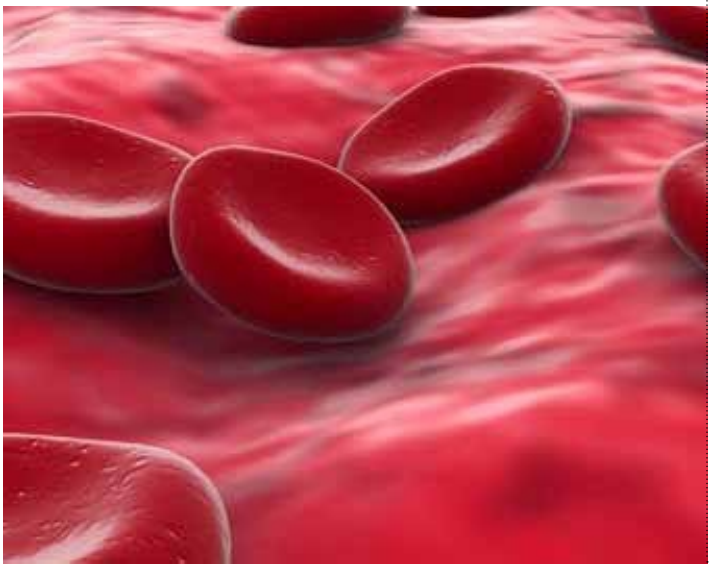
Elaine Hui, Vassiliki Bravis, Margaret Devereux and Devasenan Devendra

It is generally considered safe to continue with metformin during Ramadan as the risk of hypoglycaemia is low. However, metformin was stopped temporarily in our case due to the risk of lactic acidosis in the setting of acute renal failure.

Table 1 summarises the recommended actions for various diabetic drug regimens during Ramadan.

Before Ramadan	During Ramadan
On diet control	Continue on diet control
On oral hypoglycaemic agents: Metformin e.g. metformin 500mg tds Sulphonylurea e.g. gliclazide 80mg bd Dipeptidyl peptidase (DPP-IV) inhibitor e.g. vildagliptin 50mg bd Thiazolidinedione e.g. pioglitazone 30mg od	Metformin 500mg at Suhur; 1g at Iftar Gliclazide 40mg at Suhur; 120mg at Iftar No change in dose No change in dose
On insulin 30/70 premixed insulin bd s/c e.g. 40 units morning, 20 units evening	Switch morning insulin dose to Iftar, half evening insulin dose and take it at Suhur e.g. to 10 units morning, 40 units evening Or consider changing evening insulin to 50/50 premixed insulin
On GLP-1 agonist e.g. exenatide 10mcg bd s/c	No change in dose If in use in conjunction with sulphonylurea, dose adjustment may be needed for sulphonylurea.

Table 1: Summary of recommended actions during Ramadan.
od – once daily; bd – twice daily; tds – three times daily
s/c – subcutaneous; Suhur – sunrise meal; Iftar – sunset meal





If a patient with diabetes chooses to fast during Ramadan, this decision should be respected and an appropriate care plan should be devised, taking into account the change in eating and sleeping patterns during the month, and any necessary treatment adjustments. However, patients who are likely to encounter complications during prolonged daytime fast (such as patients with type 1 diabetes, those with poor pre-existing glycaemic control and pregnant women) should be strongly advised not to fast during Ramadan. The changes in diabetes treatment summarised above (Table 1) serve as a recommendation only. Patient variations should be taken into account when adjusting their diabetes treatment to tailor their individual needs. It is essential that these patients are encouraged to have a medical assessment and discussion with the appropriate healthcare professionals, such as their general practitioners or diabetes specialists, prior to the Ramadan fast.

It is also beneficial for patients to attend focused structured education on meal planning, glucose monitoring and the recognition and management of complications. It has been shown that a Ramadan-focused structured education programme can reduce the risk of hypoglycaemia without compromising their glycaemic control or weight6. This would allow patients to make an informed decision on whether to fast during Ramadan and to minimise any risks involved.

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DIABETES AND RAMADAN

Elaine Hui, Vassiliki Bravis, Margaret Devereux and Devasenan Devendra



Diabetes and Ramadan.
Patient Management.

Questions

Question 1: To minimize the risk of hypoglycaemia, advise patients taking short-acting sulphonylureas as follows:

a) If two or three doses are taken each day, take half the normal evening dose before dawn and the normal morning (and any midday) dose after sunset.
b) Half the dose of the drug with each meal.
c) If a single daily dose is used, take this with the dawn meal.
d) If two or three doses are taken each day, take half the normal evening dose after sunset and the normal morning (and any midday) dose before dawn.
e) Continue with the same doses as outside the Ramadan period.

Question 2: For people with diabetes who choose to fast during Ramadan, in terms of diet, we advise:

a) Eat foods that are high in dietary fibre and have a low glycaemic index.
b) Eat foods that are high in dietary fibre and have a high glycaemic index.
c) Eat foods that are low in dietary fibre and have a low glycaemic index.
d) Eat foods with a high glycaemic index until about half an hour after taking medications.
e) Eat foods with a low glycaemic index until one hour after taking medications.

Answers

Answer: 1. b)

Explanation: During Ramadan the predawn meal is followed by a prolonged period of fasting and patients tend to consume the main meal at sunset. Regardless of the type of sulphonylureas used, the timing and dosages may need adjustment and possibly reducing, particularly the dose before the predawn meal. Patients should take a larger dose of sulphonylurea at the main meal at sunset (e.g. by switching the usual morning dose plus any lunchtime dose to the evening, and the usual evening dose to the morning). When used in combination with metformin, sulphonylurea dosages may need to be reduced. For instance, long-acting sulphonylureas should be taken in the evening at a reduced dose of two-thirds that normally taken during the non-Ramadan period. With short-acting sulphonylureas, both the morning dose, taken with Suhur, and the evening dose, taken with Iftar, should be reduced by half.

To minimise the risk of hypoglycaemia, advise patients taking oral hypoglycaemic agents as follows:

i. If taking a long acting sulphonylurea, switch to a short acting preparation or metformin, or both.

ii. If a single daily dose is used, take this with the sunset meal.

iii. If two or three doses are taken each day, take half the normal evening dose before dawn and the normal morning (and any midday) dose after sunset.

Answer: 2 a)

Explanation: For patients with type 2 diabetes who choose to fast during Ramadan, careful dietary advice should be provided. Encourage patients (ideally with input from a dietician trained to deal with cultural issues) to eat foods that are high in dietary fibre (such as whole grains, fruits, and vegetables) and have a low glycaemic index (such as beans and pulses) at the pre-dawn (Suhur) and sunset (Iftar) meals to promote glycaemic control. Discourage them from eating foods with a high glycaemic index (such as more than three dates, which are traditionally used to break the fast) until about half an hour after taking drugs to minimise sharp rises in blood sugar at sunset.

The diet during Ramadan should not differ from a healthy balanced diet. Protein should comprise 10-20% of the daily calories, the remaining 80-90% being divided between fat and carbohydrates.

Some authors suggested that slow energy-release foods (such as wheat, semolina, beans, rice) should be taken before and after fasting, whereas foods high in saturated fat (such as ghee, samosas and pakoras) should be minimised.

If blood glucose is well controlled by diet alone, advise them that fasting is safe. Self monitoring of blood glucose is essential for safe fasting in patients taking antidiabetic drugs, particularly before and after the pre-dawn and sunset meals. It should guide the individual tailoring of treatment regimens.

DIABETES AND RAMADAN

Elaine Hui, Vassiliki Bravis, Margaret Devereux and Devasenan Devendra



Further Reading

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Authors

Elaine Hui
Jeffrey Kelson Diabetes Centre
Central Middlesex Hospital
Acton Lane
Park Royal
London, NW10 7NS

Vassiliki Bravis
Jeffrey Kelson Diabetes Centre
Central Middlesex Hospital
Acton Lane
Park Royal
London, NW10 7NS

Margaret Devereux
Jeffrey Kelson Diabetes Centre
Central Middlesex Hospital
Acton Lane
Park Royal
London, NW10 7NS

Devasenan Devendra
Jeffrey Kelson Diabetes Centre
Central Middlesex Hospital
Acton Lane
Park Royal
London, NW10 7NS

Corresponding author

Devasenan Devendra
Jeffrey Kelson Diabetes Centre
Central Middlesex Hospital
email: d.devendra@imperial.ac.uk



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P315

A comparative analysis of exenatide and gliclazide during the month of Ramadan

V Bravis[1,2], E Hui[1], S Salih[3], M Hassanein[4] and D Devendra[1,2,3]
[1]*Diabetes and Endocrinology, Central Middlesex Hospital, London, UK,* [2]*Investigative Sciences, Imperial College, London, UK,* [3]*Diabetes and Endocrinology, Brent PCT, London, UK,* [4]*Diabetes, Glan Clwyd Hospital, North Wales, UK*

Introduction: Type 2 diabetes (T2DM) patients who fast during Ramadan have a four-fold increase in hypoglycaemic events(HE) especially if there are on sylphonylureas. Exenatide use in muslim patients who fast during Ramadan has never been evaluated in terms of its safety during Ramadan.
Aim: To audit the impact of exenatide compared with gliclazide on weight change and HE during Ramadan in a Muslim T2DM population.
Method: Two groups of patients were assessed: group 1 received exenatide 10 mcg bd (n = 26), group 2 received gliclazide 80 mg bd (n = 17). Both groups took at least 1 g day-1 of metformin. Weight and HE were compared pre and post Ramadan.
Results: Mean baseline HbA1c in group 1 was 8.1% (SD 0.69) and group 2 8.4% (SD 0.60). In group 1 there was a mean weight change of + 0.12 kg (p = 0.55, 95%CI 0.18 to 0.93) and mean change in the frequency of HE of −0.08 (p = 0.43, 95%CI 0.24 to 0.61) during Ramadan. In group 2 there was a mean weight change of + 0.68 kg (p = 0.01, 95%CI 0.23 to 1.14), whilst the frequency of hypoglycaemia increased during the month of Ramadan by 53% (p = 0.03, 95%CI 0.08 to 0.98).
Conclusion: Gliclazide treatment in addition to metformin leads to significant weight gain and increase in hypoglycaemia during Ramadan. Exenatide does not. This observation study emphasises the safety of exenatide in terms of hypoglycaemic episodes during the month of Ramadan. We therefore do not recommend any changes in the dose of regime in patients taking only metformin and exenatide during the month of Ramadan.

Clinical care and other categories posters: Exercise

P316

An exploration of the experiences faced by individuals with Type 1 diabetes during and after exercise

G Hill[1], L Kilbride[1], G Aitken[1], J McKnight[2], R Davison[1] and J Charlton[1]
[1]*Centre for Nursing and Allied Health Care Professional Research, Edinburgh Napier University, Edinburgh, UK,* [2]*Metabolic Department, NHS Lothian, Edinburgh, UK*

Aims: To increase healthcare professionals understanding of individuals' experience of undertaking exercise.
Methods: Using a qualitative approach the experience of undertaking exercise was explored with four subjects (2 men and 2 women) who were regular exercisers. A focus group was conducted to explore issues such as self-management, hypoglycaemia and coping strategies with these individuals. Analysis of the transcript were conducted independently by three individuals independently using a thematic analysis approach.
Results: The analysis generated the following themes: Locus of control, Motivation, Trial and Error and Bespoke regimens. Indicating that to participate in exercise individuals require to be extremely motivated to overcome the issues of dysglycaemia during and after exercise. They need to spend an inordinate amount of time adjusting insulin and carbohydrate doses in accordance with the time, type and duration of exercise. The benefits of exercise to them mentally and physically outweigh the motivation and energy required to manage their blood glucose levels which what provided them with the incentive to continuing to exercise.
Conclusion: People with Type 1 diabetes who regularly exercise require motivation and energy to overcome the issues that they face. As healthcare professionals we need to consider these findings to explore strategies to assist regular exercisers and encourage participation from non exercisers.

P317

Development of an algorithm for moderate intensity exercise in Type 1 diabetes

J Charlton[1,2], G Aitken[1], R Davison[1], I Gallen[3], G Hill[1], L Kilbride[1] and J McKnight[2]
[1]*School of Nursing Midwifery and Social Care, Edinburgh Napier University, Edinburgh, UK,* [2]*Metabolic Unit, NHS Lothian, Western General Hospital, Edinburgh, UK,* [3]*Diabetic Clinic, Wycombe Hospital, High Wycombe, UK*

Aims: Exercise in Type 1 diabetes frequently causes dysglycaemia. The glycaemic response and effectiveness of an algorithm adjusting insulin and carbohydrate was assessed for moderate exercise, in comparison with usual self-management.
Methods: 14 individuals using basal bolus analogue insulin regimen, that exercised regularly and counted carbohydrate participated in the study over 2 weeks. On Days 1 and 3 of each week they undertook 40 minutes of moderate exercise at 50% VO_2max. During Week 1 participants self-managed their insulin and carbohydrate and in week 2 followed the algorithm stipulating a 30% fast acting insulin reduction pre and post exercise, and recommended carbohydrate amounts based on current glycaemic level. Continuous blood glucose monitoring was performed.
Results: Baseline mean demographics were: 38 yrs, BMI 25 kg/m^2 and HbA1c 7.5% ± 0.7%. The exercise period reduced blood glucose levels by 2.1 to 4.8 mmol/l (95%CI) in both weeks. The mean reduction in glycaemia during exercise over both weeks was −3.1 ± 2.03 mmol/l. The duration of hypoglycaemia (< 4 mmol/l) during the exercise period (95% CI = −6.0 to 1.0 mins) and the 6 hours post exercise (−11.3 to 17.1 minutes) was not significantly different between weeks. Time spent within a 4–9 mmol/l. range during exercise was not significantly different (−3 to 22.4 mins) or post exercise (−75.5 to 61.3 mins) between weeks.
Conclusion: The algorithm did not significantly alter the blood glucose drop during or after exercise. However our findings indicate a greater decrease of fast acting analogue insulin pre exercise, and changes to recommended carbohydrate are required.

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P168

The incidence of presentation of acute coronary syndrome during the month of Ramadan

P Shirley, M Devereux, E Hui and D Devendra
Jeffrey Kelson Diabetes Centre, Central Middlesex Hospital, London, UK

Aims and objectives: During the month of Ramadan, Muslims abstain from eating and drinking from sunrise to sunset. Fasting may affect diabetes patients with cardiovascular risks due to limited time allowed for food intake and omission of medications during fasting. The incidence of patients presenting with acute coronary syndromes (ACS) in relation to fasting during Ramadan have not been studied in the UK before. Our aim is to investigate the incidence of hospital admission of acute coronary syndrome, and the proportion of Muslim diabetes patients who were fasting, during Ramadan.
Methods: During the lunar month of Ramadan 2009, we reviewed all cases admitted to a district general hospital in Brent with ACS, defined according to the joint European Society of Cardiology/ American College of Cardiology 2000 statement.
Results: 30 patients were admitted with ACS. Average age was 71 years (SD 15 years). 41% (12 out of 30) had diabetes, of which 91.7% were Type 2 and 8.3% were Type 1. 2 of these diabetes patients were Muslims but did not fast during Ramadan. One patient of the total 30 had been fasting from the start of Ramadan until hospital admission. The patient did not have diabetes and his fasting glucose was 4.1 mmol-l.
Discussion: Hospital admission for acute coronary syndrome does not appear to be a major problem in Muslim diabetes patients who fasted. Future studies with larger sample size and comparison with non-fasting months are needed. Our findings are in keeping with a large population-based study conducted in the Middle East showing no differences in ACS during Ramadan and other non-fasting months.

P169

The accuracy of the modified Framingham and United Kingdom Prospective Diabetes Study cardiovascular risk algorithms in a multi-ethnic population with Type 2 diabetes: a longitudinal study in 4463 people over 5 years

RL Mehta[1], MJ Davies[1], R Baker[1], H Blackledge[2], LJ Gray[1], M Stone[1] and K Khunti[1]
[1]*Health Sciences, University of Leicester, Leicester, UK,* [2]*Directorate of Public Health, Leicester City PCT, Leicester, UK*

Refer to Oral number A49.

P170

Is 24-hour ambulatory blood pressure monitoring more useful in patients with diabetes than those without diabetes?

JC Alcolado and S Price
Centre for Endocrine and Diabetes Sciences, Cardiff University School of Medicine, Cardiff, UK

Aims and objective: Single blood pressure (BP) readings in clinic can be an over-estimate due to the ''white-coat phenomenon''. 24-hour ambulatory monitoring is often used to obtain a more accurate estimate of the BP profile. The aim of this study was to examine the correlations between single outpatient BP readings and 24-hour ambulatory monitoring in patients with and without known diabetes.
Methods: We studied 60 patients (36 with diabetes). From the medical records we obtained the clinic BP, current antihypertensive treatment, and medical diagnoses. Ambulatory monitoring was carried out using the Reynolds Medical Tracker system.
Results: For patients with diabetes, the mean clinic BP was 162 mmHg systolic (range 132–204) and 89 diastolic (70–110). The mean total average blood pressure on ambulatory monitoring was 132 systolic (109–164) and 71 diastolic (57–88). The corresponding values for the day interval were; 135 (109–160), diastolic 74 (58–88) and for the night interval, systolic 131 (99–195), diastolic 69 (55–104). For patients without diabetes, the mean clinic BP was 159 mmHg systolic (128–196) and 86 diastolic (56–114). Mean total average BP on ambulatory monitoring was 139 systolic (108–181) and 78 diastolic (58–98). Values for the day interval were; systolic 143 (110–178), diastolic 82 (60–106) and for the night interval, systolic 133 (105–184), diastolic 72 (57–92).
Conclusions: Ambulatory monitoring showed 24-hour readings on average 30 mmHg systolic and 18 mmHg diastolic lower in patients with diabetes compared with single outpatient readings. For people without diabetes the differences were on average 20 mmHg systolic and 12 mmHg diastolic ($P < 0.05$ diabetic vs non-diabetic). These findings suggest ambulatory BP monitoring may be especially important in patients with diabetes.

P171

Tailoring choice of antihypertensive combination therapy to minimise insulin resistance in patients with hypertension and Type 2 diabetes

CM McHenry[1], CN Ennis[2], B Sheridan[2], SJ Hunter[1], AB Atkinson[1] and PM Bell[1]
[1]*Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast, UK,* [2]*Regional Endocrine Laboratory, Royal Victoria Hospital, Belfast, UK*

Refer to Oral number A53.

P172

The study of cardiovascular risk factors in patients attending the diabetic renal clinic, Wisdem Centre, UHCW

N Gill and AA Syed
Wisdem Centre, UHCW NHS Trust, Coventry, UK

Aims: Cardiovascular disease is the leading cause of death in patients with diabetic renal disease. Aggressive risk stratification is important to reduce the cardiovascular morbidity and mortality. Patients with diabetes with severe Chronic Kidney Disease need close monitoring by the diabetologist and nephrologist. This audit was conducted to review the risk factor management in comparison with the JBS 2 Guidelines.
Methods: Data were collected between December 2008 to June 2009 for age, ethnicity, type and duration of diabetes, eGFR, BP, lipids and HbA1c and input from the nephrologist and analysed using Microsoft Excel. CVD risk factor targets were those recommended by Joint British Societies 2005.

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