

REVIEW ARTICLE

MANAGEMENT OF DIABETES IN RAMADAN

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Ramadan, the ninth month of Islamic calendar brings alongwith it a sense of responsibility to fast among the Muslim adult population. Though patients with chronic illnesses like Diabetes mellitus are exempted from fasting during the month if their health does not allow, they still wish to fast. This creates a challenge for the health care professionals to enable the patients with Diabetes mellitus to fast safely, without developing complications like hypoglycemia, hyperglycemia, ketoacidosis and thrombosis. This article has reviewed multiple articles published over last two decades to develop a consensus plan regarding management of Diabetes mellitus in Ramadan. Insulin sensitizers are a better option than drugs increasing secretion of insulin. Type 2 Diabetic patients can fast much safely as compare to Type 1 Diabetics.

Keywords: Diabetes mellitus; Ramadan; Fasting; Hypoglycaemia; Hyperglycaemia; Ketoacidosis; Insulin

Citation: Badshah A, Haider I, Humayun M. Management of diabetes in Ramadan. J Ayub Med Coll Abbottabad 2018;30(4):596–602.

INTRODUCTION

Fasting during Ramadan, the ninth month of Islamic Calendar is one of the five essentials of Islam. Muslims keep on fasting during daylight hours for one full Lunar month (29–30 days), and the fast can even extend upto 23 hours on the basis of terrestrial setting and time of year. Fasting during Ramadan involves abstinence from food, drink, oral medicines, sexual activity and smoking from dawn (*seher*) to sunset (*iftar*). Fasting during the month is mandatory for all healthy Muslim adults, but exemptions exist for people with chronic illnesses, like Diabetes, mentally challenged people, frail elderly, travellers, and women during menstruation, pregnancy and lactation¹. Many Diabetic patients during Ramadan insist on fasting, crafting a challenging scenario for themselves and their healthcare providers.

The International Diabetes Federation (IDF) has described Diabetes as one of the largest global health emergencies of the 21st century.² This global epidemic includes countries with substantial Muslim populations, where the relative prevalence of Diabetes is well on top of the worldwide average. More significantly, the number of Diabetic patients in these states is predicted to rise considerably over the next 25 years.^{2,3} A large study conducted on Muslim Diabetics amongst 13 Muslim countries (“EPIDIAR study” – Epidemiology of Diabetes and Ramadan) documenting 43% of Type 1 Diabetic patients and 79% Type 2 Diabetics fasted during the month of Ramadan leading to reference that approximately 40–50 million Diabetic people across the globe fast in Ramadan.⁴

In order to understand the physiology of fasting in Diabetics, it is necessary to understand the basics of carbohydrate and fat metabolism in normal

individuals. There is a slight decrease in serum glucose to 3.2–3.9 mmol/litre (58–70 mg/dl) in adults few hours after fasting.⁵ These values may vary depending on dietary styles and discrepancies in metabolism and different processes of energy utilization. The fall in glucose levels is further halted due to decline in serum insulin and upsurge in serum glucagon and growth hormone levels, thereby promoting glycogenolysis, gluconeogenesis and reducing glycogenesis.⁵ As for lipids, there is a decrease in serum total cholesterol and triglycerides in the initial days of fasting (owing to gluconeogenesis); these subsequently rise to pre-fasting levels.^{5,6} Normally, fatty acids oxidation produces ketones which can be utilised as energy substrate by skeletal and cardiac muscles, Kidney, liver and adipose tissue, thus saving glucose for continued consumption by brain and red blood cells. In Diabetic patients, this physiologic glucose response is manipulated by causal conditions and often by medications intended to augment or increment insulin secretion. Glucagon upsurge in response to hypoglycemia is not as apparent in type 1 Diabetics as in normal individuals. In Diabetics having profound insulin deficit, an extended fasting without insulin replacement can progress to extensive glycogenolysis, augmented gluconeogenesis and ketogenesis resulting into marked hyperglycaemia and ketoacidosis.⁷

The literature bulk is documenting that Ramadan’s fasting is harmless for most of type 2 Diabetics under optimal instructions and Diabetic management plan, but not for type 1 Diabetics. It appears that this is a very important area of concern for the medical field where a considerable bunch of patients presenting to the medical out-patients are diabetics. It was therefore considered to review the

literature on available data regarding management of Diabetic patients who are fasting in Ramadan, especially during this time of the year when the duration of fast is over 16 hours.

MATERIAL AND METHODS

Studies published from 1993 to 2016 were studied using the keywords “Diabetes, fasting, and Ramadan” on PubMed, Google Scholar and Medline. Thirty articles describing the physiology of fasting in type 1 and type 2 Diabetes mellitus, complications associated with Diabetes and fasting, and Diabetes management during Ramadan when most of the Diabetics are fasting were collected and reviewed to reach a consensus for the management of Diabetes in our own fasting population.

The epidemic of diabetes

Muslim population across the world is nearly 1.1–1.5 billion; thus constituting 18–25% of total population globally. Ramadan is the 9th month of Lunar Islamic Calendar and its duration fluctuates from 29 to 30 days on the basis of moon sighting. Fasting during Ramadan lasts from few hours to over 20 hours depending on geographic region and time of year. These long hours of fasting are challenging for ill patients and that’s why the Holy Quran has given exemptions to chronic ill-health Muslim followers from fasting (“Holy Quran, Al-Bakarah, 183–185”). Diabetic patients are included in this group, because long hours of fasting can promote hypoglycemia, ketoacidosis and poor drug compliance thereby posing a threat to such patients.⁶

Despite this allowance for the sick, most Diabetics are adamant on Ramadan’s fasting, creating a challenge not only for themselves but also for those responsible for their medical care. The topic of fasting in Diabetics has not been studied extensively and guidelines for one area cannot be universally applied owing to changes in duration of fast in different parts of the world. Some areas with long durations of fasting have a pleasant weather which does not lead to marked dehydration, while other areas with fewer hours of fasting come under the hot climatic zones and despite lesser duration of fast, make the patients prone to dehydration and its associated risks. Therefore, every climatic zone needs guidelines in consistence with its needs.

FASTING ASSOCIATED COMPLICATIONS IN DIABETIC POPULATION

Both type 1 and type 2 Diabetics are prone to risks from fasting.

1. Hypoglycaemia:

Type 1 Diabetics are more prone to developing hypoglycemia, which is associated with 2–4%

mortality. The frequency of hypoglycemia increases with hypoglycemia unawareness, poor glycemic control and recurrent hypoglycemia in the past needing hospitalization. According to the EPIDIAR Study, the risk of hypoglycaemia escalates 4.7-fold in type 1 Diabetics and 7.5-fold in type 2 Diabetic patients who wish to fast.⁶

A study conducted on small number of Diabetic patients (n=41) in 1998 showed a rising trend in symptomatic hypoglycemia among fasting Diabetic patients⁸, however this trend was not documented in other studies during Ramadan amongst Diabetics managed with oral hypoglycaemics or insulin therapy.⁸⁻¹⁰ Such inconsistent findings could be explained among these studies on the basis of fact that every decade, Ramadan’s fasting happens in a different weather resulting in marked variation in length and temperature of fasting; so the trend of hypoglycemia may vary according to timing and period of study conducted.

2. Hyperglycaemia:

Uysal A conducted a study in 1998 documenting a 3-fold rise in profound hyperglycemia with or without ketoacidosis in type 1 Diabetics and 5 folds increase in type 2 Diabetic patients.⁶ This can be attributed to marked decline of insulin dose by patient to avoid hypoglycemia, amplified intake of food and sugary drinks during Ramadan.

3. Ketoacidosis:

Another grave risk is that of diabetic ketoacidosis. It occurs more in patients with poorly controlled Diabetes before Ramadan. The risk is increased because of decreased insulin dose (assuming that food intake is reduced), concomitant risk for dehydration, or possible dose reduction in response to acute infection⁴. About 1.8% of type 1 Diabetic patients developed diabetic ketoacidosis (DKA) during Ramadan.⁴

4. Dehydration and thrombosis:

Limitation of fluid intake can lead to dehydration. Hot and humid climates increase the risk. Hyperglycemia also leads to osmotic diuresis resulting in fluid and electrolyte imbalance. Due to elevated levels of clotting factors, decreased concentration of endogenous anticoagulants and altered fibrinolysis, Diabetics are usually in a hypercoagulable state.^{9,10}

Dehydration also increases blood viscosity, thereby leading to thrombotic events. Studies conducted in Saudi Arabia are documenting an increase trend of retinal vein occlusion in fasting Diabetics but failed to document any increase in cerebral or coronary ischemic events in Ramadan.^{11,12}

RISK CATEGORIES FOR FASTING DURING RAMADAN IN DIABETICS

• Very high risk:

Type 1 Diabetes mellitus, severe hypoglycemic spells within the last 3 months, history of recurrent hypoglycemic attacks, hypoglycemia unawareness, acute illness, chronic dialysis, sustained hyperglycemic status, diabetic ketoacidosis and non-ketotic hyperglycemic hyperosmolar coma in preceding 3 months, pregnancy and intensive physical exertions pose very high risk for fasting among Diabetics.¹³⁻¹⁵

• High risk:

Modest hyperglycaemia having average blood glucose level of 8.5–16.5 mmol/litre (150–300 mg/dl), HbA1c of 7.5–9%, living in isolation, renal Insufficiency, drugs affecting mentation, advanced macro-vascular complications, co-morbid conditions aggravating the above, old age with ill health and poorly controlled epilepsy (predominantly aggravated by hypoglycaemia) pose high hazard for fasting among Diabetics.¹³⁻¹⁵

Moderate risk:

Well controlled glycaemic status in patients consuming short acting insulin and secretagogues or managed with combination of oral hypoglycemic agents or both oral plus insulin treatment, is a moderate risk factor for fasting in Diabetics.¹³⁻¹⁵

Low risk:

Well controlled Diabetics managed with lifestyle modification, metformin, alpha glucosidase inhibitor (acarbose), dipeptidyl peptidase-4 inhibitors, and thiazolidinediones is a low risk factor for fasting.¹³⁻¹⁵

High risk diabetic patients are counselled against fasting in Ramadan as it may result in deterioration of glycaemic status causing either severe hypoglycaemia or DKA. Diabetic patients having moderate risk can minimise their risk level if these patients consult healthcare professional's weeks preceding Ramadan and optimise diabetes management as per recommendation. Low risk diabetic patients can fast safely even without consulting a healthcare provider. Diabetic patients opting for fast against health carer advice need support so that they can fast safely and without complications.

SALIENT FEATURES OF RAMADAN FOCUSED DIABETES EDUCATION¹⁵

Dietary planning and recommendations:

- It should be a balanced healthy diet during Ramadan.
- Diet containing slow energy release foods (wheat, rice, beans, etc) should be consumed at *seher* and *iftar* timings while foods rich in

saturated fats (ghee, pakoras, samosas, etc) should be utilised negligibly.

- There is recommendation to use minimum quantity of monounsaturated oils (rape seed or olive oil etc) in cooking
- In *seher* and *iftar* timings of Ramadan, high fibre food contents (wholegrain cereals, brown rice, pulses, granary bread, beans, vegetables, fruit and salads etc) are recommended for inclusion in diet

Exercise:

- Type 2 Diabetic patients can safely perform regular light and modest exercise.
- Strenuous exercise should be discouraged due to increased risk of hypoglycemia specifically in patients consuming sulphonylureas or insulin.
- Diabetics are encouraged to carry on their routine physical activity, particularly in non-fasting hours.
- Tarawaih prayers (after the *iftar* meal) should be encouraged as part of the daily exercise regime.

Blood glucose monitoring:

- It is a misnomer that blood glucose measurement affects fasting in any shape.
- All Diabetic fasting patients should be encouraged to check their blood glucose levels at home.
- Test capillary blood glucose in the following situations:
 - I. The Diabetic patient is having suspicion of signs and symptoms of hypoglycaemia.
 - II. He/she should be advised to halt fast if hypoglycaemic event is established on blood glucose monitoring.
 - III. The Diabetic patient feels unwell (fever, gastroenteritis etc).

Diagnosing and managing complications:

Diabetic patients are strongly encouraged to be fully aware of the warning clinical features of hypoglycemia, dehydration and hyperglycemia and advised intensely to halt the fast once any such complication or acute illness develops.

Diabetics should immediately stop fasting if they develop documented hypoglycemia (having blood glucose level of ≤ 60 mg/dl or 3.3 mmol/l) as there is no assurance that further hypoglycemia will not ensue if patients observe wait and see policy. The fast must be terminated in Diabetics if blood glucose level drops to ≤ 70 mg/dl or 3.9 mmol/litre during the initial hours of fast, particularly if sulphonylureas, insulin or meglitinide are consumed at predawn timing. Similarly, the Diabetics should also break their fast if blood glucose level surpasses 300 mg/dl or 16.7 mmol/litre for reasons discussed earlier.^{6,16}

RECOMMENDATIONS FOR FASTING IN DIABETIC PATIENTS

Recommendations for fasting in Diabetic patients were first proposed at a conference in Casablanca in 1995.¹⁷ Data from the EPIDIAR Study, and guidelines established by The Muslim Council of Britain and International Diabetes Federation have been reviewed to reach a consensus on the management of types 1 and 2 Diabetes in Ramadan.

1. Diet-controlled diabetes:

In Diabetic patients managed with diet-control only, two to three smaller meals should be encouraged in non-fasting period for caloric distribution in order to avoid post meals extreme hyperglycaemic events.^{18,19}

As for patients treated with oral agents, in general as compared to insulin secretagogues, insulin sensitizers are associated with a significantly lower risk of hypoglycemia as evident in UKPDS Trial.²⁰

2. Biguanides –metformin:

Diabetic patients managed with metformin monotherapy may fast safely as the risk of critical hypoglycemia is insignificant among these patients.²¹ Dosage timing of metformin may be amended to suit when meals are being consumed. Caution needs to be exercised regarding renal impairment and dehydration.²² The risk of hypoglycemia among non-fasting Diabetic population taking metformin therapy ranges from 0 to 21% in a systematic review.²³ However, there is no data available at the moment to find out the incidence of hypoglycemia in fasting population taking metformin monotherapy.²³ *Iftar* meal is the major chunk of food consumption during Ramadan, so there is expert consensus suggesting metformin dose should be adjusted in such a manner that two thirds of the dose be taken at *iftar* and one third at *seher* timings while lunch time dose will be omitted in Ramadan.^{20,24} Thus for a patient taking metformin 500 mg three times daily, it will be recommended to split the dose as 500 mg at *seher* and 1000 mg at *iftar* time during Ramadan.

3. Thiazolidinediones:

The thiazolidinediones do not cause hypoglycemia when taken alone, but they can augment the hypoglycaemic effects of sulfonylureas and insulin.²⁵ Thiazolidinediones take 2–4 weeks to exhibit significant anti-hyperglycaemic effects and therefore are not recommended for quick substitution for anti-diabetic drugs associated with hypoglycaemia during Ramadan.²⁵

4. Sulfonylureas:

Severe hypoglycaemia is a relatively uncommon complication of sulfonylureas.²⁶ First generation sulfonylureas (glibenclamide) are documented with a higher risk of hypoglycaemia as compared to second generation sulfonylureas (gliclazide, glipizide,

glimepiride).^{25,26} Studies have already been conducted to review the use of glibenclamide and glimepiride during Ramadan (GLIRA Study).²⁷ Modifying a once daily dose of glimepiride from early morning non-fasting period to an evening dose at *iftar* in Ramadan have not been documented to alter the risk of hypoglycaemia or glycaemic status in a large prospective observational study of 332 participants in 2006.²⁸ The rate of hypoglycaemia in Diabetics consuming morning dose glimepiride in Ramadan was not studied, so whether that rate is higher than the rate in those consuming *iftar* timing glimepiride is unknown at the moment. Devendra D *et al* in 2009 reported that incidence of hypoglycemic events did not vary between a cohort of Diabetics consuming once daily glimepiride (n=21) and a cohort taking repaglinide (n=20) two times daily at *seher* and *iftar* times.²⁹ The hypoglycemic effects of gliclazide during fasting have been compared with newer anti-diabetic agents, like dipeptidyl peptidase-4 inhibitors.^{30,31}

On the basis of recommendation of GLIRA study trial, physicians should switch the timing of once daily dose of sulfonylureas (Glimepiride) from morning to evening dose at *iftar* time during Ramadan.^{24,25} As far as gliclazide is concerned, larger dose should be consumed at *iftar* time as compared to *seher*. Physicians may reduce the prescribed dose at *seher* timing if the glycaemic status of Diabetic before Ramadan was stable and well controlled. For instance, if Diabetic patient's HbA1C before Ramadan is well controlled and he/she is taking gliclazide 160 mg twice daily, clinician may modify this dose as 80 mg at pre-dawn and 160 mg after sunset during Ramadan.^{20,24}

5. Insulin secretagogues:

Repaglinide is a rapid acting insulin secretagogue. A systematic review conducted by Norris SL showed improved glycaemic control and lower incidence of hypoglycemia in patients taking repaglinide.³¹ This finding was also suggested in a randomised multicentre trial documenting good glycaemic status and fewer numbers of hypoglycemic episodes among fasting Diabetics in Ramadan when comparing repaglinide with glibenclamide. The incidence of hypoglycemia in repaglinide cohort was 0.03 per patient per month while in glibenclamide cohort it was 0.05 per patient per month. Meanwhile, patients on repaglinide had lower fructosamine levels too.³¹ Another study conducted by Bravis V in 2010 on 67 participants compared repaglinide (n=27) with a cohort of Diabetics consuming a sulfonylurea (glimepiride (n=23) or gliclazide (n=17)). Both cohorts' findings were identical as serum fructosamine, HbA1c and body weight did not alter significantly from before to after Ramadan

period. Glimepiride cohort reported hypoglycemic event in only one patient during Ramadan. These studies are suggesting rapid acting insulin secretagogues as a safer alternative to glibenclamide for fasting Diabetics in Ramadan.³² Repaglinide should be taken at *seher* and *iftar* times during Ramadan due to its short half-life.

6. Dipeptidyl peptidase 4 inhibitors (dpp-4 inhibitors):

Dipeptidyl peptidase 4 inhibitors (saxagliptin, vildagliptin, sitagliptin, linagliptin) are not associated with hypoglycemia when taken alone although they can enhance the hypoglycemic effects of sulfonylureas and insulin.³³ There is a very low risk of hypoglycemia when DPP-4 inhibitors are taken with metformin. Therefore, this is a safe option to be practised during Ramadan.^{29,34}

A retrospective data analysis among type 2 Diabetic Muslim patients documented that addition of vildagliptin to metformin therapy demonstrated a less likelihood chance of hypoglycaemia and better glycaemic status as compared to fasting Diabetics managed with metformin and gliclazide in Ramadan. Literature is favouring to add DPP-4 Inhibitors, instead of sulfonylureas, to poorly controlled Diabetic patients taking metformin monotherapy while planning to fast during Ramadan.³⁵

7. Glucagon-like peptide- 1 receptor agonists (GLP-1 agonist):

Exenatide (GLP-1 agonist) having short half-life (2 hrs) is not associated with a significant impact on fasting blood glucose.³⁶ Liraglutide is a long acting GLP-1 agonist. It is administered in injectable form as once daily dosage irrespective of meal time and is considered to be an effective option to manage fasting hyperglycemia in type 2 Diabetics.²⁹ GLP-1 agonists are used as adjunctive therapy along with other oral anti-diabetics to improve glycaemic control.³⁷ Hypoglycaemia documented in type 2 Diabetics taking GLP-1 agonists is mostly in those patients who are co-administering this drug along with a sulfonylurea group.³⁸ An Iranian audit report of 2014 is documenting that during Ramadan, when used as adjunctive therapy, GLP-1 agonist dosage needs no adjustment but the dose of other drug like sulfonylureas may need reduction to avoid hypoglycaemic events.³⁹

8. Alpha glucosidase inhibitors:

Alpha glucosidase inhibitors (Acarbose, miglitol, voglibose) exhibit their anti-diabetic effects by competitive inhibition of enzymes essential for carbohydrate digestion. They are effective when ingested with first bolus of a meal. The risk of hypoglycemia is negligible and therefore may be useful during fasting. They are only modestly effective and are therefore usually used as adjunctive

therapy along with other anti-diabetic medications for glycaemic control.⁴⁰

9. Insulin:

The basic aim of diabetes management is to sustain essential levels of basal insulin in order to avoid fasting hyperglycaemia. Administration of long acting or intermediate acting insulin along with short acting insulin prior to meals can be an effective approach to maintain sufficient basal insulin levels in Diabetics.⁴¹ Hypoglycaemia is still a risk with this management plan but it can be minimised by replacing regular insulin with rapid acting insulin analogues.⁴² A multicentre trial in 2010 documented that Diabetic patients on long acting basal insulin (Glargine) can trim down this insulin dose by 20% to minimise the risk of hypoglycaemia.⁴³ Those Diabetics managed with combination of repaglinide and single dose glargine may carry on with the same dosing schedule of repaglinide, however, the dose of glargine should be reduced by at least 20% to be on safe side to avoid hypoglycaemia.⁴⁴ Repaglinide dosage should be re-adjusted with *seher* and *iftar* timings. Studies conducted by Lawton J and Gaborit B elaborated that Diabetics with fast consuming insulin twice daily and having well controlled glycaemic status, should reduce their *seher* dosing by at least 30% and they may switch to Mix 50 insulin preparation by their clinicians if their post-prandial blood glucose levels remain persistently elevated.^{45,46}

Type 1 Diabetic utilising 4 times daily basal bolus insulin regime should be ideally counselled against fasting as it will increase the risk of altered glycaemic control.⁴⁷ Basal insulin is either intermediate acting or long acting insulin while bolus insulin is rapid acting insulin taken with food. If despite medical advice, Diabetic patient still opt for fasting, healthcare professionals should educate and guide this patient regarding carbohydrate counting. Wilbur K in 2014 conducted a study documenting that if capillary blood glucose level is ≤ 126 mg/dl (7 mmol/L), a fasting Diabetic should decrease background insulin dose by at least 20% and skip his/her mid-day dose of rapid acting insulin. However, if blood glucose level of such patient is > 126 mg/dl (7 mmol/L), then he/she needs guidance and education regarding insulin dose adjustment according to recommendation of specialist.⁴⁸

A small trial from Egypt conducted in type 1 Diabetic patient, evaluating the impact of glargine and insulin lispro or aspart divided in a 6:4 ratio of the total 24-hour insulin dose. Amongst 7 Diabetics who start fasting, 5 patients managed it for the whole month of Ramadan while 2 Diabetics halt the fast due to hypoglycemic spells. All these patients documented a steady HbA1c levels at the conclusion of Ramadan. There were no report of diabetic

ketoacidosis and severe hypoglycaemic events necessitating hospitalisation. This study cohort documented a decrease in insulin requirement by 28% during Ramadan from baseline ($p \leq 0.002$). This trial, therefore recommended decrement insulin dosage (approximately 70% of a patient's usual dose) during Ramadan.⁴⁹

Holt RI in 2013 carried on an open label study among 64 type 1 Diabetic patients. The study design was comparative and crossover. Isophane insulin was given as basal insulin to both wings of the cohort. This study documented a significantly lower 2-hour post-prandial blood glucose levels ($p \leq 0.026$) after *iftar* meal. Moreover, insulin lispro documented fewer hypoglycemic episodes in comparison to regular human insulin.⁵⁰

Limitation of majority of studies conducted on type 1 Diabetics is that these studies have limited number of participants and even some studies have omitted other population groups like elderly Diabetics, adolescents and Diabetics with co-morbid conditions such as renal insufficiency. Thus, the recommended management plan could not be applicable on all the fasting type 1 Diabetics. Moreover, there is no good data/evidence available to provide clear guidelines for those Diabetics who are not on a basal bolus insulin regime.^{51, 52}

It is important here to mention that near normal glycemic control requires use of multiple daily insulin injections (MDI) or use of continuous subcutaneous insulin pump infusion.⁵³ Tight supervision and regular adjustment in insulin dose are key points to accomplish favourable glycaemic status and circumvent hyperglycemia/ hypoglycemia in type 1 Diabetic patients.⁵⁴

FASTING IN PREGNANT DIABETICS

Uncontrolled glycemic status during pregnancy poses a high maternal and fetal risk in both type 1 and type 2 Diabetic patients. Pregnant Diabetics including gestational Diabetics are exempt from fast and are strongly advised against fasting during Ramadan.⁵⁴

CONCLUSION

Fasting during Ramadan for Diabetics is an important issue and appropriate management of these patients needs to be carried out so they can fast well without developing complications that are difficult to manage. Most of the oral hypoglycemic agents and insulins are fast-friendly; caution however, still needs to be exercised regarding timing and dosage of administration. National guidelines for diabetes and fast during Ramadan are the need of time and must be given priority by the corresponding organisations and government in consultation with renown clinicians/endocrinologists and religious scholars.

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Received: 20 August, 2016

Revised: 16 September, 2018

Accepted: 14 October, 2018

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