CHAPTER 15

Grading of evidence & areas of future research in diabetes and fasting during Ramadan

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1. INTRODUCTION

The previous iteration of the International Diabetes Foundation (IDF) Diabetes and Ramadan (DAR) practical guidelines, published in 2017 **[1]**, provided comprehensive guidance regarding fasting with diabetes during Ramadan. The consortium acknowledged that data from well-designed and adequately powered studies assessing the safety of fasting amongst people with diabetes during Ramadan was limited and allowed recommendations to be based primarily on expert opinion.

For the 2021 IDF-DAR guidelines, chapters were shared and independently reviewed by two experts (HSB and TSK; *see authors above*), who assigned a grade based on the strength of evidence and its applicability to the general population. The grading assigned was approved by 100% consensus. The grading methodology used the guiding principles from the Diabetes Canada Clinical Practice Guidelines 2018 **[2]**, which have also been adapted for the Diabetes Canada Position Statement for People With Types 1 and 2 Diabetes Mellitus Who Fast During Ramadan **[3]**.

Each reference that was used to formulate guidance was critically appraised using the criteria specified for the level of evidence (see **Table 1**). These levels took into account the characteristics of the study, the presence of conflicting findings from other studies and expert review of the findings. Thereafter, each recommendation was assigned a final grade from A through D, with grade A being the highest; (see **Table 2**). In the absence of Level 1, 2 or 3 supporting evidence, or if the recommendation was based on the consensus of the guideline development consortium, the highest grade that could be assigned was D.

TABLE 1: **CRITERIA FOR ASSIGNING LEVELS TO EVIDENCE USED IN DEVELOPING GUIDANCE**	
Level	**Criteria**
Level 1A	Systematic review or meta-analysis of high quality Randomised Controlled Trials (RCTs) a) Comprehensive search of evidence. b) Authors avoided bias in selecting articles for inclusion. c) Authors assessed each article for validity. d) Reports clear conclusions that are supported by the data and appropriate analyses. OR Appropriately designed RCT with adequate power to answer the question posed by the investigators. a) Participants were randomly allocated to treatment groups. b) Follow up at least 80% complete, (no more than 20% missing data). c) Participants and investigators were blinded to the treatment where applicable. d) Participants were analysed in the treatment groups to which they were assigned. e) The sample size was large enough to detect the outcome of interest.
Level 1B	Non-randomised clinical trial or cohort study with indisputable results.
Level 2	RCT or systematic review that does not meet Level 1 criteria above.
Level 3	Non-randomised clinical trial or cohort study; systematic overview or meta-analysis of Level 3 studies.
Level 4	Other

TABLE 2: **CRITERIA FOR ASSIGNING GRADES TO RECOMMENDATIONS**	
Grade	**Criteria**
Grade A	The best evidence was at Level 1.
Grade B	The best evidence was at Level 2.
Grade C	The best evidence was at Level 3.
Grade D	The best evidence was at Level 4 or consensus.

2. KEY RECOMMENDATIONS FROM THE 2021 IDF-DAR PRACTICAL GUIDELINES AND THEIR SUBSEQUENT GRADING AND JUSTIFICATION

2.1 Risk stratification of people with diabetes before Ramadan

(see chapter 5: Risk stratification of people with diabetes before Ramadan, Table 1 and Figure 1)

The risk stratification of individuals is a vital part of the overall strategy in assuring a safe and successful fasting experience during Ramadan for people with diabetes. It is clear that the previous methods used in risk stratifying individuals have been too rigid. This new methodology has been developed based on a wide range of evidence including RCTs, meta-analyses, systematic reviews, other forms of longitudinal studies that have informed expert opinion from leaders in the field of diabetes across the world. Additionally, the robustness of the risk scoring has been assessed in numerous case study scenarios. However, as no single controlled study has evaluated the comprehensive recommendations, against a comparator with an alternative, grading of evidence cannot be applied to the risk stratification schema. At best, they can be considered as being **Grade D, Consensus**.

2.2 Pre-Ramadan education

Pre-Ramadan education is an essential aspect of ensuring a safe fast during Ramadan for individuals with diabetes

There have been numerous studies conducted on the effect of pre-Ramadan education on outcomes during and after Ramadan. These include comparative prospective **[4-9]**, retrospective **[10, 11]** studies, systematic reviews and meta-analyses **[12]**, which included one small, randomised trial suggesting the benefit of pre-Ramadan education. As such this has been given an evidence grade of **Level 3, Grade C**.

The use of telehealth technology is beneficial and may provide a model for future education programmes for people with diabetes seeking to fast during Ramadan

Some studies have demonstrated benefits in the use of 'telehealth' but not all directly investigated populations of people with diabetes that fasted during Ramadan **[13, 14]**. Randomised trials that have looked at people with diabetes fasting during Ramadan suggest beneficial effects of technology-based monitoring tools, with reduced hypoglycaemia **[15, 16]**. The level of evidence for the recommendation to include technology-based monitoring during Ramadan is therefore **Level 2, Grade B**. Future research is needed to assess and compare different types of 'telehealth' including remote education compared to face to face education.

2.3 The Ramadan Nutrition Plan (RNP) for people with diabetes

The use of the RNP during Ramadan has been developed to help individuals obtain optimal nutrition during Ramadan. These RNP's have been culturally adapted to ensure that Muslims across the world seeking to fast during Ramadan can do so safely. The nutrition plans and strategies in this chapter have been developed by experts on nutrition that have been guided by the latest research on medical nutrition therapy. Although intuitively one would consider a diet that helps prevent glucose excursions and ensures proper nutrition during Ramadan to be of benefit, to date there have been no RCTs or comparator studies to assess the benefit of RNP. As such the level of this comprehensive RNP overall is graded as **Grade D, Consensus**.

2.4 Management of Type 1 diabetes

Fasting during Ramadan in individuals with Type 1 diabetes mellitus (T1DM) can be safe provided that strict criteria are met as outlined in chapter 9: Management of Type 1 diabetes when fasting during Ramadan

Numerous studies cited in the **chapter 9: Management of Type 1 diabetes when fasting during Ramadan** suggest that fasting during Ramadan can be undertaken safely in people with T1DM. This provides the basis for amending the risk stratification of people with T1DM. Individual components of the risk stratification system, have been investigated in observational studies and hence the recommendation that *"Fasting during Ramadan in individuals with Type 1 diabetes mellitus (T1DM) can be safe provided that strict criteria are met"* can be graded **Level 3, Grade C**.

A reduction of basal insulin dose by 10-30% in people with T1DM when fasting during Ramadan

There is debate about the best practice and approach to dose modifications to insulin regimens for people with T1DM who fast during Ramadan. Studies have reported different approaches and the development of specific guidance has been difficult. The basis for such a

recommendation is to reduce the risk of hypoglycaemia during the Ramadan fast and allowing a range of 10-30% covers the approaches of most studies presented in the chapter on the Management of Type 1 diabetes and allows for individualisation of care.

The recommendation above is based on expert opinion and on some observational studies that employed different rules for insulin dose titration and follow-up. As such the most appropriate final grade for the recommendation is **Grade D, Consensus**.

The use of premixed insulin should be discouraged

This recommendation was based on the requirement of a fixed intake of carbohydrates which can prove to be inflexible during Ramadan. People with more unpredictable eating habits e.g., adolescents, might find it especially difficult. This recommendation was based on the ISPAD guidelines and expert opinion from the guideline development consortium. But without clear evidence the highest achievable grade is **Grade D, Consensus**.

The use of CGM or FGM is superior to the traditional BG monitoring and should be the method of choice if available

The results of studies which form the basis of this recommendation have been conflicting. In general, the benefit of continuous blood glucose monitoring may not be as clear among adolescents than in adults. Where applicable and appropriate, the use of continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) systems can offer benefits to HCPs and individuals with T1DM (see the **chapter 9: Management of Type 1 diabetes when fasting during Ramadan – section 9**).

However, as the studies to date have been observational in nature, did not have a comparison control group, the results show conflicting outcomes and do not demonstrating superiority for CGM/FGM over conventional approaches to monitoring glycaemic control (SMBG) when fasting during Ramadan — this recommendation is primarily based on expert opinion. Therefore, the appropriate grading applied is **Grade D, consensus**.

In order to mitigate the issues identified with CGM or FGM in adolescents and adults, placing emphasis on education in the pre-Ramadan assessment that teaches the benefits of continuous methods to measure blood glucose might help with their clinical utility in lieu of or in addition to SMBG and so these methods should be considered for future research.

Guidance for Adults with T1DM who seek to fast during Ramadan

Evidence for insulin titrations in adults with T1DM who fast during Ramadan is based on expert opinion, therefore the recommendation is **Grade D, consensus**.

2.5 Management of Type 2 diabetes

Metformin and acarbose are safe and require no dose modifications for people with T2DM who fast during Ramadan

There are no RCTs with these two drugs in people with T2DM who fast during Ramadan. However, among non-fasting individuals there is a large body of evidence in relation to adverse events and the very low risk of hypoglycaemia associated with these drugs. Whilst it

is a reasonable assumption that these two drugs are safe to use during Ramadan, the lack of evidence allows us to only provide a grading of **Grade D, consensus**.

No dose modifications are needed for Thiazolidinediones for people with T2DM when fasting during Ramadan.

Given the low risk of hypoglycaemia it is reasonable to assume that no dose modifications are required. There are no studies which have directly assessed their use in people fasting during Ramadan but a double blind RCT showed favourable outcomes for Pioglitazone compared to other oral antidiabetic drugs **[17]**, enabling a recommendation of **Level 2, Grade B** for pioglitazone, **Grade D, consensus** for other thiazolidinediones.

The daily dose of short-acting insulin secretagogues (based on a three-meal dosing) may be REDUCED or REDISTRIBUTED to two doses during Ramadan according to meal sizes

There have been two RCTs on insulin secretagogues in people with T2DM who fasted during Ramadan **[18, 19]** that have showed a similar or a reduced risk of hypoglycaemia with repaglinide compared to sulphonylureas. Further, three observational studies have shown similar hypoglycaemia outcomes between insulin secretagogues indicating safety. The grading of recommendation for continuation of repaglinide during Ramadan is **Level 2, Grade B**, due to conflicting outcomes between the observational studies and RCTs; and **Grade C, Level 2** for gliclazide and gliclazide MR; **Grade C, Level 3** for glimepiride. The recommendation that doses of insulin secretagogues may be reduced or redistributed during Ramadan according to meal size is based on **Grade D, consensus**.

As long as Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as liraglutide, lixisenatide, exenatide have been appropriately DOSE-TITRATED prior to Ramadan (at least 2–4 weeks), NO FURTHER TREATMENT MODIFICATIONS are required

Observational studies and RCTs have compared GLP-1 RAs such as exenatide, liraglutide and lixisenatide against sulphonylureas in people with T2DM who fasted during Ramadan (see **Table 3** of the **chapter 10: Management of Type 2 diabetes when fasting during Ramadan**). The recommendation to continue GLP-1 RA during Ramadan is **Grade C, Level 3** for exenatide; **Grade C, Level 2** for liraglutide and lixisenatide; **Grade D, consensus** for others.

Dipeptidyl peptidase-4 (DPP-4) inhibitors can be used to reduce incidence of hypoglycaemia compared to suphonylureas during Ramadan

Comparative RCTs as well as a meta-analysis of RCTs have compared DPP4-I such as sitagliptin and vildagliptin against sulphonylureas in people with T2DM who fast during Ramadan (see **Table 4** of the **chapter 10: Management of Type 2 diabetes when fasting during Ramadan**). The recommendation is graded as **Level 1A, Grade A** for vildagliptin; **Level 1B, Grade A** for sitagliptin; **Grade D, consensus** for other DPP-4 inhibitors.

Modern sulphonylureas are preferred over older sulphonylureas to reduce the risk of hypoglycaemia in people with T2DM who fast during Ramadan

A double blind RCT **[20]** and large scale observational studies **[21]** have been conducted

on the use of modern sulphonylureas indirectly assessing the use of these medications compared to other antidiabetic medications. Likewise, subgroup analyses in an observational study assessing the impact of different sulphonylureas on overall rates of hypoglycaemia showed a preference for more modern sulphonylureas **[22]**. In some of these studies the risk of hypoglycaemia was comparable to DPP4-I (see **Table 5** of the **chapter 10: Management of Type 2 diabetes when fasting during Ramadan**). The overall recommendation is graded as **Level 3, Grade C**.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors should be used with CAUTION during Ramadan

Several comparative prospective and retrospective studies and RCTs have compared SGLT2I such as dapagliflozin and canagliflozin against individuals not using SGLT2I in people with T2DM fasting during Ramadan (see **Table 6** of the **chapter 10: Management of Type 2 diabetes when fasting during Ramadan**). These studies showed lower rates of hypoglycaemia when compared to SU with increasing symptoms of thirst, but no excess risk of dehydration. The recommendation that SGLT2 inhibitors can be continued during Ramadan is ***Grade C, Level 2*** for dapagliflozin **(38)**; ***Grade C, Level 3*** for canagliflozin **(34)**; ***Grade D, consensus*** for other SGLT2 inhibitors.

NO DOSE ADJUSTMENTs are required for SGLT2 inhibitors during Ramadan **Grade D, consensus**.

Dose reductions need to be made in individuals on multiple antidiabetic medications

There have been subgroup analyses in several studies assessing the additional risk of hypoglycaemia among people with T2DM on multiple antidiabetic therapies when fasting during Ramadan **[23-27]**. Based on subgroup analyses, expert opinion highlights the additional risk of multiple therapies and the recommendation to consider dose reductions is based on ***Grade D, consensus***.

Dose reductions to long and short acting insulin therapies and premixed insulin therapies (see Figures 4 and 5 of the chapter 10: Management of Type 2 diabetes when fasting during Ramadan)

Dose reductions for insulin therapies are based on expert opinion and informed by large-scale observational studies (see **Table 7** in the **chapter 10: Management of Type 2 diabetes when fasting during Ramadan**). The effect of specific dose reductions proposed in the table have not been studied as an intervention in observational studies or in RCTs, and so this recommendation is ***Grade D, consensus***.

Second generation long acting insulin analogues (IDeg/IDegAsp) have been reported to be safe with lower risks of hypoglycaemia compared to older generation mixed insulin for people with type 2 diabetes

Three studies assessing the efficacy of these newer generation insulin analogues both showed benefits. An observational study found these second generation analogues to be safe with no severe reported events of hypoglycaemia **[27, 28]** allowing a recommendation of **Level 3,**

Grade C. A phase III RCT of IDegAsp showed reduced hypoglycaemia compared to BIAsp 30 [29], enabling a recommendation of **Level 1B, Grade A** for IDegAsp.

The recommendation to have a post-Ramadan assessment

There are major changes to normal routines when fasting during Ramadan which have been highlighted in the **chapter 4: The effects of fasting during Ramadan on physical and mental wellbeing**; which will revert to normality once Ramadan ends. This provides a good opportunity to assess individual experiences and gain valuable information to produce better guidance. There has been no direct research on the impact of implementing lessons learnt from information collected from post-Ramadan assessments and as such this allows a recommendation of **Grade D, Consensus**.

2.6 Management of hyperglycaemia in pregnancy when fasting during Ramadan

Recommendations for the management of hyperglycaemia in pregnancy when fasting during Ramadan fasting

The advice against the use of glibenclamide is based on observational studies and guidance from the Food and Drug Administration (FDA). Its use should be discouraged when pregnant and fasting during Ramadan. However, grading is based on the level of evidence alone; this recommendation is considered a **Grade D, Consensus**.

Insulin dose adjustment recommendations (see Table 1 in the chapter 11: Management of hyperglycaemia in pregnancy when fasting during Ramadan)

The recommendations on insulin adjustments were primarily based on expert opinion from the guideline development consortium. As such there is a need for further research and the recommendation is **Grade D, Consensus**.

2.7 Management of diabetes among the elderly when fasting during Ramadan

These recommendations were largely based on expert opinion from the guideline development consortium and from information on elderly individuals with diabetes — primarily the DAR 2020 Global Survey. This cross-sectional study informed the needs and practices of elderly individuals with T2DM who fasted during Ramadan 2020 across many different countries. It was assumed that elderly individuals are at higher risk of comorbidities such as impaired renal function, cardiovascular disease (CVD), dementia, frailty and a risk of falls and complications such as hypoglycaemia and hyperglycaemia. The grading of evidence is **Level 3, Grade C** for increased risk of hypoglycaemia and hyperglycaemia in the elderly who fast during Ramadan. These important comorbidities favour a more conservative approach to minimise the risks of hypoglycaemia and hyperglycaemia in elderly. However, as no study has investigated such an approach in a comparative manner, this second recommendation is **Grade D, Consensus**.

3. AREAS FOR FUTURE RESEARCH

To fully understand the effects of fasting during Ramadan with diabetes and enable evidence-based recommendations, further research is needed. The criteria presented in **Table 1** have been developed to grade current guidance, but also provide a good benchmark for future studies. Future studies should consider the grading schema in their planning stage and make appropriate adjustments so as to garner a higher level of evidence.

The effects of fasting during Ramadan on physiology and wellbeing

Future research will need to consider both the short-term and long-term effects of fasting during Ramadan. Much of the changes that occur during Ramadan are temporary, including metabolic, cellular and genetic changes but also of a physical and mental nature. Evidence is inconclusive as to whether these changes have a lasting impact on maintenance of weight loss and improvements in mood or levels of anxiety after Ramadan.

People with diabetes also need to be reassured that their condition will not be exacerbated by fasting. Studies need to continue follow up of individuals with diabetes and report on outcomes after Ramadan in both T1DM and T2DM. Moreover, the psychological impact of complications such as hypoglycaemia or hyperglycaemia need to be assessed and qualitative research can help understand the needs of individuals.

Risk stratification

A dynamic, easy to use risk calculator to stratify individuals with diabetes before Ramadan needs to developed and made accessible to all healthcare professionals (HCPs) seeking to provide guidance to individuals that have diabetes and seek to fast during Ramadan. This risk tool should be updated regularly based on new evidence. Further research is required to assess additional risk factors for people with diabetes who fast during Ramadan using machine learning and artificial intelligence (AI) to include large data driven Omics and patient reported outcomes/indicators of quality of life.

Pre-Ramadan education

There needs to be further larger studies conducted into the effectiveness of pre-Ramadan education utilising online/web settings compared to in-person methods. These data will be invaluable for providing recommendations for people in circumstances where remote or online methods are the only means by which an individual can get access to patient education. This includes scenarios such as the COVID-19 pandemic whereby physical contact was reduced to help halt infectious disease transmission.

Moreover, greater evidence from RCTs are needed to compare the overall effectiveness of pre-Ramadan education against suitable controls on the successfulness of fasting during Ramadan among people with T1DM and T2DM.

The Ramadan Nutrition Plan (RNP) for people with diabetes

The RNP method needs to be assessed in RCTs to assess its benefits and to understand areas of improvement. Further research into medical nutrition therapy during Ramadan is needed to generate data in people of different ages, cultures and personal preferences to enable generalisability and tailoring of guidance.

Management of type 1 diabetes

Advanced insulin technology, such as insulin pumps, have shown promising results and this will need to be confirmed in larger scale studies, among different groups of people with T1DM. In addition, further research should also commence on the use of CGM/FGM to demonstrate superiority over conventional SMBG methods.

Outcomes in adults with T1DM who fast during Ramadan is scarce. Future studies should aim to include more heterogenous populations in terms of age, other comorbidities and insulin types and regimens in RCTs of individuals with T1DM who fast during Ramadan.

Management of type 2 diabetes

RCTs are needed for different classes of antidiabetic medications assessing dose changes to enable evidence based dose modification.

AI based machine learning techniques should be developed to predict outcomes for individuals with T2DM that seek to fast during Ramadan. Large amounts of data will be needed for these technique and sources such as continuous glucose monitoring devices could be very useful.

Management of hyperglycaemia in pregnancy when fasting during Ramadan

Specific research in pregnant women with gestational diabetes mellitus (GDM) or T2DM who fast during Ramadan are needed. Observational studies of volunteers who fast during Ramadan and their respective treatment regimens may help formulate evidence based guidance.

Management of diabetes among the elderly when fasting during Ramadan

Observational studies and RCTs are required in elderly individuals with T1DM and T2DM and differing levels of comorbidities who fast during Ramadan.

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