Ramadan and DIABETES CARE

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Foreword

Most books are labors of love, products of passion, and direct outcomes of determination. This passion and determination is needed from all stakeholders—editors, contributors and publishers. If lucky, a few books strike an equally loving and passionate response from readers.

This well-referenced, pleasantly laid out book, *Ramadan and Diabetes Care*, under the editorship of Professor Abdul H Zargar and Dr Sanjay Kalra, has all these elements, and much more. The editors and contributors have chosen a subject that impacts the lives of one-third of mankind, yet which we all practice, without any formal training in this field. The current book synthesizes all available evidence, combines it with experience, and with what the editors term as 'logical empiricism'. It covers not only the non-pharmacological and pharmacological management of diabetes in *Ramadan*, but also addresses issues related to counseling, to women, and to the young as well as elderly. Detailed pathophysiological explanations are also provided in the chapter on Endocrinology of Fasting. Contributors from three continents have contributed to the book and their combined expertise makes this international masterpiece a joy to possess, and to read.

The motive of the editors and contributors seems to be a rare combination in today's world, i.e. upliftment and optimization, both of science and spirituality. With the excellent and exhaustive deliberations on the challenging subject matter done in a practical, reader-friendly manner, I am sure, this book will achieve both aims. I pray that the multiple efforts behind this book translate into safe, uplifting fasting, for millions of believers across the world.

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Preface

Although Islam is the second largest religion worldwide, it bears more than its fair share of the diabetes pandemic. The brunt of this modern epidemic is felt more acutely by Islamic countries, which face rapid modernization and urbanization, accompanied by drastic lifestyle changes.

The 'Top Ten' list (2010), for the number of people with diabetes, lists India (rank 2), Bangladesh (rank 8), Egypt (rank 9), and Indonesia (rank 10); all these countries have large populations which believe in Islam. The projected list for 2030 predicts an increase in the diabetes population in Islamic countries; while India maintains its second position, Bangladesh (rank 5), Egypt (rank 8), and Indonesia (rank 9), are joined by Pakistan at the 10th place (International Diabetes Federation, Diabetes Atlas, 5th edition).

The strain of diabetes upon Islamic nations is observed to a much greater extent when the prevalence of diabetes in adults is measured. The 2011 list ranks the Islamic countries, i.e. Kuwait (rank 3), Lebanon (rank 5), Qatar (rank 6), Saudi Arabia (rank 7), Bahrain (rank 8) and United Arab Emirates (UAE) (rank 9) among the 10 nations with highest prevalence of diabetes. The same risk names figure in the 2030 projection, albeit at different ranks (Saudi Arabia moves up to 6th place, while Lebanon, Qatar, Bahrain and UAE show a relative improvement at 7th, 8th, 9th, and 10th positions, respectively).

For adherents of Islam, *Ramadan* is one of the five essential pillars of religion. For those with diabetes, *Ramadan* presents a metabolic challenge with potential health hazards of hypoglycemia as well as hyperglycemia. With adequate preparation and planning, however, most people with diabetes can experience, pleasant and satisfying fasting experience, without any negative impact on health. In fact, fasting has been shown to have multiple biopsychosocial health benefits.

This book humbly aims to help people with diabetes experience these benefits of *Ramadan*, in a healthy manner. Through the evidence and experience, collated by contributors from North America, Africa, and Asia, we hope to touch health care professionals across the globe.

These health care providers, in turn, should be able to help millions of people with diabetes achieve the twin blessings of health and spiritual upliftment.

Abdul H Zargar
Sanjay Kalra

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We express our sincere gratitude to all the contributors for their efforts. Clinicians from three continents have shared their knowledge to fill the void for a comprehensive book on *Ramadan* and diabetes. Their enthusiasm and energy cannot be described in words.

We would like to sincerely thank M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India, for the opportunity to publish this title with them. A word of thanks for Dr Neeraj Choudhary, Senior Medical Editor and Ms Madhvi Thakur, Editorial Coordinator, for all the editorial support and for tirelessly working to bring out this book in its final shape and form, in a very short span of time. The speed with which this book was coordinated across countries is a testimonial to their efficiency and to the wonders of 24/7 collaboration that technology has made possible.

Most of all, we thank our patients, who trust us with their health, and ask umpteen questions regarding fasting in *Ramadan*, and motivated us to plan this book.

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Section 1

Overview

CHAPTERS

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Chapter 1

Overview

Sanjay Kalra

Abstract

Successful completion of *Ramadan* is a great achievement for believers and provides spiritual merit. Helping others in their achievement is equally meritorious. Through its chapters, this book tries to facilitate the observance of healthy *Ramadan* fasting, for millions of Islamic adherents with diabetes. This book is a sincere attempt to solve this paradoxical challenge for diabetes care professionals who have to manage diabetics observing the *Ramadan* fast. It provides practical guidance regarding various aspects of diabetes management during the holy month.

HEALTH

"The most beloved by *Allah* of things He is asked to grant is (Al-aafiyah) good health" (*Tirmidi*).

Health is a state of a life that all living beings aim for: A condition of complete physical, mental and social well-being, and not merely the absence of disease or infirmity.[1] As physicians, we are privileged to be able to help our fellow human beings try and achieve this state.

At times, however, our treatments and cures may end up being worse than the disease or disorder itself. This sometimes happens because of side effects or adverse reactions to our drugs. More often than not, however, patients complain of a high index of intrusion of treatment. This is especially true for people with diabetes, who have to deal with this chronic condition on long-term basis.

INTRUSION IN HEALTH

Intrusion of treatment, in this context, means a forced change in one's routine lifestyle, caused by a particular management strategy. For example, being asked to take six meals a day may be considered as intrusion by a person habituated to two major

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meals. Another example of intrusion can be a prescription for injectable therapy, or for frequent glucose monitoring, which conflicts with strongly held religious or cultural beliefs.

The intrusion of diabetes, and diabetes therapy, into one's lifestyle, becomes more pronounced in societies with a strong sociocultural ethos. Such communities, in general, tend to observe religious and cultural events, such as fasts and feasts, with great enthusiasm and public participation.

RAMADAN

"*O ye who believe! Fasting is prescribed to you as it was prescribed to those before you, that ye may (Learn) self-restraint,*" (Al-Quran 2:183).

One such observance is *Ramadan*, the holy month of fasting, ordained as one of the five central pillars of Islam. Followed by billions of adherents, spread across all continents, the *Ramadan* fast provides spiritual upliftment and wellbeing to people who practice the Islamic faith.[2] Keeping the *Ramadan* fast, however, poses physical challenges to all persons. These challenges are magnified in persons with diabetes, whose metabolic milieu may not be geared to prolonged fasting.

Apart from the physical stress associated with fasting, however, people with diabetes also face psychological and social obstacles during *Ramadan*. The overlap of *Ramadan* and diabetes, in fact, becomes a perfect case for the study of the biopsychosocial model of health, so elegantly coined by Unger in 1977.[3]

BIOPSYCHOSOCIAL MODEL

The biopsychosocial model was created to explain the various nonbiological determinants which impact health.[3]

This model has stimulated debate about health and disease, and has been utilized not only in psychiatry, but also in chronic disease such as diabetes.[4] The biopsychosocial model is required for an indepth understanding of the Islamic person's perspective on *Ramadan*. One of the important aspects of any individual, while defining health, "is the need to' be normal", "feel normal", and "appear normal". The concept of "appearing normal" becomes even more important in close knit societies, where premium is laid on homogeneity rather than exceptions.

In *Ramadan*, when social contacts between friends and family increase, the need to "appear normal" increases. For the person with diabetes, normalcy includes the ability to observe the holy fast, join in group prayers, and take part in festival meals.

PERSON CENTERED CARE

The person-oriented nature of the preceding statements is verbalized in the supposedly modern concept of patient centered care.[5] Islamic theology, however, unequivocally promotes a robust patient centered philosophy.[6] Numerous verses from the Holy *Quran*, and evidence from the *Hadiths*, speak for this.

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THE ROLE OF THE PHYSICIAN

The physician plays an important role in achieving the desired definition of health. In the context of *Ramadan*, this is easier said than done. Creating concordance between biological demands of the body (insulin requirement) and pharmacokinetic properties of prescribed medication becomes a challenge, as rigid dietary and physical activity patterns have to be followed.

The traditional model of medical care entails patient acceptance of physician-defined regimes without much consideration for patient lifestyles and habits. While this approach to diabetes care may have its benefits, it does not work in *Ramadan*.

The rules of *Ramadan* fasting, which been ordained to promote self-restraint and self-discipline amongst devout believers must be respected. Even though Islam provides for exemption from fasting on medical grounds, many people prefer to fast, to achieve spiritual gain.[7] The preference for religious fasting at the cost of metabolic disturbance, is the patient's decision. While one can debate the degree to which patient empowerment should be encouraged.[8] *Ramadan* offers a special challenge. Not allowing people to fast may lead to psychological stress and/or social stress, which by themselves may lead to poor glycemic control. This fact has to be balanced with the potential disturbance in glycemia that can be caused by fasting.

As long as the patient's life, organs or limbs are not put at risk, religious fasting should be allowed for people with diabetes. It is the physician's duty to ensure the person with diabetes receives appropriate pre-*Ramadan* counseling,[9] and proper adjustment of glucose lowering drugs.

This can be achieved by a planned and systematic approach, involving patient education, patient empowerment and shared decision making.

NEWER DRUGS AND TECHNOLOGIES: THE KNOWLEDGE PARADOX

The advent of newer drugs, devices and technologies, over the past decades has revolutionized diabetes praxis. Paradoxically, this has made diabetes care simpler, as well as more complex, both for diabetes care professionals and for people with diabetes. This paradox holds true for *Ramadan* as well. The availability of designer molecules, both oral and injectable, with less risk of hypoglycemia, makes it easier for devout believers to observe the *Ramadan* fast. Long-acting drugs, requiring lesser frequency of administration, are suited for the dietary patterns that the *Ramadan* fast demands.[10] At the same time, the sheer number of antidiabetic drugs, and the permutations and combinations in which they can be used, present a challenge to the physician. Utilization of all available therapeutic modalities, in optimal, based either on evidence, or on logical empiricism,[11] needs constant upgradation of knowledge.

Narrated by Usamah Bin Shareek (may Allah be pleased with him): 'I was with the Prophet (PBUH) and some Arabs came to him asking "O messenger of Allah, should we take medicines for any disease?" He said, "Yes, o you servants of *Allah* take medicine as *Allah* has not created a disease without creating a cure except for one". They asked which one, he replied "old age".

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THE FLOW OF THIS BOOK

This book hopes to solve this paradoxical challenge for diabetes care professionals who have to manage people observing the *Ramadan* fast. It provides practical guidance regarding various aspects of diabetes management during the holy month.

Apart from the knowledge of clinical pharmacology and clinical diabetology, proper management of diabetes in *Ramadan* requires detailed understanding of pathophysiological and psychosocial aspects as well. These are covered in chapters on the endocrinology of fasting, counseling and risk stratification.

The therapeutic challenge of diabetes care is addressed in various ways. The nonpharmacological and drug management of diabetes are also discussed in detail. The various domains of nondrug therapy: nutrition, physical activity and stress management, are given their deserved place in the schemata of the book. Similarity, the sempiternal topics of insulin and oral therapy during *Ramadan* get full attention. Along with this, the monitoring of glycemic control, an essential part of diabetes care, is discussed. Special issues which arise during *Ramadan* are also included. Fasting in women and in adolescents is given separate coverage in the book.

Successful completion of *Ramadan* is a great achievement for believers and provides spiritual merit. Helping others in their achievement is equally meritorious. Through its chapters, this book tries to *facilitate* the observance of healthy *Ramadan* fast, in millions of *Islamic* adherents with diabetes.

He (PBUH) said: "No blessing other than faith is better than well-being".

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Chapter 2

Introduction

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Abstract

Health is the key to our happiness, and what we consume directly affects our health. Islam encourages Muslims to ensure that they are mindful of their health. Fasting during the month of *Ramadan* is one of five pillars of Islamic practices. During the Islamic fast, Muslims must refrain from smoking, eating, drinking, sexual activity, consuming oral medications and using intravenous fluids. In addition, they are encouraged to do more acts of piety, i.e. prayer, charity, or reading the Quran during this month. *Ramadan* fasting induces favorable changes on metabolic parameters, reduces oxidative stress and inflammation, promotes cardiovascular benefits, improves brain function and boots immunity. However, *Ramadan* benefits require some careful considerations with an adequate pre-*Ramadan* medical assessment and education as well as conservation of healthy dietary habits and adopting a healthy lifestyle during and after the fasting period.

Health is the key to our happiness, and what we consume directly affects our health. Islam encourages Muslims to ensure that they are mindful of their health. Holy Prophet Muhammad (peace be upon him and his progeny) said: "Take advantage of the good health before illnesses afflict you". He also encouraged Muslims to try their best to adopt a healthy living lifestyle that includes a healthy diet, regular mental and physical exercise and a balance between spirituality and materialism.

Muslims comprise nearly a quarter of the world's population with nearly 1.7 billion followers.[1] Fasting during the month of *Ramadan* is one of five pillars of Islamic practices, which also include the following: *Shahadah*, meaning faith in one God and faith in the prophet (Muhammad, and all other prophets); *Salah*, meaning five prayers a day; *Zakah*, meaning 2.5 percent annual capital gain deduction, taken from the rich and given to the poor; Haj, meaning one pilgrim's visit to Mecca in a lifetime, whenever possible; and *Ramadan* fasting. Quran says "O you who believe! Fasting is prescribed for you, as it was prescribed for those who came before you; that you will perhaps be God-fearing." (Al-Quran 2:183).

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Fasting is known in the Arabic language as "Sawm" and literally means "abstention from". During the Islamic fast, Muslims must refrain from smoking, eating, drinking, sexual activity, consuming oral medications and using intravenous fluids. In addition, they are encouraged to do more acts of piety, i.e. prayer, charity, or reading the Quran during this month.

Fasting occurs in the 9th month of the Islamic calendar (*Hijra*) which is lunar based. The Islamic calendar has 354 days thus precedes every year by 10–11 days. The period of fasting lasts from dawn to dusk. The meal consumed at dawn and dusk is known in Arabic as *Suhur* and *Iftar* respectively.

Ramadan month can occur in any of the four seasons and the duration of restricted food and beverage intake can vary from 11–20 hours depending upon the exact time of sunrise and sunset in each country or region. Over the coming years, 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 chronic illnesses who wish to fast.

Fasting does not apply to all Muslims. If it is considered to be detrimental to an individual's health then the Quran states fasting should be avoided: "So everyone of you who is present (at his home) during that month should spend it in fasting, but if anyone is ill, or on a journey, the prescribed period (should be made up) by days later. Allah intends every facility for you; He does not want to put to difficulties. (He wants you) to complete the prescribed period, and to glorify Him in that He has guided you; and *perchance ye* shall be grateful". (2:185).

Those exempted from fasting include:

- The frail and elderly
- Children (until they reach puberty)
- Those who have a chronic condition whereby participating in fasting would be detrimental to their health
- Those who cannot understand the purpose of fasting, i.e. those who have learning difficulties or those who suffer from severe mental health problems
- Travelers (those traveling greater than 50 miles)
- Those acutely unwell
- Menstruating women
- Pregnant and breastfeeding women.

Chapter 2, verse 184 of the Quran makes it explicitly clear that people who have an illness or medical condition of any kind that makes fasting injurious to their health are exempted from fasting. To compensate for the missed fasts, they must fast later when they are healthy; if this is not possible due to long-term illness, they must feed the poor.

Islamic fasting is different from other types of fasting:

- As compared to other diet plans, in fasting during *Ramadan*, there is no malnutrition or inadequate calorie intake since there is no restriction on the type or amount of food intake during *Iftar or Suhur*
- Fasting in *Ramadan* is voluntarily undertaken, as opposed to being a prescribed imposition from a physician
- In Islamic fasting, we are not subjected to a diet of selective food only (i.e. protein only, fruits only, etc.).

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- Additional prayers are prescribed after the dinner. These prayers constitute appropriate level of physical activity (equivalent to moderate physical activity).

What is clear is that some patients with chronic illnesses insist on fasting even though they are permitted not to by Islamic rules. The population-based Epidemiology of Diabetes and *Ramadan* 1422/2001 (EPIDIAR) study demonstrated that among 12.243 people with diabetes from 13 Islamic countries, 43 percent of patients with Type 1 diabetes and 79 percent of patients with Type 2 fast during *Ramadan*, lead to the estimate that worldwide more than 50 million people with diabetes fast during *Ramadan*.[2]

For many people, the key question regarding fasting is whether it is good or bad for our health? The answer to this requires a quick overview of what happens inside the body during fasting: the physiology of fasting.

Fasting triggers a complex array of neural, metabolic and hormonal adaptations that maintain energy supply to the brain. Fasting state induces significant changes in carbohydrate and lipid metabolism, favoring glycogenolysis, gluconeogenesis, and lipolysis. Short-term fasting increases proteolysis and decreases protein synthesis. However, as the duration of fasting increases, there are adaptive mechanisms leading to preservation of lean mass; especially in obese subjects. Fasting leads also to a fall in insulin and a rise in counter-regulatory hormones mainly glucagon and catecholamines.

Muslims with diabetes, who wish to fast *Ramadan* are at risk of adverse events and the risks may increase with longer fasting periods. Major risks associated with fasting in patients with diabetes include:[3]

- Hypoglycemia
- Hyperglycemia
- Diabetic ketoacidosis
- Dehydration and thrombosis.

All patients with diabetes, who wish to fast during *Ramadan* should undergo a medical assessment.[3] They are categorized as at high, medium or low-risk of adverse events during the fasting period. People with diabetes assessed to be at high-risk are advised not to fast because they are much more likely to experience severe hypoglycemic episodes and ketoacidosis. People at moderate risk should be educated and supported before the start of *Ramadan* to make the necessary changes to reduce and control their risks. Those assessed as being at low-risk should be able to fast without health care supervision.

Prior to fasting, diabetics need to have appropriate education and treatment adjustments and advice. The following principles of pre-*Ramadan* considerations should be followed:

- Assessment of the metabolic control
- Adjustment of the diet protocol for *Ramadan* fasting
- Adjustment of the drug regimen (e.g. changing long-acting hypoglycemic drugs to short-acting drugs to prevent hypoglycemia)
- Encouragement of continued appropriate physical activity
- Recognition of warning symptoms of dehydration, hypoglycemia and other possible complications.

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The EPIDIAR study noted a 7.5-fold increase in the incidence of severe hypoglycemia during *Ramadan* in patients with Type 2 diabetes. To minimize such complications, guidelines recommend a pre-*Ramadan* medical assessment of diabetic patients specifically addressing lifestyle as well as timing and dose changes of antidiabetes medications. Available data indicate that incretin-based antidiabetic agents may have a role to play in the management of Muslim patients with diabetes during *Ramadan*, particularly to reduce their risk of hypoglycemia during the long daytime fasting periods.

Healthy, stable and well-informed Type 1 diabetics are able to fast safely; but need to be supervised and managed with greater care and strict attention to their diet, daily activities, glycemic control, and insulin dosage adjustments.

Recent studies corroborate safety of *Ramadan* fasting in diabetic patients with stable comorbidities (hypertension, dyslipidemia, cardiovascular disease and kidney disease); especially if they had a pre-*Ramadan* medical assessment and educational counseling. In such patients, medical advices regarding medications schedules, drug interactions and nonpharmacological measures should be provided.

The health effects of Islamic *Ramadan* fasting have recently been the subject of scientific inquiry, with most of the research being performed in the last 2 decades. In 1996, an International Conference was held in Casablanca, Morocco and about 50 papers were presented. The conclusions taken from this meeting were that *Ramadan* fasting had beneficial effects on health especially on some cardiometabolic parameters and digestive tract.[4] Later, numerous epidemiologic studies showed positive effects of *Ramadan* fasting on various parameters in diabetic and healthy subjects. *Ramadan* fasting induces favorable changes on metabolic parameters, reduces oxidative stress and inflammation, promotes cardiovascular benefits, improves brain function and boots immunity. It has also several spiritual, social and psychological benefits. *Ramadan* fasting would be an ideal recommendation for treatment of some metabolic and inflammatory diseases. It should be noted, however, *Ramadan* benefits require some careful considerations such as necessity of an adequate pre-*Ramadan* medical assessment and education as well as conservation of a healthy dietary habits and adopting a healthy lifestyle.

This book aims to review the available evidence with regards to the following topics:

- How pre-*Ramadan* medical assessment should be carried out?
- What are the physiological changes that occur during *Ramadan* fasting?
- How fasting patients with Type 2 diabetes should be managed?
- How fasting patients with Type 1 diabetes should be managed?
- How stress and emergencies should be managed?
- How should *Ramadan* fasting be managed in the elderly?
- Is it safe for diabetics to fast during *Ramadan*?
- Which patients should be advised not to fast?
- For those who fast, what is the optimal therapeutic regimen?
- Should patients with diabetes travel during *Ramadan*?
- What are the benefits of *Ramadan* fasting in diabetic and healthy subjects?
- Is it safe for diabetics with comorbidities to fast during *Ramadan*?

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Chapter 3

Pre-Ramadan Counseling

Altamash Shaikh

Abstract

Counseling and *Ramadan*-specific/structured education are the mainstay of success of safe fasting. Adherence to optimal management of diabetes in *Ramadan* remains poor, hence, health care providers must spend quality time in counseling patients. Understanding the local, social, cultural, economical, and behavioral aspects of patients is integral in *Ramadan*-specific education. Mass awareness is vital initial step towards this goal. All patients and their families be counseled regarding risks and rewards of fasting. Warning symptoms and signs of emergency events must be explained. Counseling strategies, content and benefits are discussed in this chapter.

INTRODUCTION

Awareness of *Ramadan*-specific education and its challenges have been into clinical practice since the meeting in Casablanca on *Ramadan* and diabetes. Adherence to optimal practices in the management of diabetes in *Ramadan* remains poor, despite of the presently available treatment options, hence, health care providers must spend quality time in counseling patients.

One study found that counseling before *Ramadan* was received by only about one-third of patients. Education specific to *Ramadan* has profound beneficial effect on fasting once patients received adequate counseling. However, irrespective of the fasting in *Ramadan*, counseling forms the main backbone in the management of diabetes, worldwide.

GOALS OF COUNSELING

- Individualization of treatment
- Eventless fasting, for patients willing to fast.

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PREREQUISITES

Patient centered approach needs to be implemented while addressing *Ramadan*-specific diabetes education. Counseling all the diabetic patients pre-*Ramadan* is a must, whether they will be fasting or not.

Structured diabetes counseling before *Ramadan* includes educating patients, health care providers, and patient's families.

Provide counseling at least 8–12 weeks before *Ramadan*.

Provide adequate time for the patients and families to get ready for change in lifestyle pattern during *Ramadan*. Use of local language is advocated for better dispersion of counseling content.

Counseling has to be provided by the health care provider to the patient in individual and/or can be done in groups. Patients should be clearly explained the risks involved in fasting and concerns of preventable complications. Patients' local, social, cultural, economical and attitudinal beliefs must be kept in mind before counseling. Then the changes in diet or treatment regimen should be started, so that patients welcome *Ramadan* fast on a stable and accepted treatment regimen.

Training of medical personnel in counseling is of paramount importance in areas of high illiteracy and for the regions with poor resources and the underprivileged.

Most important part of counseling the diabetic patients for *Ramadan* is that each aspect has to be highly individualized.

AWARENESS REVOLUTIONS/CAMPAIGNS

The step in *Ramadan* focused/specific diabetes education is revolutionary campaigns to create awareness among general public, health care providers and patients. This can be done in various ways, through hospital notices or other medias. Patients feel beatitude during *Ramadan* and worship more in this holy month. Awareness through religious leaders by meeting lmams in the mosques and letting them to talk to general public is successful way of spreading education about diabetes.[1]

RAMADAN EDUCATION AND ROLE OF THE HEALTH CARE PROVIDERS

Health care providers should receive and impart *Ramadan*-specific structured education, in addition to the following:

Adjustment of Nondiabetes-related Drugs

Avoidance or cautious use of drugs like diuretics (hypovolemia, dehydration), reduction in dosages of drugs causing dry mouth (e.g. Anti-Parkinsonian drugs).

New statin prescriptions should be avoided just prior to *Ramadan*, as fatigue and or myalgias are common and may hamper the ability to fast. However, should there be a necessity to initiate statin, this may be done preferably at lower doses. Patients on stable doses of statin may continue their regimen.

Avoid nephrotoxic drugs. If given should be properly monitored, e.g. gentamycin group.

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Avoidance of drugs causing reduced mentation.

Overzealous use of vitamin D, to prevent hypercalcemia which may manifest as thirst, dry tongue and lethargy.

Adjustment of Diabetes-related Drugs

Metformin can be used as two-thirds dose at *Iftar* and one-third dose at sunrise meal (*Suhur*). Glitazones if used, should not be initiated with other hypoglycemics for control during *Ramadan*, as they take 2–3 weeks' time for their antihyperglycemic effects. Availability and low cost of sulfonylureas makes them attractive options. Shorter acting newer sulfonylureas may be used with caution and counseling in *Ramadan*. Glinides (repaglinide and nateglinide) can be used twice daily for their short duration of action.

Patients may consult local Islamic scholar about limitations of breaking the fast (apart from scientific parameters as mentioned below); or for other issues like the ways to make-up for not fasting, in accordance with the holy *Quran*.

Patients should be counseled to approach and seek medical care when any of the complications occur.

COUNSELING STRATEGIES

These can be of the following types:

Individual Counseling

Like individualized treatment, face to face counseling gives opportunity for the patients to talk to their health care providers. Understanding the problems on a individual basis by a particular patient in *Ramadan*, impacts and enhances outcomes of counseling.

Group/Peer Counseling

This may be effective at a local level where a group or large masses may be able to gather, and then counseled. Such session may be of one to two hours sessions. Physician, religious leaders may take a role in addressing groups **(Table 1)**.

Table 1: Preparing for counseling

Patient centered approach, highly individualized counseling
Provide counseling 8–12 weeks before *Ramadan*
Consider local, social, cultural, economical attitudinal beliefs and literacy levels
Ramadan comes in various seasons and climatic conditions
Provide *Ramadan*-specific/structured diabetes education
Spreading awareness through medical personnel or religious leaders
Adjustment of prescription for diabetes related and unrelated medicines

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Family Counseling

For patients who want to fast and are also dependent on their family members for treatment and daily routine, would require family counseling. Nonetheless, in Type 1 diabetics, desirous of fasting family is involved in economical, emotional and technical ways. Educating all in the family, reducing their exaggerated anxiety and fears is prudent in such cases.

COUNSELING CONTENT FOR THE PATIENTS

The following needs to be dealt in-depth with diabetes patients fasting in *Ramadan*.

Pre-Ramadan Check

Patients should be educated about the importance of pre-*Ramadan* clinical evaluation inclusive of; clinical profile, biochemistry, appropriate comorbidities assessment. It should begin at least 2–3 months in advance. This medical assessment should include a minimum of complete physical examination, an assessment of metabolic control, and laboratory tests (inclusive of but not limited to: fasting and postprandial glucose, lipid profile, urine acetone, glycated hemoglobin, spot urine microalbumin, creatinine, self-monitoring of blood glucose). Few patients may need more detailed evaluation depending on their current control and complication.

Fasting Risks

The four major risks involved in fasting are:

1. Hypoglycemia.
2. Hyperglycemia.
3. Diabetic ketoacidosis.
4. Dehydration and thrombosis.

Warning symptoms of hypoglycemia must be told to every patient, so as to recognize hypoglycemia in a very early stage and prevent catastrophes.

Type 1 Diabetes Mellitus

Patients with Type 1 diabetes are more prone for emergencies compared to Type 2 do patients fasting in *Ramadan*. Basal bolus regimen stands the best for them.

Patients must be informed that they may need to be seen at least two times during *Ramadan* for adjustment of their treatment regimen, more often with illness or glycemic fluctuations.

Feeding Roster

Planning of sunrise meal (*Suhur*) and sunset meal (*Iftar*), reinforce adherence to regular dietary habits and refrain from delicious indulgence. Individualization of diet is vital considering patients' local customs and associated risk factors. Thus, the

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dietary prescription should take into account the nutritional needs, metabolic milieu, concurrent comorbidities, social scenario and pocket potency of the patients.

At the sunrise meal (*Suhur*), preparations with slowly digesting and absorbing properties like complex carbohydrates are preferable, including slow energy releasing foods (e.g. made of wheat or rice or beans) depending on their staple food. Patients may be also advised to have their *Suhur*, just before the time of start of fasting hours, instead of eating late night and sleeping without getting up for sunrise meal (*Suhur*).

At sunset meal (*Iftar*), patients should eat diet composed of simple carbohydrates. Avoid sweets or dense sugary (*halwas, firnis, malpuas*) food items. Avoid large meals, fatty meals (*bhajias, samosas, crispies*). Discourage overeating/binging.

Some patients may do well with daily dietary and weight recordings, and self-assessing on the pattern and quantum of intake. This should be supervised by the health care provider.

Change in weight of more than 2–3 kilograms should prompt evaluation in these patients.

Inappropriate diet, untimely eating patterns are the most common reasons for health issues in diabetic patients in *Ramadan*.

Thus, health care providers must provide guidance on food feasibility and avoid feasting by patients.

Prayers and Rituals

Quran recitation is done regularly in *Ramadan*. It should preferably be done in parts (small sections), more so in the elderly diabetic, who may be on poly pharmacy and may add to dry mouth and fatigue. This reading may be increased or started after sunset meal (*Iftar*), when hydration has been sufficient.

Elderly diabetics if they feel lethargic or weakness in later half of the day while fasting they should pray in sitting posture, as getting up from prostration may lead to syncope in some patients (orthostatic hypotension due to autonomic neuropathy). This is especially for *Asar* and *Maghrib* prayers, as few patients may not be able to assimilate energy immediately.

Prayers are a part of daily routine, however they are performed with great intensity during *Ramadan*. When performed for spiritual benefit, the *Tarawih* prayer also has a scientific benefit,[2] as a form of physical activity.

Treatment Regularity and Dosage Review

All diabetes patients must take their treatment regimen regularly and precisely in the *Ramadan* adjusted prescribed dosages.

Patients Controlled on Lifestyle Modification Only

Continuation of lifestyle modifications and to remain compliant with it should be reminded and reinforced to all patients willing to fast. They should be made aware of control of their dietary habits, failing which there are chances of hyperglycemia. Two

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to three smaller meals, besides scheduled physical activity in the postsunset meal (*Iftar*) period helps prevent hyperglycemia.

Patients on Oral Regimen

All treatment modalities need considerable review before and while during *Ramadan*. Impulsive modifications of oral or insulin regimen may lead to fluctuant glucose profile and must be avoided. Short acting drugs are preferable. Lifestyle changes as above and taking oral dosages of tablets as per individual need must be taken regularly, to obtain smooth glycemic profiles.

Patients on Insulin and Incretin-based Therapies

Patients must be counseled in details about adjusting their regimens well in advance, so as to start fasting on a stable prescription. When on insulin regimen, dosages should be tailored to meet individual demands. In general two-thirds of dose can be given at sunset meal (*Iftar*) and remaining one-third at sunrise meal (*Suhur*). For details see chapter on insulin and Type 2 diabetes.

Monitoring and Recording

Ramadan-specific diabetes diaries can be made for monitoring and recording (for details see chapter on insulin and *Ramadan*).

Patients should be counseled that monitoring does not constitute to breaking of fast. It is to be done to allow for a complete and safe fast. Monitoring of glucose values need not be overemphasized in a diabetic patients management. Patients should have a source of blood glucose monitoring. Some may require to checking multiple times daily, like Type 1 diabetes patients or Type 2 on insulin. Specifically monitoring should be done when an illness ensues or symptoms occur. Generally this should be as given in **Table 2**.

Table 2: Monitoring glucose values in *Ramadan*

Monitoring for hypoglycemia/hyperglycemia
2 hours post (*Suhur*) meal (*Iftar*) and Half an hour pre-*Iftar*
2 hours post-*Iftar*/dinner
Monitoring for exercise
Pre-and postexercise in susceptible patients only
Monitoring on insulin
Pre-*Iftar*:
2 hours post-*Iftar*
2 hours post-dinner
2 hours post-*Suhur*

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Glycemic Excursion Response

Hypoglycemia

Not only the patients but also their immediate family/relative or caretakers must be counseled and taught to recognize symptoms and signs of hypoglycemia. Prevention and avoidance of hypoglycemia in vital. Any intense activity in the hours prior to breaking fast [Sunset meal (*Iftar*)] should be discouraged. Risk of hypoglycemia is about four to seven times more in fasting patients.[3,4] With *Ramadan*-specific education, hypoglycemia reduces by four-fold, and also helps in weight reduction.[3]

Hyperglycemia

With sudden decrease in insulin doses just prior to *Ramadan*, in Type 1 diabetes has more chances of hyperglycemia with impending diabetic ketoacidosis. Patients should avoid doing such self-dosages. Thus, the health care provider has to discuss not only about the dosages and checks but also counsel against gulping of food or skipping of meals or heavy meals to avoid after effects of hyperglycemia. Change in individual attitude towards diabetes is important determinant for successful fasting.[5]

Prompt Rehydration

Apart from hypoglycemia, another immense preventable issue is dehydration. Diabetic patients should be counseled to take fluids adequately in between sunset meal (*Iftar*) and sunrise meal (*Suhur*), i.e. nonfasting hours.

Intake of water should be supervised by patients themselves and family members. This avoids dehydration, electrolyte imbalance, thrombosis especially in hot climatic conditions and long hours of fasting.

Worsening of hypercoagulable state and the subsequent risk, is due to intravascular contraction and then increased viscosity of blood. Hence, in some patients antiplatelets may be considered. This is integral in areas where fasting hours are prolonged 18–20 hours.

Exercise Regimen

Daily physical activity/routine can be maintained in *Ramadan*. Both resistance and aerobic exercise can be done in *Ramadan* depending upon the comorbidities. Utmost care to be taken to avoid hypoglycemia.

Avoid exercise prior to sunset meal (*Iftar*). It may be done postsunset meal (*Iftar*), post-*Isha* prayers or in some postmidnight *Tahajjud* prayers.

Walking and stationary cycling may be good options when performed. Avoid exercise in the late hours of fasting prior to sunset meal (*Iftar*).

Breaking the Fast

At no time fasting should be continued if there are symptoms and/or signs of hypoglycemia. With time this only worsens and leads to unwanted medical issues and may even endanger life. General tendency is to preserve and still observe the fast.

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This must be discouraged at all levels, and patients have to be counseled to revert to nonfasting state and avoid any such temptation. Thus, in any diabetic patients with glucose value of < 60 mg/dL (3.3 mmol/L) fast must be broken immediately, and treatment be sought, as no human can vouch for further decline in glucose levels.

When blood glucose values are < 70 mg/dL (3.9 mmol/L) in the early hours post-sunrise meal (*Suhur*), then also fast should be broken in patients oral (sulfonylurea, meglitinide) or insulin taken at *Suhur*.

Avoidance of fasting on "sick days". Avoidance with hyperglycemia blood glucose more than 300 mg/dL (16.7 mmol/L).

Diabetes and Religious Exemptions

Fasting should not be done by patients whose condition may deteriorate leading to adverse medical conditions. There are various exemptions from fasting in *Ramadan*, to name a few very elderly/young, the traveler, the sick, the pregnant/lactating mother. Careful counseling of such categories of diabetes patients may prevent any medical/endocrine emergencies. For such patients and or bedridden there is a provision to compensate by various means. Local *Islamic* scholar may be contacted and patients or their family members can do the needful.

Risk Stratification

Patients may be divided into four risk categories, based on clinical expertise and experience namely: very high risk, high risk, moderate risk and low risk. (The reader is directed to chapter on risk stratification for details.)

Pregnancy, Lactation and Ramadan

Although exempted, some pregnant ladies deem themselves as possibly normal and insist on fasting. Not in the first trimester with severe hyperemesis but women generally, do fasting in their second trimester safely. They should be counseled individually to avoid any hypoglycemia throughout the period of fasting. (Treatment details in chapter on Insulin in Type 2 diabetes.)

Sleep and Rest

Adequate rest is crucial even in the month of *Ramadan*. Sleep disturbances are noted due to modern *Ramadan* practices. Patients should be advised to take a short nap in the afternoon period when feasible and avoid overnight shopping and socializations. Long waking hours and sedentary behavior add to inadequate sleep and stress.

Ramadan Stress Rejuvenation

Diabetes in its long-term causes both oxidative stress and mental/cognitive stress. Patients may be rejuvenated by decreasing any stress that may occur. This can be accomplished by managing their diet, dosages and *Ramadan*-specific diaries, constant motivation and group discussions.

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Stress can also be perished by appropriate family education and counseling,[6] resolving any conflicts due to disease.

Prior Ramadan Experience

Some self-experiences by the diabetic patients may be carried forward as a result of prior fasting in *Ramadan*. Any such perception by the patient may be persistently followed in eventual years. For example, he or she may have had hyperglycemia and has fasted without any complication or a under recognized subclinical hypoglycemia and or hyperglycemia. The health care provider should identify these facts and feeling of an individual patient and provide correct and fresh counseling, pertaining to *Ramadan*.[7]

On the other hand few patients may have done well in earlier years and may thus benefit with present diabetes counseling and *Ramadan*-specific education, for better outcomes in future fasts.

Warning Signs

Any slightest symptoms or signs of hypoglycemia or hyperglycemia or dehydration should be immediately taken care off. They should be advised to immediately treat the hypoglycemia and/or seek for medical help in cases of severe cases.

Team Work

Patients, family members, health care providers (doctors from various specialties, nutritionists, counselors) and local *Islamic* scholar when required. This may even be needed during and post-*Ramadan*, for successful future fruition.

BENEFITS OF PRE-RAMADAN COUNSELING

- Strengthens patient physician bond. Patients continue the counseling education in their lives later beyond the month of *Ramadan*.
- Improves intake of fiber-rich diet, reduction in body weight and body mass index.
- Improves understanding of diabetes and its treatment.
- Reduced frequency and severity of risks and complications.
- Reduces the cost of treating expected complications.
- Adds and empowers patients with various skills required in management of diabetes.
- Sustained improvement in glycated hemoglobin at the end of one year.

SUMMARY

In order to have an effective counseling it is necessary to understand patients' lifestyle during *Ramadan*, to avoid any dissociation between patients and health care provider **(Table 3)**.

Lifestyle modification, dietary adjustment, treatment adherence are cornerstone of successful *Ramadan* fasting.

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Table 3: Points to counseling patients before *Ramadan*
Pre-*Ramadan* check-up
Risk stratification
Feeding pattern
Treatment prescription, regularity and monitoring
Response to glycemic profile
Warning signs of complications
Breaking the fast
Religious exemptions
Exercise regimen
Rehydration and rest
Stress rejuvenation

Glycemic stability must be achieved in all patients, who are conscious of their fasting and compliance must be assured, directly or indirectly through patients or families. All patients must be explained warning signs of complications. Counseling has contributed lots in diabetes management and also benefits in *Ramadan*.

CONFLICT OF INTEREST

None.

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Chapter 4

Endocrinology of Fasting

Ines Slim, Mahdi Kamoun, Mouna Feki Mnif

Abstract

Fasting during *Ramadan* is a religious duty for all healthy adult Muslims and implies abstention from food and drink from dawn to sunset. Fasting triggers a complex array of neural, metabolic and hormonal adaptations that maintain energy supply to the brain. Fasting state induces significant changes in carbohydrate and lipid metabolism, favoring glycogenolysis, gluconeogenesis and lipolysis. Short-term fasting increases proteolysis and decreases protein synthesis. However, as the duration of fasting increases, there are adaptive mechanisms leading to preservation of lean mass; especially in obese subjects. Fasting leads also to a fall in insulin and a rise in counter-regulatory hormones mainly glucagon. Prolonged fasting is a strong physiological stimulus equivalent to a biological stress that activates the hypothalamic-pituitary-adrenal (HPA) axis. However and during *Ramadan* fasting, some brain's cellular mechanisms of stress resistance are activated to protect neurons from the deleterious effects of this HPA axis activation. These metabolic and hormonal mechanisms of adaptation to fasting could be altered in patients with diabetes mellitus who are continuing to fast despite the advice of their doctors to not.

We review in this chapter the current understanding of the physiopathology of short-term fasting especially during *Ramadan* and its metabolic and hormonal effect in healthy subjects and in patients with diabetes mellitus.

INTRODUCTION

The practice of prolonged fasting for political or religious purposes is increasing all over the world, and a physician is likely to encounter such circumstances especially when it occurs in patients suffering from chronic diseases such as diabetes mellitus (DM).

Abstinence from food and liquid during daylight hours is observed by Muslim individuals during the Holy month of *Ramadan*. Even though the Quran exempts the sick persons from fasting, many people with diabetes still fast during this religious period. People living with diabetes who want to fast as part of their religious faith need to be mindful of their actions and the safety in relation to their own health.

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Although fasting implies an intentional abstention from food, the physiologic adaptive mechanisms that come into play during this type of food deprivation are similar to starvation or food limitation.[1] Fasting triggers a complex array of neural, metabolic and hormonal adaptations that maintain energy supply to the brain, protect lean mass and promote survival.[2]

We review in this chapter the current understanding of the physiopathology of short-term fasting especially during *Ramadan* and its metabolic and hormonal effect in healthy subjects and in patients with DM. We have based on Medline search for articles published between 1950 and April 2013 using the following MeSH terms: ("*Ramadan* fasting" or "Islamic fasting" or "religious fasting" or "prolonged fasting") and ("diabetes" or "diabetes mellitus" or "physiopathology" or "metabolism" or "endocrinology" OR "hormones"). Cochrane database was also used as well as some local journals in Islamic countries.

DEFINITION, HISTORY AND CIRCUMSTANCES OF FASTING

Definition and Circumstances of Fasting

Fasting is defined as an abstention from food, and often also from drink, for a various period. Fasting is observed in several conditions such as political reasons, religious practice, or pathological conditions such as mental anorexia. Duration as well as different psychological aspects depending on the circumstance of fasting should be considered as it could influence the risks during fast and the quality of their management.

History of Religious Fasting

Since early times, fasting has been practiced in connection with religious ceremonies as it has been advocated for spiritual development and promotion of health. Fasting as a religious practice developed independently among different people and religions worldwide. Fasts are observed among Jews, Christians, Muslims, Confucianists, Hindus, Taoists, Jainists, Buddhists in some countries and adherents of other religious faiths.

Particularities of Fasting in Muslims

Ramadan fasting is one of the five pillars of Islam; and is observed by millions of Muslims all over the world. *Ramadan* is the 9th month of the Islamic lunar calendar. Every day during this month, all Muslims fast from first light until sundown, abstaining from food, drink, smoking and sexual relations during daylight hours.[3]

Although the Quran clearly exempts sick people from fasting (2:183-185; 2:187; 2:196), many Muslims with diabetes may not consider themselves sick and choose to fast, despite medical advice to the contrary. According to the large population-based and transversal survey conducted in 13 countries and including 12,914 diabetic Muslims; the Epidemiology of Diabetes and *Ramadan* study (EPIDIAR study); the

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estimated prevalence of fasting during *Ramadan* was 43 percent for Type 1 DM and 86 percent for Type 2 DM.[4]

Furthermore, the time of onset of *Ramadan* is based on the lunar calendar which is different from the most commonly used international civil calendar (Gregorian calendar). Subsequently, the duration of daily fast and the overall period of the month of *Ramadan* vary each year depending on the geographical location and season. During summer, such as this year, in temperate regions and northern latitudes, the fast may last up to 18 hours per day. This variability of the length of daylight, and therefore the length of fasting, has considerable consequences especially for a person living with diabetes; and makes fasting more challenging physically, mentally and emotionally.

Nevertheless, as *Ramadan* is perceived by Muslims as a period for self-purification, self-discipline, austerity and charity, as a time of worship and contemplation and as an opportunity to strengthen family and community ties,[5] all these perceptions might provide a soothing sensation and well-being that can make patients more receptive for therapeutic education. It could be considered as an excellent opportunity to motivate and empower patients to be more observant to their treatment, to accept insulin therapy in order to improve their glycemic control and to enhance the self-management of the disease. It is also an opportunity to stop smoking.

Understanding the benefits and limitations of fasting and following the right nutritional guidelines will help fasts to live better this month.

METABOLIC AND HORMONAL CHANGES DURING RAMADAN FASTING IN HEALTHY PERSONS

The transition from the fed state through brief fasting and into prolonged starvation is mediated by a series of complex metabolic, hormonal and glucose-regulatory mechanisms.

More than 30 years ago, Felig has conveniently divided the transition from a fed to a fasted state into three stages: (1) the postabsorptive phase, 6–24 hours after beginning fasting, during which cerebral glucose requirements are maintained primarily via glycogenolysis (75%) and to lesser extent via gluconeogenesis (25%); (2) the gluconeogenic phase, from 2–10 days of fasting (during which glucose requirements are met using gluconeogenic amino acids, lactate, pyruvate and glycerol); and (3) the protein conservation phase beyond 10 days of fasting, characterized by decreasing protein catabolism as fat stores are mobilized and tissue use of free fatty acids and ketones increases.[6]

Interestingly, even though geographic location and season are taken into account, the duration of fasting during *Ramadan* never reach 24 hours. Subsequently major metabolic adaptations are limited to postabsorptive phase.

The metabolic and endocrine effects of fasting during *Ramadan* in healthy subjects are summarized in **Table 1**. These effects may be influenced by genetic and environmental factors, such as nutrition habits and the length of fasting day, which may differs with season and countries.

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Table 1: Metabolic and endocrine effects of *Ramadan* fasting on healthy Muslims

Metabolism/Organ	*Effects*
Carbohydrate	Glycogenolysis in the liver, some degree of gluconeogenesis in longer fasting days
Lipids	Variable, depending on the quality and quantity of diet and weight change
Caloric intake	Variable, decreases during the day, at night increases
Body weight	Variable, mostly decreased or unchanged
Liver	Slight increase in indirect bilirubin in the first half of *Ramadan* fasting
Kidneys	Small, insignificant changes in serum urea, creatinine and uric acid
Hematological profile	Small decrease in both iron and total iron binding capacity
Neuropsychiatric	Change in chronotype and sleep patterns; increase in the prevalence of headaches; decrease in parasulcide
Endocrine glands	Decrease in insulin secretion and raise of glucagon, catecholamines and GH production Slight changes in protein binding of T4 and T3 and in serum calcium concentration Small reversible shifts in cortisol, testosterone and prolactin secretions
Gastrointestinal tract, heart, lungs and eyes	None

Source: Adapted from reference 14

Metabolic Effect of Ramadan Fasting in Healthy Muslims

Effects of Fasting on Carbohydrate Metabolism

The effect of experimental short-term fasting has been already described in the literature[1,7,8] **(Figure 1)**. It has been found that a slight decrease in serum glucose to around 3.3–3.9 mmol/L occurs in normal adults a few hours after fasting start.[8] However, during fasting, this reduction in serum glucose tends to cease due to increased gluconeogenesis in the liver with amino acids as the primary substrates, and related decrease in insulin concentration and a rise in glucagon and sympathetic nerve activity.[1,9] Glycogen stores, along with some degree of gluconeogenesis may maintain normal blood glucose levels.[9]

As fasting progresses, plasma glucose levels fall significantly whereas the level of glucagon rises.[10] The fall in plasma glucose level is greater in nonobese female than in nonobese male subjects.[11] The lower lean body mass-to-adipose ratio in female[12] and estrogen and progesterone modulation of tissue uptake[13] have been suggested

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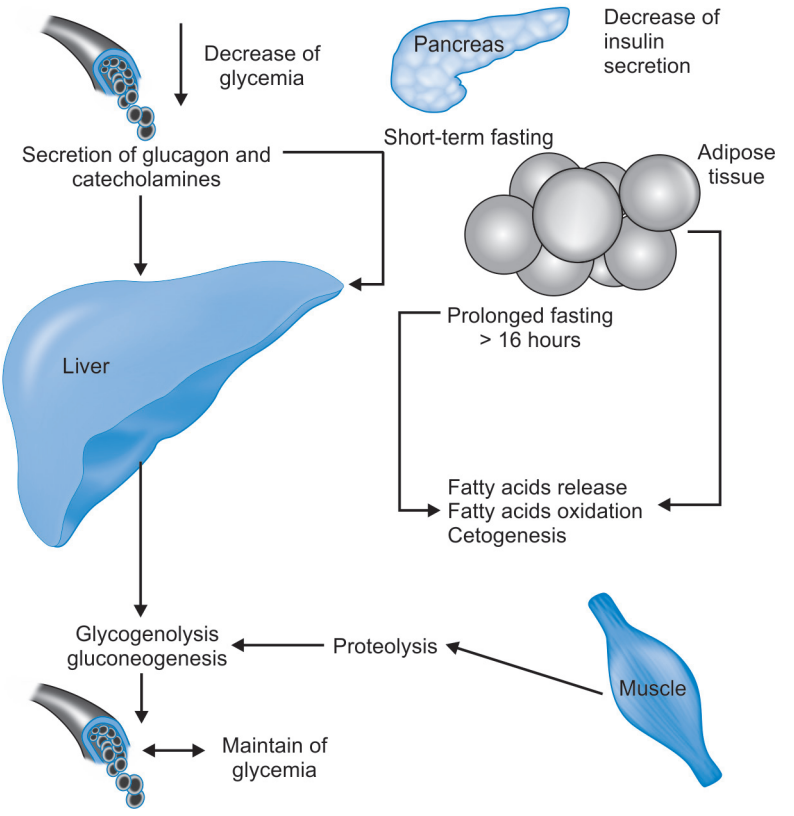

Figure 1: Endocrinology of fasting in healthy individuals

as possible explanations of this sex difference. Women are also known to become ketotic more rapidly than men during fasting, and ketosis appears to decrease gluconeogenesis, thereby indirectly affecting plasma glucose levels.[1]

During longer fasting days of more than 16 hours often associated with heavy compensatory meals, the hepatic stores of glycogen (providing about 75% of glucose requirements), along with some degree of gluconeogenesis (coming from precursor acids, lactate, pyruvate and glycerol) maintain serum glucose levels within normal limits.

Although, humans cannot synthesize glucose directly from fat, the energy derived from oxidation of free fatty acids facilitates hepatic glucose synthesis from lactate and glycerol.[1]

As a consequence, serum glucose level during *Ramadan* fasting is very variable. It may decrease slightly in the first few days of *Ramadan* with minimal level reported at 63 mg/dL, normalizing by the 20th day and showing a slight rise by the 29th day.[14]

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Effects of Fasting on Lipid Metabolism

Fasting leads to a depletion of liver glycogen during the first 18–24 hours.[6] Muscle; another site of glycogen stores; lacks glucose-6-phosphatase and therefore cannot release glucose directly into the bloodstream.[15]

Fat in the form of neutral triglycerides in adipose tissue provides the largest and most efficient storage of body energy and constitutes 85 percent of all potentially available calories.[16]

As we mentioned above, physiological adaptations during the month of fasting lead to an increase in reliance on fat as a source of fuel during daytime fasting.[17] Indeed, in the transition from a fed to fasted state, fat stores are rapidly mobilized. Lipolysis, which is the hydrolysis of triglycerides to free fatty acids and glycerol, is stimulated by a fall in insulin levels and a rise in glucagon levels. In the fasting state, free fatty acids are mobilized, taken up by the liver where they are partially oxidized to ketone bodies (ketogenesis) or resynthesized into triglycerides (lipogenesis).[6]

Regulation of ketogenesis is dependent on substrate availability; that is, free fatty acids; and transport into the hepatic or renal mitochondria where oxidation occurs. The enzyme responsible for this transfer, carnitine acyltransferase, is indirectly stimulated by glucagon in the absence of insulin.[6]

Effects of Fasting on Protein Metabolism

Data from fasting studies showed that leucine flux, proteolysis, and oxidation are elevated in response to short-term energy deficiency.[18] However, as the duration of fasting increases, there are adaptive mechanisms with reduced protein turnover and lowered amino acid catabolism leading to preservation of lean mass; especially in obese subjects. Indeed, obese subjects who fasted during long duration (3–16 weeks) showed suppression of protein flux and oxidation; and a greater portion of weight loss appears to come from adipose stores rather than the lean-mass compartments.[19] Furthermore, increased renal reabsorption of ketone bodies during fasting has a nitrogen sparing effect providing feedback inhibition of protein catabolism.[20]

Hormonal Changes during Ramadan Fasting in Healthy Muslims

The important roles of insulin and glucagon in the adaptation to fasting have already been discussed and have been reviewed extensively by others showing a fall in insulin and a rise in glucagon levels[1,6] Other endocrine changes also occur during fasting, including thyroid hormones, growth hormone and gonadotropins[14] **(Table 1)**.

Changes in Insulin and Glucose Counter-regulation Hormones

In order to maintain a minimum level and constant plasma glucose above 0.45 g/L and to preserve the stock of tissue protein, the body uses the decreased peripheral utilization of glucose, the energy supplied by the oxidation of carbohydrates and lipids and regulation by insulin and hormones of counter-regulation.[8]

As the fasting progresses, gluconeogenesis become progressively necessary in order to insure the formation of glucose from three carbon precursors including

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lactate, pyruvate, amino acids and glycerol. In this process, cortisol is the principal stimulus for the catabolism of muscle protein. Simultaneously the decrease in insulin and rise in catecholamine production results in lipolysis in the adipose tissue and a rise in the level of free fatty acids, which replaces glucose as the essential fuel for use by other tissues of the body.[1,14]

Growth hormone (GH) plays a key role in protein, carbohydrate and fat metabolism. It also has known lipolytic effects[21] and may be diabetogenic in large doses or in smaller amounts in the absence of insulin.[22] Its secretion fluctuates widely during the day with a major increase during early sleep.[22] Prolonged fasting is known to enhance progressively GH secretion in addition to other known stimuli such as hypoglycemia, exercise, certain amino acids, catecholamines, stress and certain drugs (for example, L-dopa, vasopressin).[1]

The effect of fasting on GH secretion appears to vary among obese and nonobese subjects.[1]

It is also apparent from several studies that glucose homeostasis during fasting is dependent in part on the presence of GH.[1,23]

Changes in Other Hormones

During *Ramadan* fasting, the sleep-wakefulness cycle is also altered. This leads to changes in levels of leptin, neuropeptide-Y (NPY) and insulin that play an important role in the long-term regulation of energy intake and energy expenditure.[24] Also, it has been shown that changes of sleep schedules and psychological and social habits during *Ramadan* may affect the rhythmic pattern of a number of hormonal variables, i.e. melatonin, steroid hormones (cortisol, testosterone), pituitary hormones [prolactin, luteinizing hormone (LH), follicular-stimulating hormone (FSH), GH and thyroid-stimulating hormone (TSH)] and thyroid hormones[25] **(Figure 2)**.

Leptin and NPY are two key peptides involved in the regulation of body weight and energy balance. Energy restriction studies have indicated that serum insulin and leptin levels are decreased with fasting, along with an increase in levels of NPY. However, contradictory results were reported when energy intake was increased during *Ramadan*, reflecting a state of positive energy balance due to a compensatory increase in food intake during the night.[2]

Melatonin is considered to be the best marker for circadian rhythm. Melatonin level has been reported to decrease during *Ramadan* fasting, possibly due to the nocturnal rise in cortisol level and decreased glucose and tryptophan provisions. Nevertheless, in these studies, melatonin profile kept the same circadian pattern.[25,26]

Short-term fasting influences normal circadian rhythm of cortisol secretion rather than average daily cortisol production. Previous research has shown that during *Ramadan* fasting, circadian cortisol rhythm was displaced (with a change from morning to evening peaking), but responsiveness to corticotropin remained unaltered.[25,27]

Short-term fasting induces a decrease in plasma T3 that, more likely due to a decreased activity of Type 2 iodothyronine deiodinase. This deiodinase allows tissues to adapt to the lower calorie requirement during fasting.[28] Despite the decrease in T3 levels, clinical hypothyroidism does not develop. TSH values do not rise, as might be

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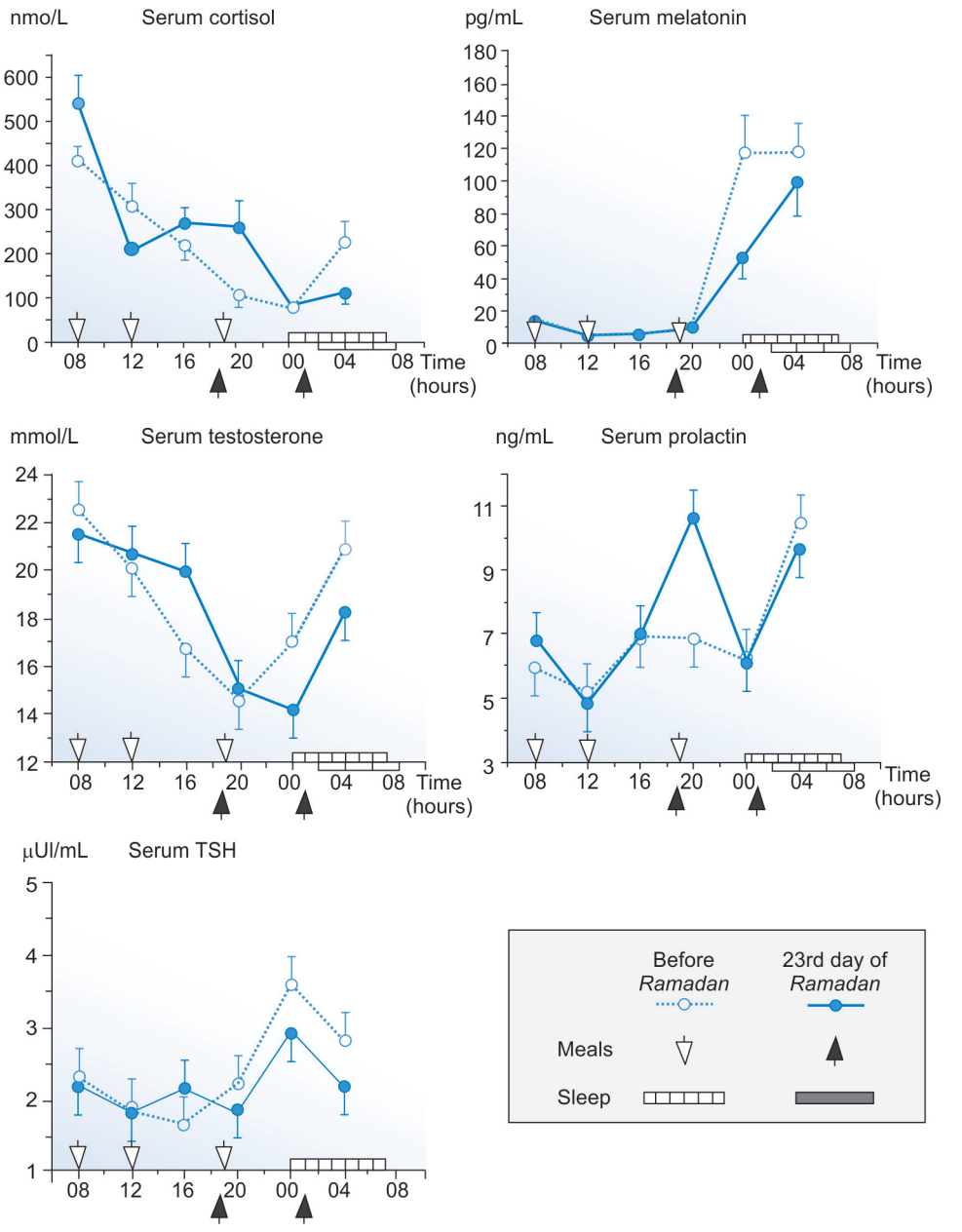

Figure 2: Patterns of some hormones on the control day (before *Ramadan*) and on the 23rd day of *Ramadan*. Each time point is the mean and SEM of 10 subjects. Cortisol rhythm showed biphasic pattern, with a rise in serum levels in the afternoon. Melatonin maintained its circadian rhythmicity during *Ramadan*. The circadian rhythm of serum TSH was also preserved, but its amplitude was flattened during *Ramadan*. There was delayed the onset of the increase of testosterone during *Ramadan*. Prolactin showed an increased evening peak. There were no significant changes in the 24-hour mean concentrations of the measured hormones except for melatonin which reduced significantly and FSH which showed significant but slight decrease.[25]

Abbreviations: SEM—Standard eroor of the mean; TSH—Thyroid-stimulating hormone

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expected in primary thyroid dysfunction. Azizi[29] has already shown that basal TSH concentrations may decrease in short-term fasting or remain unchanged in prolonged fasting (more than three weeks). In addition, TSH response to thyrotropin-releasing hormone (TRH) infusions may be blunted[29] or unchanged.[30]

In Islamic fasting, no alterations in serum concentrations of testosterone, gonadotropins and prolactin have been detected in normal males; though a slight decrease in FSH levels was reported in one study.[24] In prolonged fasting, serum LH response to GnRH infusion is typically normal, but serum FSH response to GnRH may be blunted during fasting.[31]

Ramadan fasting did not result in significant change in serum concentration of parathyroid hormone (PTH). Mean serum concentrations of calcium may decrease slightly 10-day after the beginning of fasting; however, no subnormal values can be seen.[32]

Neuroendocrine Effects of Ramadan Fasting

Prolonged fasting is a strong physiological stimulus equivalent to a biological stress that activates the hypothalamic-pituitary-adrenal (HPA) axis. This activation leads to massive catecholamines and glucocorticoids release in the first phase of fasting (the first 7 days).[33] The biological mechanisms of this activation may include reduced availability of cerebral glucose, reduced insulin and leptin levels, and the sensation of hunger.[33] Interestingly and during *Ramadan* fasting, some brain's cellular mechanisms of stress resistance are activated to protect neurons from the deleterious effects of HPA axis activation. These mechanisms include a synthesis of stress-resistance proteins and release of brain-derived neurotrophic factor (BDNF).[34] BDNF is involved in the regulation of serotonin metabolism, synaptic plasticity, and improvement in cognitive function as well as mood.[35-37] Additionally, the production of ketone bodies may also contribute to the mood enhancement of fasting; possibly through anticonvulsant properties.[38]

Emerging evidence indicates that endocannabinoid system is a regulator of the stress response via its anti-stress properties. Deficits in endocannabinoid signaling result in an increase in HPA axis activity as well as depressive and anxiogenic behavioral responses[39,40] Similarly, endogenous opioid peptides endorphins may play a role in the defensive response of the organism to stress.[41] A recent study including 27 healthy volunteers showed that serum endorphin and endocannabinoid levels significantly increased until day 21 of *Ramadan* fasting.[41]

The serotonin system is strongly involved in diet regulation. Experimental studies have demonstrated increased brain availability of serotonin and tryptophan during fasting.[42]

EFFECT OF RAMADAN FASTING IN PATIENTS WITH DIABETES MELLITUS

Diabetes mellitus is characterized by impaired metabolic features and hormonal secretion especially of insulin. Therefore, mechanisms adaptation to fasting, described above could be altered, depending on the type of diabetes, the duration of the disease

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and the presence or no of diabetic complications and comorbidities. Subsequently, this may require a specific management of diabetic patients who decide to fast despite their doctors advice to not.

Change in Caloric Intake and Weight during Ramadan Fasting

Change in Caloric Intake

During *Ramadan*, two main meals are usually consumed, before sunrise, known in Arabic as "*Sohur*", and after sunset, known as "*Iftar*". It is generally assumed that there is decrease in daily caloric and carbohydrate intake in patients with Type 1 and Type 2 DM.[8,43,44]

Even though people abstain from any oral intake from sunrise to sunset, an increase in daily caloric intake during *Ramadan* has been shown in especially at the "Iftar" meal with excessive compensatory eating during nonfasting period.[8,45]

The change in dietary pattern involves a change in the content too, with increased ingestion of large quantities of sugary fluids, fried foods and carbohydrate-rich meals traditionally prepared for *Ramadan*; which may contribute to weight gain and hyperglycemia. A recent randomized and controlled trial including 72 Muslim subjects with Type 2 DM have shown that the overall calorie consumption vary significantly before fasting, 15 days after initiation of fasting and at the end of fasting with a substantial increase during mid-*Ramadan* fasting ($p = 0.0001$).[8] The study of detailed energy consumption showed significant increase in carbohydrate ($p = 0.041$), but more notably in protein and fat consumption ($p = 0.001$ and $p = 0.0001$ respectively).[8]

In addition to changes in meal frequency, sleep duration at night and daily physical activity are reduced,[5] although believers may do more body movements during long night prayer known as "*tarawih*".

All these changes may influence the glycemic control, lipid profile, weight and dietary intake.[45,46]

Change in Weight and Body Mass Distribution during Ramadan Fasting

In experimental fasting, weight loss is rapid, averaging 0.9 kg/day during the 1st week and slowing to 0.3 kg/day by the 3rd week. This early rapid weight loss is primarily due to negative sodium balance.[1]

During *Ramadan*, weight and body mass index did not change before and 15 days after *Ramadan* in patients with Type 2 diabetes well control on diet or oral hypoglycemic medications in pre-*Ramadan* phase and who have received dietary advice and adjustment of the timing of their medications.[47] In obese women with Type 2 diabetes, fasting during *Ramadan* resulted in significant weight loss (–3.12 kg; $p < 0.01$), as well as in energy intake (1488 ± 118 vs. 1823 ± 262 kcal/day).[48] Beshyah et al. have observed weight loss in the majority of diabetic patients of different baseline weight and treated by oral hypoglycemic agents or insulin; suggesting that the calorific value of the food and drink taken during the nighttime nearly compensates for the abstinence.[49]

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The reduction in body weight might be temporary, depending on the types of foods that are eaten after the breaking of the fast at sunset.

Effect of Ramadan Fasting on Glycemic Control

Several studies have demonstrated no change in hemoglobin glycated (HbA_{1c}) or fructosamine levels[50-52] in patients with DM during *Ramadan*. Vasan et al. have reported a significant reduction in fasting and postprandial glucose during mid-*Ramadan*.[8] However, the variation in glycemia leading to severe hypoglycemia or hyperglycemia constitutes the main issue for patients with diabetes fasting for prolonged periods during *Ramadan* especially when it occurs in hot seasons. Physiopathological mechanisms leading to hypoglycemia and hyperglycemia in fasting diabetic patients are presented in **Figures 3 and 4** respectively.

The EPIDIAR study showed that daytime fasting during *Ramadan* increased the risk of severe hypoglycemia by 4.7-fold in Type 1 DM and 7.5-fold in Type 2 DM, in addition to an increase by 5-fold of the incidence of severe hyperglycemia in patients

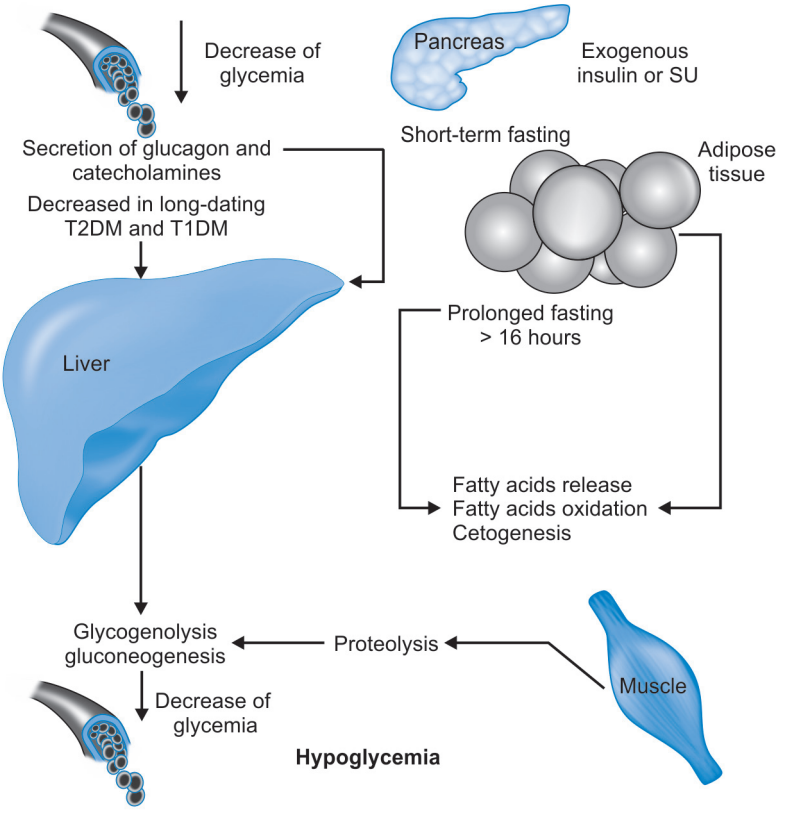

Figure 3: Endocrinology of fasting in diabetic patient—risk of hypoglycemia

Abbreviations: T2DM—Type 2 diabetes mellitus; T1DM—Type 1 diabetes mellitus; SU—Sulfonylurea

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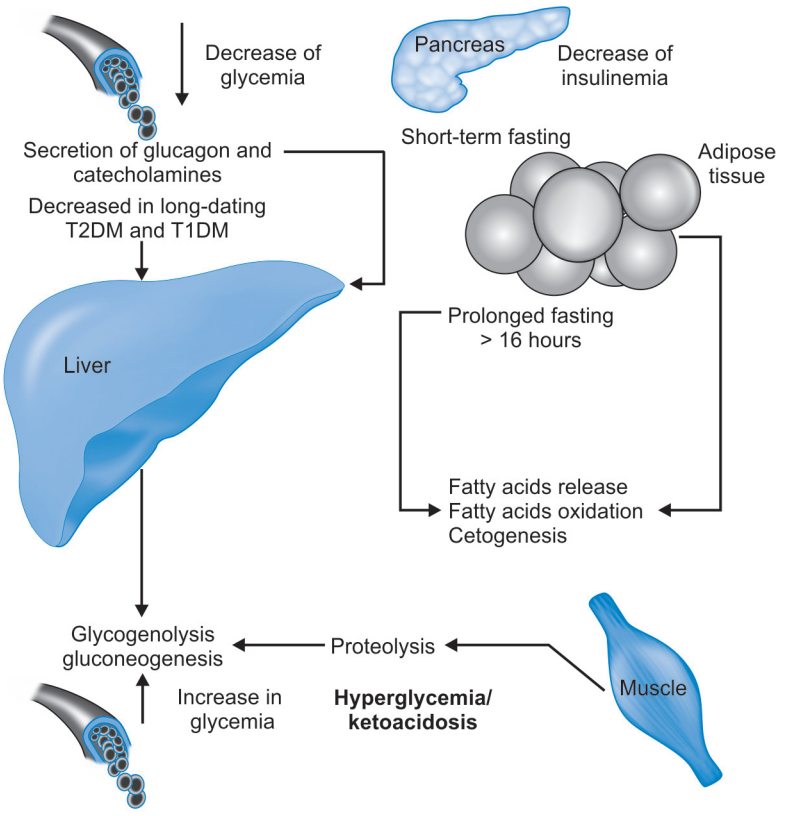

Figure 4: Endocrinology of fasting in diabetic patient—risk of hyperglycemia

with Type 2 DM **(Table 2)**.[4] No episodes of diabetic ketoacidosis (DKA) have been reported in small studies including fasting patients with T1 DM treated by insulin analogs or insulin pump therapy.[53-55]

In a multicenter observational study (n = 1374), symptomatic hypoglycemia occurred in about 20 percent of diabetic patients on sulfonylurea with or without metformin who fast during *Ramadan*,[55,56] whilst other studies have not shown a significant increase in the risk of hypoglycemia during *Ramadan* in patients treated with oral diabetic medications or insulin[57,58]

A recent review about glycemic emergencies identified several risk factors for DKA associated with fasting during *Ramadan* such as: patients with T1DM; excessive reduction of insulin dosages based on the assumption that food intake is reduces during this month so that they prevent hypoglycemia; patients with hypercoagulation state; moderate to severe hyperglycemia before fast, renal insufficiency, advanced micro and macrovascular complications; dose reduction during infection that cannot be able to meet sufficiently the stress demanded induced by raised catecholamines and steroids.[59]

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Table 2: Number of severe hypoglycemic and hyperglycemic events per month reported in the EPIDIAR study[4]

	Type 1 diabetes			*Type 2 diabetes*		
	Before Ramadan	*During Ramadan*	*P Value*	*Before Ramadan*	*During Ramadan*	*P Value*
Overall population						
Severe hypoglycemia	0.03 ± 0.1	0.14 ± 0.6	0.0174	0.004 ± 0.02	0.03 ± 0.28	<0.0001
Severe hyperglycemia/ ketoacidosis	0.05 ± 0.08	0.16 ± 0.51	0.1635	0.01 ± 0.05	0.05 ± 0.35	<0.0001
Patients who fasted>15 days						
Severe hypoglycemia	0.02 ± 0.05	0.12 ± 0.48	0.9896	0.003 ± 0.02	0.02 ± 0.22	0.0034
Severe hyperglycemia/ ketoacidosis	0.05 ± 0.08	0.15 ± 0.51	0.6701	0.009 ± 0.04	0.04 ± 0.30	0.0015

Date are means ± SD

In addition to hypoglycemia and hyperglycemia, diabetic patients who decide to fast during *Ramadan* are exposed to the risk of dehydration and thrombosis due to the limited fluid intake especially in prolonged fasting and hot seasons.[59]

Interestingly, many researchers clearly showed the benefits of therapeutic education before and during *Ramadan* to guarantee sustained good glycemic control. Indeed, The *Ramadan* Prospective Diabetes Study has demonstrated the potential importance of an appropriate education package for this time of year, in this instance delivered by a doctor and a dietician.[60] Hui and Oliver[61] also describe low glycemic variability in people with Type 2 diabetes following pre-*Ramadan* assessment and adjustments for fasting.

Effect of Ramadan Fasting on Micro- and Macrovascular Complications

Long-term mortalities and morbidities studies in patients with Type 1 DM or Type 2 DM, DCCT and UKPDS respectively, demonstrated the strong link between chronic hyperglycemia and microvascular complications, and in a lesser degree between chronic hyperglycemia and macrovascular complications. However, there is no reported information linking repeated yearly episodes of short-term hyperglycemia or glycemic variability and diabetic complications during *Ramadan* fasting. Some studies have reported controversial results about the outcome during *Ramadan* fasting of already pre-existing complications.[59] In patients fasting *Ramadan* and presenting severe dehydration, orthostatic hypotension may develop especially in patient with pre-existing autonomic neuropathy.[59]

EFFECT OF RAMADAN FASTING ON CARDIOVASCULAR RISK

There have been several studies related to the incidence of vascular events during *Ramadan*, and the majority has concluded that there is not an increased rate of such

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events during *Ramadan*, either in patients with established vascular disease or in those with no previous history compared to nonfasting months, although in presence of some vascular risk factor such the significant increase of low-density lipoprotein cholesterol concentrations.[50,62,63] Indeed, the implications of lipid profile during *Ramadan* fasting for cardiovascular risk are not entirely clear. Moreover, most of studies in both normotensive and hypertensive individuals showed little or no effect of *Ramadan* fasting on blood pressure.[64] Finally, the effects of *Ramadan* fasting on parameters of inflammation and oxidative stress (such as homocysteine, C-reactive protein); which are known as contributors to the increased risk of cardiovascular diseases range of disease; have also been studied, again with conflicting results.[64]

OTHER HEALTH RISKS OF RAMADAN FASTING

Rare medical complications of short-term fasting include gout, urate nephrolithiasis, postural hypotension and cardiac dysrhythmias. The particular association of liquid protein-supplemented fasting and sudden cardiac death is well reported, though the mechanism is still unknown.[62]

Long-term consequences on morbidity and mortality are also challenging with limited available evidence as most of the changes in blood biochemistry and cardiovascular risk factors that occur during *Ramadan* are rapidly reversed.[64]

CONCLUSION

Metabolic and hormonal changes generally support the safety of fasting in *Ramadan* for most diabetic patients: no worsening of diabetic control and no significant change in metabolic parameters were observed. Nevertheless, patients who choose to fast should be deliberately advised to modify their treatment during *Ramadan*. Subsequently, the patient should be 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 hypoglycemic agents, especially sulfonylureas, may well be necessary during *Ramadan* (cf. chapter 12: Incretin-based therapies and fasting during Ramadan).

Conflict of interest: none to declare.

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Chapter 5

Risk Stratification of People with Diabetes

Altamash Shaikh

Abstract

It is a challenge to the treating health care professional to understand and implement the treatment of diabetes in *Ramadan* so that it allows the patients to fast, without any disease-related or iatrogenic complications. Stratifying the patients has benefits in both ways to patients and physicians. Events can be minimized and complications prevented, with proper implementation of treatment and risk stratification. Clinical profile, disease complications, expertise and experience have led to the following categories: very high, high, moderate and low-risk. This chapter deals with various aspects and levels of risk encountered in diabetes in *Ramadan*.

INTRODUCTION

Ramadan is a month of fasting where Muslims all over the world fast, however, diabetic patients are exempt from fasting. But some patients insist to do so. It becomes a challenge to the treating health care professional to understand and implement the treatment of diabetes in such a way that it allows the fast to happen without any disease-related or iatrogenic complications. This chapter deals with the prioritizing the diabetic patients, at different risk levels based on various clinical factors, and how to solve them in an efficient manner.

WHY STRATIFY?

Although diabetic patients themselves know to some extent the changes involved in his/her daily routine during *Ramadan*, as health care professional we should do this in a systematic and simpler way.

Bringing down the dangers of disease or its complications stands the first in the list when we try to do this.

The recent EPIDIAR[1] study revealed that the risk may be high in some diabetes patients. Thus, it is necessary to stratify patients into various risk categories which will

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help both patients and physicians. At the level of patients it will prevent any acute complications, e.g. hypoglycemia, etc. At the level of health care professional it will, decrease the challenge that one would face while treating diabetes in the community.

Thus, stratifying diabetic patients who wish to fast in the month of *Ramadan* as per their profiles into various risks is beneficial. National recommendations state to risk stratify patients during *Ramadan* for uncomplicated fasting.[2]

WHAT ARE THE RISKS?

The risks involved in a diabetic patient while fasting are no different than another diabetic patient who may not fast due to various reasons. We need to understand these risks as they may occur more during fasting if not patients are not informed about such risks.

To list it out the major risks involved are **(Table 1)**:

- Hypoglycemia
- Hyperglycemia
- Diabetic ketoacidosis
- Dehydration and thrombosis.

HOW TO STRATIFY?

Although, there is lack of statistical figures and data from clinical or pharmacological studies, expert consensus is available for risk stratification. Depending on the patients clinical profile and the propensity of complications, patients can be grouped into the following categories,[3] inclusive of both Type 1 and Type 2 diabetes mellitus:

- Very high
- High
- Moderate
- Low-risk.

WHOM TO STRATIFY?

Let us see these various levels of risk stratification.

Very High-Risk

Depending on the activity levels, acuteness of problem, actual glucose levels, autoimmunity in diabetes the following patients fall into very high-risk group.

Table 1: Major risks associated with fasting in *Ramadan* with diabetes

Hypoglycemia
Hyperglycemia
Diabetic ketoacidosis
Dehydration and thrombosis

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Hypoglycemia

Hypoglycemia when requires third party assistance is severe, and can be prevented by stratification and proper counseling. In the EPIDIAR study, hypoglycemia was seen 7.5 times more in Type 2 diabetes and those with significant sudden lifestyle changes. Also, extreme changes in oral or insulin regimen just before *Ramadan* was a risk factor (*see* chapter on counseling the patient before *Ramadan* for details). Patients with hypoglycemia unawareness may be at the greatest risk for further complications. The following patients are high-risk group due to hypoglycemia:

- Severe hypoglycemia within the 3 months prior to *Ramadan*
- A history of recurrent hypoglycemia
- Hypoglycemia unawareness.

Hyperglycemia

High blood glucose or a episode of hyperosmolar hyperglycemic coma in the previous 3 months is detrimental to health for the patients willing to fast. Too much reduction in current treatment dosages of diabetes medication can lead in a hyperglycemic excursion. In the EPIDIAR study, hyperglycemia was 5 times more common in Type 2 diabetes. In clinical practice, it is observed that patients who indulge in large meals or sugary food items are known to have hyperglycemia and or diabetic ketoacidosis. The following are very high-risk group patients due to hyperglycemia:

- Sustained poor glycemic control
- Ketoacidosis within 3 months prior to *Ramadan*
- Hyperosmolar hyperglycemic coma within the previous 3 months.

Activity Levels

Patients doing labor work or hard work while fasting are at increased risk of dehydration and or thrombosis and need extra fluids to surmount these risks (*See* chapter on exercise and *Ramadan* for detail).

Acute Illness

It is advisable always for patients in this group to avoid fasting.[4] However, medical conditions with acute illness in this group are:

- Acute peptic ulcer
- Severe bronchial asthma, pulmonary tuberculosis
- Cancer
- Overt cardiovascular diseases—recent MI or sustained angina
- Hepatic dysfunction
- Severe infections.

Chronic Dialysis

Diabetic patients with established chronic kidney disease and on regular maintenance hemodialysis are at increased risk of plasma glucose level fluctuation, and hence are categorized into this risk group.

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Type 1 Diabetes Mellitus

Patients with Type 1 diabetes mellitus are more prone for both hypoglycemia and hyperglycemia. The chances hyperglycemia in Type 1 patients with or without diabetic ketoacidosis was three times more, which further increased if they were poorly controlled before *Ramadan*.[1] Patients in this group need extra care and costs, more risk for complications, and stratified as very high-risk.

High-Risk

Earlier moderate hyperglycemia (average blood glucose 150–300 mg/dL or A_{1C} 7.5–9.0 percent) was considered as high-risk stratified group for fasting in *Ramadan*, however with changes in availabilities in treatment modalities, this may not be so. Also, with control and better management of their comorbid conditions the additional risk factors may be reduced, thus further reducing the risk while fasting.

The following are stratified as high-risk group, mainly depending on presence of complications, modality of treatment and age of the patients:

Diabetic Complications and Treatment Related

Patients in this group have less chances of major complications as listed in **Table 1**, compared to very high-risk group. But these may be variable, if not controlled and maintained towards their target, may land up in acute problems. Whether deterioration in glomerular filtration or reduction in ejection fraction these need to be monitored carefully and stabilized before fasting in *Ramadan*. Fasting may cause dehydration and subsequent giddiness and or postural hypotension due to diabetic autonomic neuropathy. Also, gastroparesis may pose problems as there may be a mismatch between gastric emptying and the antihyperglycemic effect of treatment. The following are stratified as high-risk group patients in this subcategory:

- Patients with renal insufficiency
- Patients with advanced macrovascular complications—coronary artery disease, cerebrovascular disease word and severe retinopathy
- Patients with word autonomic neuropathy—gastroparesis and postural hypotension.[4]

Psychosocial Issues Related

It is noted in clinical practice that, patients living single/alone away from family[5] may be at a high-risk, for complications, whether on a oral regimen or on insulin injections. These may need more emphasis in clinics pertaining to all aspects of diabetes management for smooth eventless fasting.

Staying with ones own family is what we always prefer, hence family should also be considered while stratifying. Especially when concurrent drugs used for the patients affect mentation, this should be addressed to patients and their families. This also provides benefit in any avoidable complication. With the family into consideration, elderly care can be enhanced to a great extent, with diabetes and comorbidities. Following patients are the high-risk stratification as per the psychosocial issues into consideration:

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Table 2: Risk stratification in *Ramadan*
Very high-risk
Severe hypoglycemia within the 3 months prior to *Ramadan*
A history of recurrent hypoglycemia
Hypoglycemia unawareness
Sustained poor glycemic control ketoacidosis within 3 months prior to *Ramadan*
Type 1 diabetes
Acute illness
Hyperosmolar hyperglycemic coma within the previous 3 months
Performing intense physical labor
Pregnancy
Chronic dialysis
High-risk
Renal insufficiency
Advanced macrovascular complications
Living alone and treated with insulin or sulfonylureas
Patients with comorbid conditions that present additional risk factors
Old age with ill health
Treatment with drugs that may affect mentation
Moderate risk
Well-controlled diabetes treated with short-acting insulin secretagogues
Low-risk
Well-controlled diabetes treated with lifestyle therapy, metformin, acarbose, thiazolidinediones, and/or incretin-based therapies in otherwise healthy patients

- Patients living alone and treated with insulin or sulfonylureas
- Treatment with drugs that may affect mentation
- Elderly patients with ill health.

Moderate Risk

Diabetes patients treated with oral drugs like repaglinide or nateglinide which are short-acting and are well-controlled, generally have good glycemic stability. But if proper counseling is not done and advise not adhered they may be at moderate risk for complications.

Low-Risk

Diabetes patients who are well-controlled with lifestyle modification, and drugs with very low-risk of glycemic excursions like metformin, acarbose, thiazolidinediones,

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and/or incretin-based therapies (DPP4 inhibitors and GLP1 analogs) and also are otherwise healthy, have a low-risk when stratified for fasting in *Ramadan*.

SPECIAL SITUATION

Pregnancy and Lactation

Ladies with pregnancy or lactation may insist on fasting. Some group considers them in very high-risk group but some may not consider this so. (*See* chapter on Insulin in Type 2 diabetes for details).

BENEFITS OF RISK STRATIFICATION

- More emphasis on patients who are likely to develop complications
- Extra care to these patients avoids undue and unforeseen morbidity
- Better patient and disease management
- Eventless fasting.

SUMMARY

All diabetic patients need specialized and individualized care when fasting in *Ramadan*. This can be identified by prioritization and categorization of patients into various risk. Type 1 diabetics, elderly, autonomic neuropathy may present problems but can be tackled with setting the targets and family involvement. **Table 2** gives a list of factors that put the patient to high-risk of complications during the fasting period. Nearly every event can be minimized and complications prevented with proper implementation of treatment and risk stratification.

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Chapter 6

Beneficial Effects of Ramadan Fasting on Health

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Abstract

Numerous epidemiologic studies showed positive effects of *Ramadan* fasting on various parameters in diabetic and healthy subjects. *Ramadan* fasting induces favorable changes on metabolic parameters, reduces oxidative stress and inflammation, promotes cardiovascular benefits, improves brain function and boots immunity. Additionally, there is growing evidence that *Ramadan* fasting may have an anti-cancer role. It has also several spiritual, social and psychological benefits. *Ramadan* fasting would be an ideal recommendation for treatment of some metabolic and inflammatory diseases. It should be noted however that *Ramadan* benefits require some careful considerations such as necessity of an adequate pre-*Ramadan* medical assessment and education as well as conservation of a healthy dietary habits and adopting a healthy lifestyle. This paper summarizes current knowledge of beneficial effects of *Ramadan* fasting in diabetic and healthy subjects.

INTRODUCTION

Ramadan fasting is one of the five pillars of Islam. Muslims fast every day during this month from dawn to sunset and refrain from drinking and eating. The fasting period may vary depending on the geographical location of the country and the season of the year. Muslims with diabetes and other chronic diseases are exempted from fasting when fasting may lead to harmful consequences.[1] However, many patients insist on participating in *Ramadan* fasting. The EPIDIAR study from 13 Muslim countries reported that 42.8 percent of patients with Type 1 diabetes and 78.7 percent of patients with Type 2 diabetes fasted for at least 15 days during *Ramadan*.[2]

The health effects of Islamic *Ramadan* fasting have recently been the subject of scientific inquiry, with most of the research being performed in the last 2 decades. In 1996, an international conference was held in Casablanca, Morocco and about 50 papers were presented. The conclusions taken from this meeting were that *Ramadan* fasting had beneficial effects on health especially on some cardiometabolic parameters and digestive tract.[3] Later, numerous epidemiologic studies showed positive effects of *Ramadan* fasting on various parameters in healthy and unhealthy populations.

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This paper summarizes current knowledge of beneficial effects of *Ramadan* fasting in diabetic and healthy subjects.

BENEFICIAL RAMADAN FASTING EFFECTS ON DIABETIC PATIENTS

Globally, approximately 50 million Muslims with diabetes fast for 1 month each year.[4] There is growing evidence to suggest that; given appropriate pre-*Ramadan* medical assessment; fasting is safe for the majority of Type 2 diabetic patients. Healthy stable and well informed Type 1 diabetes are also able to fast safely.[5]

Glycemic Control

In properly educated, well-informed and motivated persons with diabetes, under good medical supervision, no significant aberrations in their blood glucose values were reported during *Ramadan* fasting. *Ramadan* can also lead to a reduction in serum fructosamine and HbA_{1c} levels in Type 2 diabetic patients.[6-8] In a recent study, systematic pre-*Ramadan* assessment with appropriate therapeutic adjustments and educational advice was associated with low glycemic variability in Type 2 diabetic subjects during *Ramadan*.[9] However, it should be noted that *Ramadan* fasting can lead to further deterioration in glycemic control in patients with previously poor control.[10]

Acute Diabetic Complications

In a recent prospective study, the authors showed that, with active glucose monitoring, therapeutic adjustment, dietary counseling and patient education, the majority of the diabetic patients did not have any serious acute complications during *Ramadan* (hypoglycemic episodes, diabetic ketoacidosis or hyperosmolar hyperglycemic state).[4]

Anthropometric Parameters

A review of the literature shows a controversy about weight changes in diabetic patients during *Ramadan*. Many studies reported a significant reduction in Type 2 diabetic patients' weight during *Ramadan*.[10,11] Some reports have shown no change or even a slight increase in weight of these patients.[12] Such discrepancies could be explained by the variations in lifestyle factors particularly those related to food intake and physical activity.[10,11]

Insulin Secretion and β-Cells Function

In a study conducted on streptozotocin-induced diabetic rats, intermittent fasting (IF) without caloric restriction improved glucose tolerance and enhanced β-cell mass.[13] In humans, there were reports about significant decrease in insulin and insulin resistance among Type 2 diabetic patients after *Ramadan* fasting.[8,14]

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Lipid Profile

Several studies among patients with Type 2 diabetes mellitus reported decreased total cholesterol (TC), triglyceride (TG), very-low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) as well as increased high-density lipoprotein cholesterol (HDL-C) levels after fasting in *Ramadan*.[15] The changes in lipid profile, however, may vary depending on the quality and quantity of food intake, and physical activity.[16]

Micro and Macro-Vascular Complications

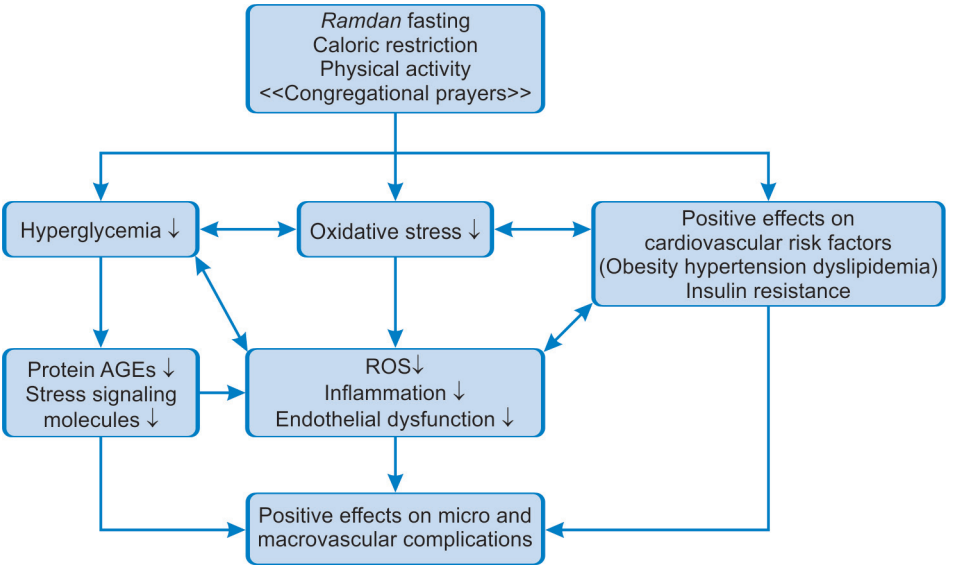
Using a mouse model, Tikoo et al. demonstrated nephroprotective effect of IF in diabetes by reducing oxidative stress and inducing favorable changes in the expression of some signaling molecules.[17] In humans, no studies related to the benefits of IF on diabetic micro and macrovascular complications are available. However, we would expect such benefits on based on the anti-inflammatory and antioxidative properties of *Ramadan* fasting as well as its positive effects on cardiovascular risk factors (*see* infra) **(Flow chart 1)**.

BENEFICIAL RAMADAN FASTING EFFECTS ON NONDIABETIC PATIENTS

Anthropometric Parameters

Several previous findings showed a significant decrease in body weight during *Ramadan*.[18,19] In normal nondiabetic individuals, an average weight loss of 1.7–3.8 kg

Flow chart 1: Suggested mechanisms for the beneficial effects of *Ramadan* fasting on micro- and macrovascular diabetic complications



Abbreviations: AGEs—Advanced glycation endproducts; ROS—Reactive oxygen species

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has been reported in different studies, the loss being greater in overweight persons.[20] *Ramadan* fasting could also induce a decrease in body fat percentage and waist circumference.[18] Interestingly, weight loss was reported even without any reduction in the total daily energy intake.[18]

Favorable effects of *Ramadan* fasting on different anthropometric parameters could be explained by the regulatory mechanisms that the body activates during fasting such as insulin hyposecretion and increased glucagon. These mechanisms favor a predominant lipolytic state, with a higher tendency to utilize fat rather than glucose as a source of energy, and hence a higher fat oxidation. Furthermore, part of the weight loss may be related to the negative fluid balance as water intake usually decreased during *Ramadan*.[18,21]

Fasting Blood Glucose

Some studies showed no significant changes in the serum level of glucose, while the result of some other reports showed higher or lower fasting blood glucose level after *Ramadan* fasting.[22] These controversies may be explained by different food habits, amount of calorie intake, the number of fasting days, period of daily fasting, time of sampling, genetic background and daily activity in different reports.[22]

Lipid Profile

Many studies showed that the values of TC, TG, VLDL-C, LDL-C, cholesterol/HDL and LDL/HDL ratio were significantly decreased and HDL-C increased significantly after *Ramadan* fasting in healthy, nondiabetic subjects.[23,24] Such beneficial effects were independent of taking statins and were maintained for at least 1 month after *Ramadan*.[25,26] Similar to diabetic patients, the changes in lipid parameters of healthy subjects may vary depending on the dietary habits and level of physical activity. Increased consumption during *Ramadan* of monounsaturated and polyunsaturated fatty acids as well as decreased consumption of saturated fatty acids were associated with favorable changes in lipid profile.[23]

Blood Pressure

It is well known that fasting is associated with catecholamine inhibition and reduced venous return, causing a decrease in the sympathetic tone, which leads to a decrease in blood pressure. In line with these hypotheses, many studies showed that *Ramadan* fasting led to significant decrease in systolic and diastolic blood pressure in normotensive as well as hypertensive patients.[18,27,28] Hypertensive patients may fast *Ramadan* safely if they continue to take their previous antihypertensive medications.[27]

Inflammation and Oxidative Stress

Recent data support the hypothesis that *Ramadan* fasting by healthy subjects can effectively reduce inflammatory processes as evidenced by significantly reduced levels of leukocytes and circulating proinflammatory cytokines such as IL (interleukin)-1β, IL-6, and the tumor necrosis factor-α (TNF-α).[18,28] Interestingly, this reduction in cytokine levels was documented even when caloric intake was not significantly

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restricted upon fasting.[18] Fasting during *Ramadan* leads also to a significant decrease in homocysteine concentrations, which may play a significant role in the development of atherosclerosis.[29]

Heat shock proteins (HSP) are ubiquitously synthesized in virtually all species and it is hypothesized that they might have beneficial health effects. Recent studies have identified circulating Hsp as an important mediator in inflammation.[30] A recent study involving 32 healthy men showed that *Ramadan* fasting increased serum Hsp along with an improvement in serum lipid profile.[31]

Oxidative stress can be defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidative defense mechanisms of the body. There is now considerable data to support a link between oxidative stress, cardiovascular tissue injury, cancers and ageing.[32] *Ramadan* fasting may alleviate oxidative stress; especially if accompanied with body weight and fat mass percentage reductions.[33,34] The ability of *Ramadan* fasting to reduce oxidative stress and the levels of proinflammatory cytokines upon fasting may drive a speculation that *Ramadan* fasting could have positive effects in patients who suffer from rheumatoid arthritis, a disease that had been reported to be characterized by an oxidative damage as well as an increased activity of the proinflammatory cytokines.[18,35]

Other Metabolic Parameters

Halberg et al. showed that IF (fasting every 2nd day for 20 hours for 15 days) increased whole body insulin-mediated glucose uptake in a sample of eight healthy men. In this study, insulin sensitivity was estimated by the euglycemic hyperinsulinemic clamp technique which is the gold method for measuring insulin action. There were also increases in circulating adiponectin; an adipocyte-specific hormone with potential insulin sensitizing effects. Interestingly, the body weight and the percent body fat were maintained stable throughout the intervention.[36]

Shariatpanahi et al. showed that the combined change in the number and timing of meals and portioning of the entire intake into only two meals per day may increase insulin sensitivity [estimated by reciprocal index of homeostasis model assessment of insulin resistance (1/HOMA-IR)] in healthy subjects with the metabolic syndrome even when the decrease in energy consumption is minimal.[11]

Ramadan Fasting and Cardiovascular Health

Acute Cardiovascular Events

There have been several studies of the incidence of vascular events during *Ramadan*, and the majority has concluded that there is not an increased rate of such events during *Ramadan*, either in patients with stable cardiac disease or in those with no previous history of cardiovascular diseases.[16,37,38]

Cardiovascular Diseases Risk

Ramadan fasting practice was found to give benefits against cardiovascular diseases among the patients with multiple cardiovascular risks factors. In a recent prospective observational study, the authors demonstrated that *Ramadan* fasting led to significant

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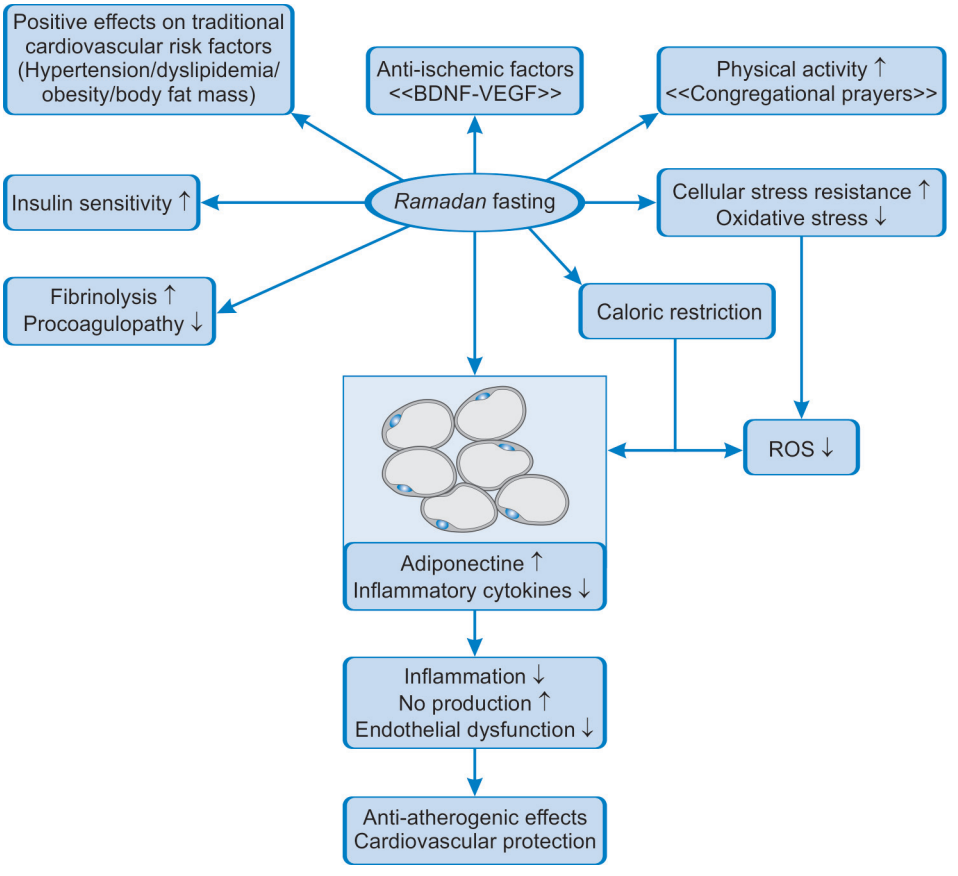
improvement in 10 years coronary heart disease risk (based on Framingham risk score) in a group of patients with at least one cardiovascular risk factor (including history of documented previous history of either coronary artery disease, metabolic syndrome or cerebrovascular disease in past 10 years).[22]

Mechanisms of cardiovascular protection of *Ramadan* fasting may include beneficial influences on either classic cardiovascular risk factors or the inflammatory status of the body. Fasting may also enhances synthesis of angiogenic, antiapoptotic and antiremodeling factors. In a rat model, Katare et al. aimed at evaluating the effect of IF on cellular and ventricular remodeling and long-term survival after chronic ischemic heart failure. They demonstrated that IF reduced ventricular fibrosis and hypertrophy; enhanced cardiac function; and improved the long-term survival after chronic heart failure. Interestingly, they showed that IF up-regulated the expression of angiogenic factors (VEGF) and increased the levels of brain-derived neurotrophic factor (BDNF) which is known with its anti-ischemic proprieties.[39] **Flow chart 2** illustrates suggested mechanisms for the cardioprotective effects of *Ramadan* fasting.

Flow chart 2: Suggested mechanisms for the cardioprotective effects of *Ramadan* fasting



Abbreviations: BDNF—Brain-derived neurotrophic factor; VEGF—Vascular endothelial growth factor; ROS—Reactive oxygen species; NO—Nitric oxide

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Digestive System

Fasting in *Ramadan* allows the digestive system to rest from the normal demands of processing and breaking down food, freeing up system resources to cleanse and purify the body of accumulated harmful dietary toxins, thereby allowing more effective healing and tissue repair. The liver also takes rest as it is the main factory of food metabolism. To achieve this benefit, Muslims should adhere to the tradition (*sunnah*) by abstaining from having too much food after breakfast. The Prophet Muhammad (peace be upon him) said, "The son-of-Adam never fills a bowl worse than his belly. Some bites are enough for man to prop his physique. Had he wished otherwise, then one third for his food, and one third for his drink, and one third for his breath". It is of benefit to the body that the break of fasting starts with some dates (as indicated in the Prophetic tradition). Dates are rich in glucose and fructose, which have a great caloric benefit especially for the brain, and are useful in raising the level of sugar gradually in blood, thus reducing the feeling of hunger and the need for large quantities of food.

Regarding the impact of *Ramadan* fasting on patients with gastrointestinal diseases, the findings have been heterogeneous. Mehrabian et al. showed that patients under proton pump inhibitors treatment can fast safely and will not face an increased risk of complications.[40] It has even been claimed that long-term hunger may contribute to healing of persistent ulcers by improving the control of stomach secretion.[41] Moreover, Tavakkoli et al. found no correlation between *Ramadan* fasting and the severity of inflammatory bowel diseases.[42]

Renal Function

There is a growing public belief that *Ramadan* fasting deteriorates kidney function in some patients. This seems to be not always true. A recent study showed that *Ramadan* fasting did not have adverse effects on renal function parameters; rather it improved these parameters.[43] Furthermore, several studies conducted on kidney transplant patients showed no significant changes in the serum values of creatinine, urinary protein excretion or glomerular filtration rate during fasting.[44] Renal protective effect of fasting may be explained by its antioxidative properties.[43] Fluid deprivation during fasting may cause volume contraction and moderate dehydration. The prophetic tradition mandates that *Suhur* (a meal before the dawn) be delayed and Iftar (the breakfast meal) be expedited, thus reducing the time period of dehydration as much as possible. The effect of *Ramadan* fasting on patients with renal impairment is still unclear, although findings of some studies have shown good tolerance and safety of fasting in these patients.[45]

Ramadan Fasting and Coagulation and Hemostatic Factors

Intermittent fasting may have beneficial effects on certain hemostatic markers and on coagulation status. Previous reports demonstrate that *Ramadan* fasting led to a decrease in dimer and fibrinogen levels as well as factor VII activity and plasminogen activator inhibitor Type-1 (PAI-1) in comparison to pre- and postfasting levels.[46-48] *Ramadan* fasting may also increase bleeding and coagulation time and cause *in vitro* decrease in the platelet responses of different aggregating agents (ADP, adrenaline and collagen).[49]

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Ramadan Fasting and Immunity

Fasting may boost the immune system via several mechanisms, such as by elevating macrophage activity; improving the cell-mediated immune response; increasing immunoglobulin levels; increasing neutrophil bactericidal activity; and enhancing natural killer cell activity.[50,51] Furthermore, catabolism increases because of cellular breakdown, leading to elevated macrophage activity.[52] Finally, the amplification of the 24-hour pattern of growth hormone secretion during fasting may have a positive role in strengthening the immune system.[53]

Ramadan Fasting and Fertility

Ramadan fasting did not have any adverse effect on the fertility of healthy men. Fasting could even improve the total sperm count, the gonadotropin hormone concentrations and the testosterone level in fertile males. Furthermore, fasting may have some effect on oligozoospermics. One study demonstrated beneficial effect of the *Ramadan* fasting on spermatogenesis through changes in the hypothalamo-pituitary-testicular axis and a direct effect on the two testicles.[54]

Ramadan Fasting and Brain Health

Calorie restriction; elicited either by daily reduction of energy intake or by IF; results in enhancement of synaptic plasticity and promotion of the survival of neurons. Neuroprotective mechanisms of fasting may include antioxidant and anti-inflammatory properties of fasting, decrease in activity of proapoptotic factors, increase in antiaging proteins, and increase in levels of neuroprotective factors such as brain-derived neurotrophic factor (BDNF). Low levels of BDNF are linked to dementia, Alzheimer's, memory loss and other brain processing problems. IF regimens and caloric restriction have been demonstrated to attenuate the risk of neurodegenerative disorders (such as Alzheimer's or Parkinson's). Interestingly, ketone bodies; produced during fasting; may exert additional neuroprotective activity, beyond their antiepileptogenic properties.[55-59] *Ramadan* fasting may also increase brain availability of serotonin, endogenous opioïd and endocannabinoids, leading to positive effects on mental disorders such as depression.[60]

Flow chart 3 illustrates suggested mechanisms for the positive effects of *Ramadan* fasting on brain function and mental health.

Ramadan Fasting and Cancer Risk

In animal models, IF and caloric restriction inhibit several cellular pathways that can lead to cancer.[61,62] Interestingly, minimal caloric restriction in conjunction with intermittent feeding may be sufficient to achieve positive results in term of the reduction in cancer risk. In a study conducted in mice models, the authors showed that healthy mice given only 5 percent fewer calories than mice allowed to eat freely experienced a significant reduction in cell proliferation in several tissues, considered an indicator for cancer risk. The authors suggested that a 5 percent reduction in

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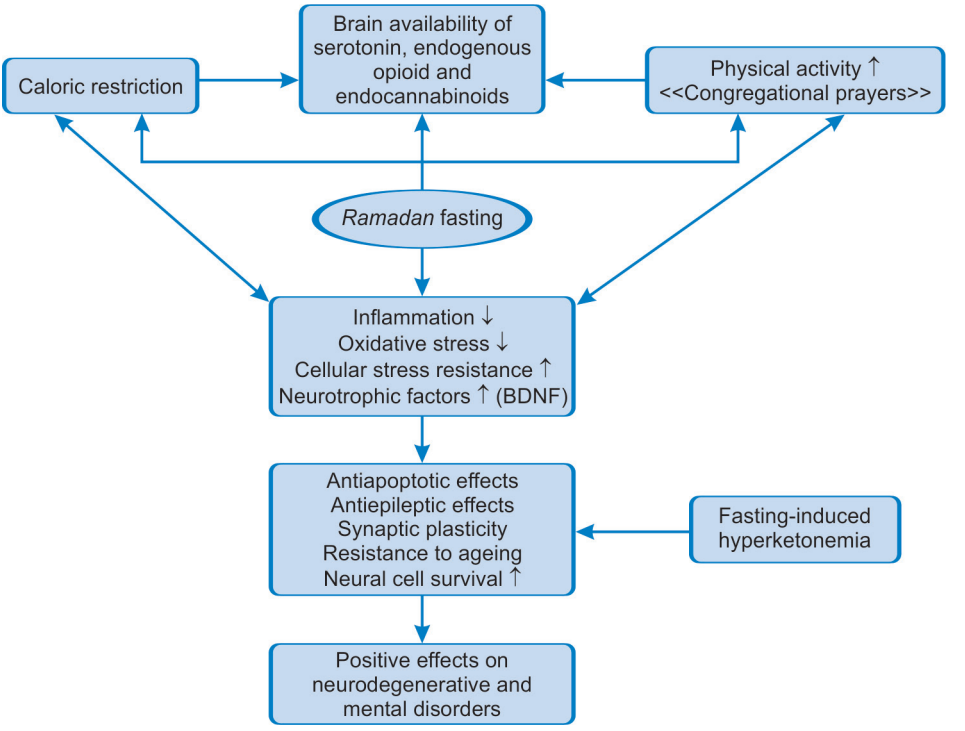
Flow chart 3: Suggested mechanisms for the positive effects of *Ramadan* fasting on brain function and mental health



Abbreviations: BDNF—Brain-derived neurotrophic factor

calories would be the equivalent of reducing about 100 calories a day in a human diet.[63] In another animal study, a group of researchers found that IF was able to delay the progression of a variety of tumors and to potentiate chemotherapy, improving cancer-free survival.[64]

In humans, there are no firm conclusions about the relation between IF and cancer risk. However, we would expect anti-cancer role of IF and caloric restriction; as they may modulate signaling molecules involved in carcinogenesis **(Flow chart 4).**

Ramadan Fasting and Nutritional Status

Islamic fasting is different from other types of fasting. There is no malnutrition or inadequate calorie intake during *Ramadan* as there is no restriction on the type or amount of food intake during *Iftaar* or *Sahur*. Several studies indicate that dietary changes pertaining to caloric intake, as well as macro- and micronutrient intake, may not differ over the period of *Ramadan*.[33,65] The lack of such differences negates the common belief that Muslims tend to overcompensate in terms of food intake during this fasting month.

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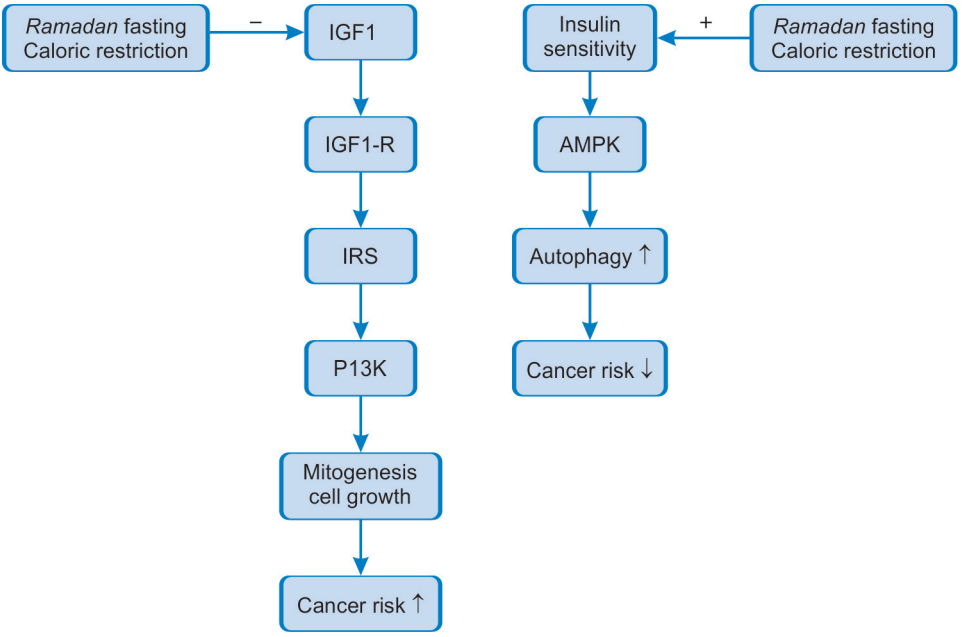
Flow chart 4: Suggested mechanisms for the anticancer effect of *Ramadan* fasting



Abbreviations: IGF-1—Insulin-like growth factor 1; IGF1-R—Insulin like growth factor 1 receptor; IRS—Insulin receptor substrate; PI3K—Phosphatidylinositol 3-kinase; AMPK:AMP—Activated protein kinase

Physical Activity in Ramadan

Whilst such possibilities of reducing food intake may vary from person to person, the congregational night prayers of the month of *Ramadan* seem to be universally adopted. These prayers include; "*Tarawih*" that is performed approximately 1–2 hours after sunset (depending on time zone); unlimited number of nonobligatory "*Nafl*" prayers; and "*Tahajud*" that is performed after midnight at least in the last 10 days, may, arguably, constitute appropriate level of physical activity equivalent to moderate physical activity.[23]

Psychological Effects of Ramadan Fasting

Psychological effects of *Ramadan* fasting are also well observed by the description of people who fast. *Ramadan* fasting encompasses direction to develop spiritual, moral and social values. Muslims undergoing spiritual fasting describe a feeling of inner peace and tranquility. The Prophet Muhammad (peace be upon him) has advised them "If one slanders you or aggresses against you, tell them I am fasting". Thus, personal hostility during the month of *Ramadan* is minimal. In an investigation in Jordan, a significant reduction of parasuicidal cases was noted during the month of *Ramadan*.[66] Muslims believe that fasting is more than abstaining from food and drink. Fasting also includes abstaining from falsehood in words or deeds, and from arguing, fighting, and having lustful thoughts. Therefore, fasting strengthens control

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of impulses and helps develop good behavior. This purification of body and soul harmonizes the inner and outer spheres of an individual.[20]

Muslims encouraged being doing more acts of piety, prayers, charity or reading the *Quran*. Recitation of the *Quran* not only produces a tranquility of heart and mind, but improves the memory. According to a study by Dr Ahmed El Kadi, of Akber Clinic in Panama, Florida, the recitation of or listening to the *Quran* have positive effects on the body, the heart and the mind, irrespective of whether the listener was a Muslim or non-Muslim, Arab or non-Arab.[67]

Muslims cannot consume alcohol and use smoke in any form during the month of *Ramadan*. Those people who are addicted to such habits, it is the best time for them to quit these habits, which are spoiling their health and wasting their money. Since they are restraining themselves from these habits for one month, they should continue to do so, for the rest of their life. In the United Kingdom, the *Ramadan* model has been used by various health departments and organizations to reduce cigarette smoking among the masses, especially among Africans and Asians.[68]

CONCLUSION

Ramadan fasting has numerous benefits on diabetic and healthy subjects. It induces favorable changes on metabolic parameters, reduces oxidative stress and inflammation, promotes cardiovascular benefits, improves brain function and boots immunity. *Ramadan* fasting has also spiritual, social and psychological benefits. *Ramadan* fasting would be an ideal recommendation for treatment of some metabolic and inflammatory diseases. It should be noted however that *Ramadan* benefits require some careful considerations benefits such as necessity of an adequate pre-*Ramadan* medical assessment and education as well as conservation of a healthy dietary habits and adopting a healthy lifestyle.

Conflict of interest: None to declare.

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Section 2

Nonpharmacological Management

CHAPTERS

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Chapter 7

Monitoring Diabetes Patient during Ramadan

Abdul Jabbar

Abstract

The development of tools to monitor diabetes treatments has been one of the important landmarks in the management of diabetes mellitus and has revolutionized diabetes care with significantly influence on disease-outcome. Glycosylated hemoglobin (HbA_{1c}) and Self Monitoring of Blood Glucose (SMBG) are the 2 most widely studied and cited monitoring tools. HbA_{1c} reflects overall control and risk of complications whereas SMBG charts the pattern of daily glucose profile. On the other hand SMBG is the main tool for day-to-day care and decision making and should be an essential component and education before *Ramadan*; physician could avail this important spiritual occasion to make their patients learn how to monitor their glucose and use the information to better manage their diabetes not just during *Ramadan* but well beyond to achieve the target goals.

INTRODUCTION

The three important milestones in the management of diabetes mellitus which have revolutionized the diabetes care and have significantly influenced the outcome are the discovery of insulin in 1921, the development of oral therapies in 1950 and the development of tools to monitor diabetes treatments.

The two most widely studied and cited monitoring tools are glycosylated hemoglobin (HbA_{1c}) and self-monitoring of blood glucose (SMBG). HbA_{1c} reflects overall control and risk of complications whereas SMBG charts the pattern of daily glucose profile.

It is crucial to differentiate between checking blood glucose versus monitoring as SMBG. Patients cannot monitor their glucose without checking, but unfortunately patients often check their glucose without truly monitoring it which implies that they must understand what to do with the glucose reading and what measures to take.

In patients with diabetes who intend to fast during *Ramadan*, SMBG is the important tool as during this month a long established treatment regimen, including medications, physical activity and diet plan is going to change for fasting during

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Ramadan and without proper glucose monitoring; even the best of patients or physicians cannot decide the changes in management plan necessary. Hence it is important that in pre-*Ramadan* patient education session, they are educated so they acquire the knowledge and skills to stratify their risk for fasting and to adjust their therapy so as to keep the blood glucose in the desired range without hypo- or hyperglycemia.

The landmark epidemiological diabetes in *Ramadan* study, EPIDIAR 2001,[1] has shown that fasting during *Ramadan* exposes these patients to an increased risk of hypoglycemia, hyperglycemia and may even lead to diabetes ketoacidosis (DKA) and nonketotic hyperosmolar hyperglycemia (NKHH). As far as SMBG in Type 2 diabetes mellitus (T2DM) is concerned, the findings are not consistent regarding its usefulness in patients who are not on insulin in outside of *Ramadan*[2] but like pregnancy in diabetes, *Ramadan* provides a good opportunity to educate and motivate patients about the utility of this tool and they are willing to learn for their aspirations to fast during this holy month. In a recent systemic review by Clar et al. they concluded against the clinical effectiveness of SMBG in improving glycemic control in people with T2DM on oral agents and stated it to be not cost-effective. On the other hand, the fasting during *Ramadan* stresses the recommendations from International Diabetes Federation (IDF) guidelines on SMBG[3] in noninsulin treated T2DM. The guidelines summarizes that "SMBG should be used only when patient with diabetes have the knowledge skills and willingness to incorporate SMBG monitoring and therapy adjustment into their diabetes care plan in order to attain agreed treatment goals". Nevertheless, in some studies, SMBG has demonstrated the efficacy in improving outcomes. Even before the modern convenient and easy to use glucometers became available, Evan et al.[4] published his findings that SMBG is useful and specifically that increasing the frequency of SMBG was linearly correlated with reductions in HbA_{1c} among Type 1 diabetes mellitus (T1DM) patients. Among patients with T2DM, a higher frequency of SMBG was associated with better glycemic control in those who were on insulin and were able to adjust their regimen.[5]

Ramadan Education and Awareness in Diabetes (READ) program[6] provided structured education to one group comprising education about physical activity, meal planning, glucose monitoring, hypoglycemia, dosage and timing of medications and showed significant decrease in the total number of hypoglycemic events.

The frequency of glucose monitoring is not well defined or evidence based although most experts agree that T1DM patients should monitor their glucose at least four times a day, most commonly fasting, before each meal and bedtime. The new insights into the importance of postprandial hyperglycemia also emphasizes the need for post-meal glucose monitoring is equally if not more important. For patients with T2DM, frequency of monitoring varies, depending on the medication and whether the patients are adjusting their dose or have achieved their targets. As patients with T2DM usually do not adhere to frequent blood glucose monitoring, it has been recommended that people with diabetes who use insulin should perform SMBG at least four times per week, of which at least two should be fasting and two post-meal.[4]

As per IDF guidelines, there are situations in which short term focused SMBG may be beneficial even to noninsulin treated T2DM patients. Although *Ramadan*

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and fasting are not mentioned specifically in the guidelines, because of the risk of hypoglycemia, this recommendation should be implemented in this setting till we have more evidence available. Similarly meal-based SMBG is also very important in helping patients understand the impact of postprandial hyperglycemia particularly seen after rich *iftar* dinner during *Ramadan*.[7]

In the EPIDIAR study,[1] it was reported that only 67 percent of T1DM patients and 37 percent T2DM patients were monitoring their blood glucose. The most commonly referenced recommendation for management of diabetes during *Ramadan*[8] makes it essential that patients intending to fast during *Ramadan* should have the means to monitor their blood glucose levels multiple times daily. Although the recommendations are based on expert opinion mostly, most diabetologists managing these patients recognize that SMBG is significantly helpful in decision making about dose adjustments for both the physicians and self adjusting patients. It is also recommended that importance of SMBG should be an essentials component of structured education program before *Ramadan* in all centers and clinics managing these patients.

There is little published data about the timings and frequency of SMBG in the context of *Ramadan*. In general, it is agreed that pre-*Iftar* (before the sunset meal) blood glucose represents fasting blood sugar outside *Ramadan*. It is important that patients in particular are educated that in religion, pricking and drawing blood for SMBG during the fast does not break or violate the fast otherwise due to this misunderstanding, they do not check blood glucose till after breaking their fast (*iftar*). Guideline published by Azizi et al.[9] suggest that SMBG should be performed just before the sunset meal and 2–3 hours after that iftar meal. It could also be performed before the *Suhur* meal to adjust the insulin dose in some patients. The recent *Ramadan* Prospective Diabetes Study[10] used a 10 point monitoring schedule in their study, with 2 points on each day for 5 consecutive days.

We know that in studies and clinical trials due to close observation and supervision, patients are more likely to adhere and those who do not are excluded from analysis, but in real life situation to expect such compliance is usually not rewarded. In our center, we advise patients to agree to monitor for first three days to get a feel of glucose profile and adjust their dose. They are educated the check their blood glucose on getting up in the morning and around noon time to first to assess the risk of hypoglycemia. If on these points their blood glucose is more than 100 mg/dL, in general the risk of hypoglycemia is low but still varies with their medication. Then again they should check pre-*Iftar* and should be above 80 as expected for fasting blood sugar outside of *Ramadan* after 8–12 hours overnight fast. If the first 2 points are less than 100 mg/dL, they should be watchful and if less than 80 mg/dL, they should break the fast and adjust their *Suhur* dose for next day. Once this has been taken care of, they should check their *post-Iftar* (main sunset meal) to assess the risk of hyperglycemia and adjust the Iftar dose of medications. Pre-*suhur* SMBG is also useful to assess risk of nocturnal hypoglycemia and adjust dose at *suhur*. Patients should be given a *Ramadan* logbook to keep a record of SMBG, with *Ramadan* point reference exemplified in **Figure 1**.

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Week days	Before *suhur*	Insulin *suhur* injection	At morning	Mid-day	Before *iftar*	Insulin *iftar* injection	1-2 hours after *iftar*	2-3 hours after *iftar*	Insulin injection	Before bed if any	During night	Notes
Saturday												
Sunday												
Monday												
Tuesday												
Wednesday												
Thursday												
Friday												

Please note:
Not necessary to check at all points. Discuss with your doctor or diabetes educator?
Checking at morning and midday to assess risk of hypoglycemia during the fast: More than100 mg/dL preferable
Checking before iftar is equivalent to fasting in normal days
Check 1-2 or 2-3 hours after iftar depending on bigger meal, assesses risk of high blood sugar: Less than 160 mg/dL preferred.

If at any time your blood glucose is less than 70 mg/dL (3.8 mmol/L)... You should break the fast.

Figure 1: *Ramadan* logbook

GLYCOSYLATED HEMOGLOBIN

The use of glycosylated hemoglobin (HbA_{1c}) has become a standard for assessing long-term glycemic control and most studies have correlated HbA_{1c} level with the risk of developing complications. But due to average red blood cell life of being 120 days, and as the glycosylation occurs continuously, the HbA_{1c} measurement represents predominantly the level of control during the previous 2 months period. In the setting of *Ramadan*, it may be a useful monitoring tool for retrospective assessment of worsening or improvement in diabetes control but is rarely useful in helping the management during *Ramadan*.

Clinical trials studying new therapies may still use it to document improvement or non-worsening of glycemic control during *Ramadan* which is very common due to over-eating and less strict glycemic control to avoid hypoglycemia during the fast.

FRUCTOSAMINE

The main advantage of fructosamine is that it is a measure of blood glucose control over the past 2–3 weeks and hence could give more precise information about glycemic control in the preceding *Ramadan*. Although a better tool compared to HbA_{1c} in relation to *Ramadan* and a useful tool for clinical trials to assess intervention around *Ramadan*, its value in everyday care is not established.

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1,5-Anhydroglucitol (1,5-AG) Hyperglycemia Marker

1,5-Anhydroglucitol (1,5-AG) hyperglycemia marker is a new glucose monitoring tool to assess glucose peaks and may be useful to assess glycemic peaks after heavy *iftar* meals. Although there are no studies during *Ramadan*, it has been reported that A_{1c} average glucose levels can vary widely between patients, and fasting and infrequent finger stick glucoses often miss glucose peaks and their durations. Nearly 40 percent of diabetes patients in "good control" have significant glucose variability.[11] The test measures a glucose-like sugar called 1,5-Anhydroglucitol (1,5-AG) found in most foods. When blood glucose is well-controlled, most 1,5-AG is reabsorbed in the renal proximal tubules, so the serum 1,5-AG level stays high. People without diabetes have median 1,5-AG values above 20 μg/mL. When hyperglycemia occurs, excess glucose blocks reabsorption of 1,5-AG and it is excreted in the urine. Every time blood glucose spikes above 180 mg/dL, the body loses 1,5-AG. The more frequent the glucose spikes, the lower the 1,5-AG (GlycoMark) result will typically be.[12] In Summary, glucose monitoring is one of the important milestones in the management of diabetes and its importance is all the more important in the setting of fasting during *Ramadan*. SMBG is the main tool for day to day care and decision making which should be an essential component and education before *Ramadan* and patient and physician could avail this important spiritual occasion to make patients learn how to monitor their glucose and use the information to better manage their diabetes which could continue well beyond *Ramadan* to achieve the target goals.

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Chapter 8

Nutrition Recommendations for Persons with Diabetes during Ramadan

Sarita Bajaj

Abstract

Ramadan the sacred month of Islam, dutifully observed by all the adult Muslims. Sawn is one of the five pillars of Islam, where the individual is required to keep fast from dawn to dusk every day of the month, when they are not allowed to drink or eat anything, even oral medications are not permissible. Individuals are allowed to have a morning meal before sunrise, i.e. *Suhur* and a meal after evening, i.e. *Iftar*.

This period of fasting, however, can cause serious complications in people with chronic illnesses like diabetes. In fact the holy Quran exempts such people from keeping fast. But because of the strong faith and conviction, despite all contraindication, people sometimes refuse to do so. With the rising prevalence of diabetes because of the changing lifestyle, management of diabetes during this period of fasting has become a subject demanding singular consideration. The fundamental aspects of management include medical counseling, nutrition and readjustment of treatment regimen. This articles attempts to give a comprehensive protocol for the management of diabetics observing fast during the period of *Ramadan*.

INTRODUCTION

Ramadan is the holy month of Islam, it is observed in the 9th month according to the Islamic calendar. It lasts from 28–30 days according to the season. The time of the month of *Ramadan* is variable as it is observed according to the lunar calendar. It is the time when the revelation of the Quran was bestowed upon men through the holy man prophet Muhammad. It is obligatory on part of all adult Muslims to observe fast during the whole month devoting themselves to the almighty.

Fasting, i.e. swam has to be observed each day of the month of *Ramadan*, lasting from dawn to sunset. Fasting is one of the five pillars of Islam, which include:

- Announcement of faith
- *Swam*, i.e. fasting
- *Zakaat*, i.e. charity, the right of the poor to the wealth of financially able
- *Salaat*, i.e. praying five times a day
- *Hajj*, i.e. once in a lifetime pilgrimage to Mecca.

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Although it is obligatory on part of all adult Muslims to observe fast during the month of *Ramadan*, but there are certain exemptions which are as follows:

- People suffering from chronic illnesses
- Pregnancy
- Menstruation
- Travel.

HOW THE FAST IS OBSERVED

Fasting is done from dawn to dusk. Each day before dawn, Muslims observe a prefast meal called *Suhur*. At sunset, families hasten for the fast-breaking meal known as *Iftar*.

DIABETES AND FASTING DURING RAMADAN

It is estimated that there are around 1.5 billion Muslims worldwide—up to 25 percent of the world's population. The population-based epidemiology of diabetes and *Ramadan* (EPIDIAR) study (involving 12,243 people with diabetes living in 13 Islamic countries) found that about 43 percent of people with Type 1 diabetes and 79 percent of people with Type 2 diabetes fast during *Ramadan*.[1] The prevalence of diabetes is on the rise because of the changing lifestyle and; therefore; it becomes necessary to pay special attention to the management of diabetics during *Ramadan*.

THE PHYSIOLOGICAL STATE OF DIABETICS DURING RAMADAN[2]

Fasting leads to decrease in the circulating glucose levels and a concomitant decrease in the secretion of insulin. Rise in the levels of counter regulatory hormones, i.e. glucagon and catecholamines stimulates glycogenenolysis and gluconeogenesis thereby maintaining glucose concentrations in the physiological range. In patients with diabetes, however, insulin secretion is altered by the underlying disease and the various pharmacological agents designed to alter insulin secretion. In patients with Type 1 diabetes, glucagon secretion may fail to increase appropriately in response to hypoglycemia. Epinephrine secretion is also defective in some patients with Type 1 diabetes due to a combination of autonomic neuropathy and defects associated with recurrent hypoglycemia. In patients with severe insulin deficiency, a prolonged fast in the absence of adequate insulin can lead to excessive glycogen breakdown and increased gluconeogenesis and ketogenesis, leading to hyperglycemia and ketoacidosis. Patients with Type 2 diabetes may suffer similar perturbations in response to a prolonged fast; however, ketoacidosis is uncommon, and the severity of hyperglycemia depends on the extent of insulin-resistance and/or deficiency. Fasting by diabetic patient can lead to several acute complications like hypoglycemia, hyperglycemia, diabetic ketoacidosis, dehydration and thrombosis. Nutritional recommendations are designed to minimize the negative impact of fasting on metabolism **(Figure 1)**.

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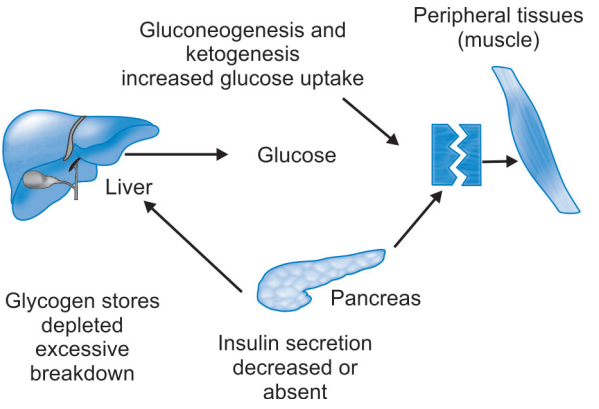

Figure 1: Pathophysiology of fasting in diabetes

EFFECT OF FASTING ON VARIOUS METABOLIC PARAMETERS IN DIABETICS

Variations of Blood Glucose

During fasting in normal persons it has been found that a slight decrease in serum glucose from 3.9 mmol–3.3 mmol (60 mg/dL–70 mg/dL) occurs a few hours after fasting has begun. However, the reduction in serum glucose ceases due to the increased gluconeogenesis in the liver. This occurs because of a decrease in insulin concentration and a rise in glucagon and sympathetic activity.[2]

On the other hand in most diabetic patients significant change in their glucose control.[3] In a few studies where variations of blood glucose from prefasting levels were noted, it was suggested that these could be due to variation in the amount or type of food, physical activity, or irregular medicine taking. However, in most cases, no episode of acute complications (severe hypoglycemic or hyperglycemic) occurred in patients under medical management.[4,5]

HbA_{1c} Levels and Fructosamine Levels

Glycosylated hemoglobin gives an idea about the blood glucose control in the past 6–8 weeks whereas as fructosamine, i.e. glycated albumin helps us to assess blood sugar control in the past 2–3 weeks. During *Ramadan* HbA_{1c} showed no significant changes in diabetics in several studies.[6]

Body Weight

During fasting it has been noted that there is a decreased physical activity and a tendency to overeat when the fast is broken. During *Ramadan* more dishes and refined foods are prepared than other days. This may lead to increased food intake. It

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is also thought that patients with the fear of hypoglycemia avoid exercising leading to minimal or no decrease in body weight or even increase in body weight despite the fast. This controversy in body weights has been noted when a review of the literature on weight changes in diabetics was done. In normal persons different trends in changes in body weight are also noted during *Ramadan*. A study by Frost and Pirani, where energy intake was significantly higher during *Ramadan* than after *Ramadan* (3,680 kcal/day vs. 2,425 kcal/day) revealed a mean weight increase from 58.9 kg to 60.3 kg at the end of *Ramadan*.[7] In both normal and diabetic population, especially in overweight diabetics, it seems that regulation of food intake and physical activity is important to attain desirable weights during and after *Ramadan*.

Lipid Metabolism

In Islam there is no restriction on the quantity or type of food after opening fast and this may contribute to the differences noticed in lipid profiles. In both normal persons and diabetics there have been conflicting results on the effect of dietary fat on changes in blood cholesterol levels.

Patients with Type 2 or Type 1 diabetes mostly show no change or slight decreases in cholesterol and triglycerides.

Like in healthy persons, several studies have reported increases in high-density lipoprotein (HDL) cholesterol in diabetics during *Ramadan*.[8,9] One report points to an increase in low-density lipoprotein (LDL) cholesterol and a decrease in HDL-cholesterol. The differences in the results could be explained by the lack of standardizing energy intake and physical activity, which could have an effect on the lipid metabolism

A review by Nomani[10] has suggested that when energy is limited, a dietary fat increase from 30 percent–36 percent favors a reduced breakdown of body protein including labile LDL cholesterol receptors that are protein in nature.

There is an increase in blood cholesterol levels with increasing or decreasing weight from normal weight levels. During *Ramadan*, no significant difference was noticed in blood cholesterol levels before and after fasting period when there was no significant difference in body weight either.

Uric Acid[11]

Several studies have reported non-significant increases in urea and uric acid concentrations during *Ramadan*. Increase in uric acid correlated positively with weight loss. Uric acid is formed as a product from purine metabolism and during *Ramadan* with weight loss it is postulated that this factor and the concomitant dehydration while fasting may lead to raised uric acid levels.

PRE-RAMADAN CONSIDERATIONS IN DIABETICS

- Assessment of the metabolic control
- Assessment of any comorbidities or intercurrent illness
- Formulating a diet protocol

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- Adjustment of the drug regimen (shifting from a long-acting drug to short acting drug regimen to prevent hypoglycemic episodes)
- Encouraging physical exercise
- Educating about the danger signs and risk factors associated with hypoglycemia, dehydration and thrombosis.

COMPLICATIONS THAT MIGHT BE ASSOCIATED WITH FASTING IN DIABETICS

Fasting in diabetics with deranged blood sugar levels can be associated with various risks that include hyperglycemia, hypoglycemia, diabetic ketoacidosis and thrombosis.

Hypoglycemia

Reduced food intake is a well-known indicator for developing hypoglycemia and therefore is quite common during *Ramadan*. Approximately 4 percent of deaths may occur because of hypoglycemia during this period. EPIDIAR study indicated 4.7 fold increase in incidence of hypoglycemia in Type 1 diabetes and 7.5-fold increase in Type 2 diabetes during *Ramadan*.

Hypoglycemia is defined as blood sugar levels below 70 mg percent. If not managed promptly it can be fatal. It can be easily identified if a high-risk behavior is present such as being discussed, i.e. fasting in diabetics and can also be easily managed bedside till further assistance arrives by the lay man themselves. Identification of the risk factor and relating it to symptomatology can be life-saving. Thereby it is important to appraise the diabetic patients and their family members about the symptoms when they should suspect hypoglycemia.

Symptoms associated with hypoglycemia:

- Feeling hungry
- Tingling of the lips
- Trembling or shakiness
- Blurred vision
- Profuse sweating
- Difficulty in concentration
- Anxiety or irritability
- Vagueness or confusions
- Altered sensorium
- Palpitation
- Seizure
- Loss of consciousness
- Coma.

Hyperglycemias

EPIDIAR study indicated a five-fold increase in the incidence of hyperglycemia requiring hospitalization during *Ramadan* fasting.[1] This can be attributed to excessive

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lowering of the glucose lowering medications as well as excessive food intake post-fasting period.

Hyperglycemia is defined as blood glucose level more than 300 mg percent.

Symptoms pertaining to hyperglycemia:
- Weight loss
- Headache
- Fatigue
- Loss of concentration
- Increased thirst
- Frequent urination.

Diabetic Ketoacidosis

Patients with high blood glucose levels before fasting are at increased risk for developing diabetic ketoacidosis. It is a medical emergency which can prove fatal and has to be aggressively treated.

Symptoms associated with diabetic ketoacidosis:
- Nausea and vomiting
- Excessive thirst
- Frequent micturition
- Abdominal pain which can be mild to severe in intensity
- Shallow and fast respiration, i.e. kussmauls breathing
- Lethargy
- Altered sensorium
- Loss of consciousness and coma.

Dehydration and Thrombosis

Reduced intake of fluids accompanied by hard labor can lead to excessive dehydration. Increased frequency of micturition due to hyperglycemia can exacerbate the problem. This dehydration can lead to increased risk of thrombosis already prone patients.

Symptoms of dehydration include:
- Dry mouth
- Muscle cramps
- Nausea
- Vomiting
- Palpitations
- Thread pulse
- Giddiness
- Sunken eyes
- Dry tongue and skin.

Symptoms suggestive of thrombosis:
- Pain or swelling at the blood clot site
- Severe ache in the affected area like lower limb thrombosis

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- Prominent veins, i.e. engorgement of veins
- Itchy skin
- Rash
- Warm skin
- Pain on movement of the affected limb which subsides on rest, i.e. intermittent claudication.

RISK STRATIFICATION OF PATIENTS WITH DIABETES DURING RAMADAN[12]

Patients at High Risk

- Those with severe and recurrent episodes of hypoglycemia and unawareness
- Those with poor glycemic control
- Those with ketoacidosis in the three months before *Ramadan*
- Those who experience hyperosmolar hyperglycemic coma within the three months before *Ramadan*
- Those with acute illness
- Those who perform intense physical labor
- Pregnant women
- Those with comorbidities such as advanced macro vascular complications, renal disease on dialysis, cognitive dysfunction, uncontrolled epilepsy (particularly precipitated by hypoglycemia).

Moderate Risk

Well-controlled patients treated with short acting insulin secretagogue, sulfonylurea, 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.

MANAGEMENT OF DIABETICS DURING RAMADAN

First and foremost all diabetics should be restrained from observing fast during *Ramadan* as they are already exempted from fasting according to Quran also. But owing to the conviction and faith of people in their religion it is extremely difficult to make them understand. Here comes the very important aspect of management of diabetics during *Ramadan* and as already discussed earlier due to the steady rise in the prevalence of diabetes this becomes a matter of great concern.

Medical Counseling

Diabetics who intend to keep fast during the month of *Ramadan* shall visit their family physician or local practitioner at least a month before for the complete assessment of

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the general condition of the patient as well as to assess the degree of diabetic control by the patient in the past few months. The physician should also determine if any comorbities are present or not.

This would help the physician to stratify the patient according to the risk factors present.

Physician should duly forewarn the concerned individual about the complications associated and restrain them from observing the fast.

Dietary Advice

- The standard guidelines recommended by the American Diabetes Association have to be followed even during fasting which includes:[13]
- Hypocaloric diet that is low fat or low carbohydrate
- Minimal trans-fat consumption
- Monitoring the carbohydrtaes intake with regards to calorie intake
- Glycemic index reflects how consumption of a particular food can affect blood sugar levels
- Routine supplements of vitamins, antioxidants are not required
- The dietary goals recommended by various expert committees of WHO shall be also followed, i.e.
  - Dietary fat shall be limited to approximately 15–30 percent of the total daily intake
  - Saturated fats should not contribute more than 7 percent of the total energy intake; unsaturated fat should be substituted for the remaining of the fat requirement
  - Complex carbohydrate diet shall be taken constituting approximately 55–60 percent of the total dietary intake
  - Excessive consumption of refined carbohydrate such as *paratha*, *puri*, *samosas*, *chevera*, *pakodas*, *kebabs*, etc. should be avoided; small amount carbohydrate rich in natural fiber should be taken
  - Alcohol consumption is to be avoided
  - Salt intake should not me more than 5 g/day
  - Protein should be about 10–15 percent of the total dietary intake
- General recommendations[14]
  - Dietary indiscretion during the nonfasting period with excessive gorging, or compensatory eating, of carbohydrate and fatty foods contributes to the tendency towards hyperglycemia and weight gain and should be avoided.
  - Intake of whole wheat bread, vegetables, beans and fruits should be encouraged as they are excellent sources of dietary fiber which prevents constipation and reduces gastric acidity. Refined products and sweets get digested very quickly in comparison to complex carbohydrates (whole grains and cereals) as they are digested slowly.
  - Avoid dehydration by drinking sufficient water between Iftar and sleep
  - Choose sugar-free drinks or water to quench thirst. Addition of sugar to drinks shall be avoided.

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- Spicy foods and caffeinated drinks shall be avoided.
- Avoid smoking cigarettes which is also against the custom of fasting during *Ramadan*.
- Predawn meal should be taken as late as possible before the start of the daily fast. This will spread out the energy intake more evenly and result in more balanced blood glucose when fasting.
- Eat foods such as wheat, semolina and beans both at *Suhur* (predawn) before beginning the fast, and at *Iftar* (sunset meal) because these foods release sugar slowly. This will stabilize blood sugar levels and help to reduce cravings and appetite through fasting hours.
- At *Iftar* (sunset meal) it is also advised to eat foods that release sugars quickly, such as fruits, which will rapidly increase blood sugar levels, followed by slow-acting carbohydrates.
- Distributing energy intake over two to three smaller meals during the non-fasting interval may help to prevent excessive post-meal hyperglycemia.

Rest and Exercise[15]

- The previous exercise plan shall be modified in intensity to avoid episodes of hypoglycemia, although light level of exercise like walking and stretching exercise can be continued as usual. Even the periods of *Salaat*, i.e. the prayer, can also be considered a part of the exercise.
- Ideal time to exercise is early in the morning, before fast or in the evening after fast.
- Avoiding exercising during fasting hours.
- Adequate rest in terms of adequate sleeping hours is also important.

Frequent Blood Sugar Monitoring

A blood sugar tracker like the one showed below can be used for blood sugar monitoring **(Figure 2)**.

Blood glucose monitoring is part of the home based management. This can adequately guide the individual about his dietary as well as drug requirement. It can also forewarn he individual in advance about any impending complications such as hyperglycemia, hypoglycemia or diabetic ketoacidosis.

One should break the fast immediately and seek advice from their healthcare professional if he/she encounters the following readings.

- Hypoglycemia (low blood sugar)—blood glucose less than 60 mg/dL (3.3 mmol/L)
- Hyperglycemia (high blood sugar)—blood glucose higher than 300 mg/dL (16.7 mmol/L).

Home-based Management

- As mentioned above self-monitoring of blood glucose level is quite helpful in managing diabetics during the fast
- Regular urine acetone level assessment especially in Type 1 diabetics

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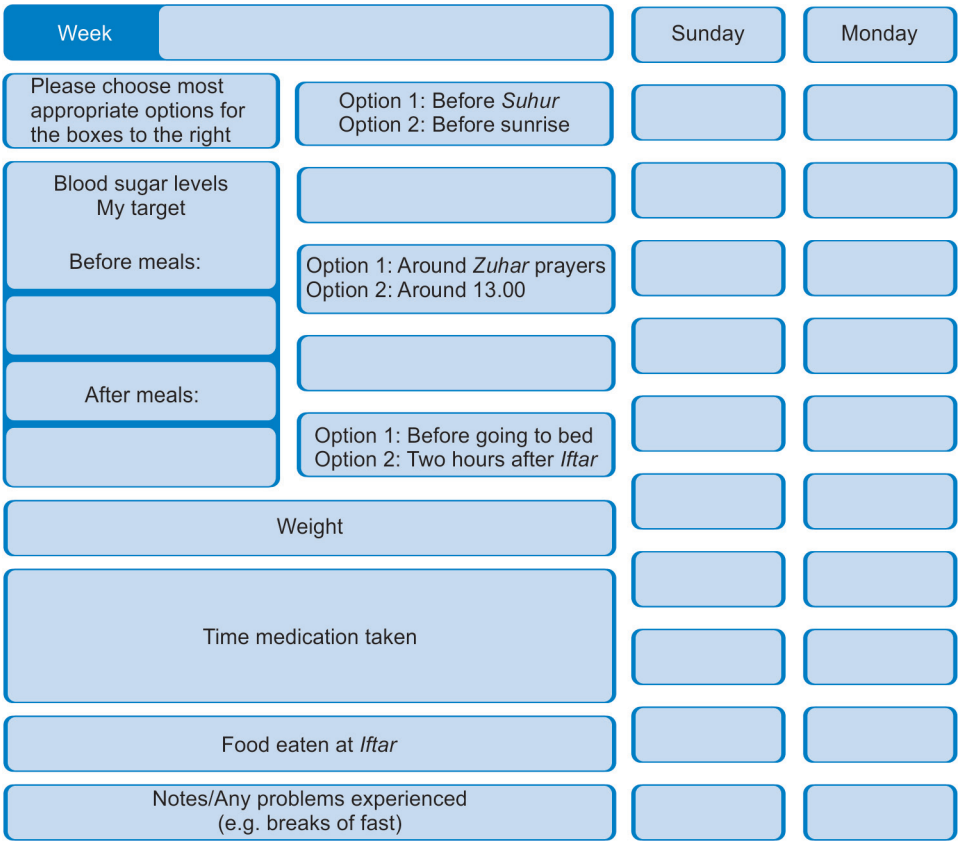

Figure 2: Blood sugar tracker used for blood sugar monitoring

- Individuals shall be well-informed and educated about the warning symptoms associated with the various complications that can arise during this period.
- Measuring daily weights and informing physicians of weight reduction (dehydration, low food intake, polyuria) or weight increase (excessive calorie intake) above two kilograms
- Recording daily diet intake (prevention of excessive and very low energy consumption)
- Education about breaking fast as soon as any complication or new harmful condition occurs
- Immediate medical help shall be sought in case of any emergency
- Last but not the least, educating the family members about the various aspects of management of the diabetics, i.e. Dietary goals, nutrition, exercise program, complications associated, symptoms accompanying these complications for early identification, management of the same. For instance, in case of hypoglycemia eating foods that release sugars quickly shall be administered like fruit juice, five sweets, e.g. jelly babies, glucose gel or three or more glucose tablets.

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Revision of the Treatment Regimen

Both Type 1 and Type 2 diabetes individuals require readjustment of their treatment regimens. The adjustments are based on the change in the eating patterns and the amount of physical activity during *Ramadan*.

- Treatment regimens suggested for Type 1 diabetics
  - *Three dose insulin regimen*: Two doses before the meals (after sunset and before sunrise) of short-acting insulin and long-acting insulin in the late evening. A study on multiple insulin injection didn't record any increase in the acute complications and hence concluded that it can be administered safely along with proper self blood glucose level monitoring and close professional supervision.[5]
  - *Two dose insulin regimen*: A combination of short-acting conventional insulin or analogue insulin along with intermediate acting insulin before the two meals that is *Suhur* and *Iftar*. Two papers where it was noticed that administration of insulin lispro or regular insulin with NPH twice daily before the morning and evening meals was associated with less excursion of postprandial blood glucose levels and episodes of hypoglycemia more with insulin lispro. Therefore, insulin lispro is recommended in Type 1 diabetics during *Ramadan*.[16,17]
  - *Continuous subcutaneous infusion*: Individuals on continuous subcutaneous insulin infusion shall be advised to reduce their basal dose and increase the bolus doses before the morning and evening meals.[18]
- Treatment regimen for Type 2 diabetics[19]
  - Short-acting oral hypoglycemic agents are preferred over the long acting oral hypoglycemic agents.
  - In general insulin sensitizers are less commonly associated with hypoglycemia, therefore patients on metformin can safely continue with the same during fasting. However, the timing of the doses should be modified: two-thirds of the total daily dose to be taken immediately before the sunset meal, with the other-third taken before the pre-dawn meal.
  - Sulfonylureas are believed to be unsuitable for use during fasting because of the inherent risk of hypoglycemia; they should be used with caution. Newer members of the sulfonylureas (gliclazide MR, glimepiride) have been shown to be effective, resulting in a lower risk of hypoglycemia.
  - The problems facing people with Type 2 diabetes who take insulin are similar to those associated with Type 1 diabetes, although the incidence of hypoglycemia is lower. Again, the aim should be to maintain necessary levels of basal insulin. A key objective is to suppress output of glucose from the liver to near-normal levels during fasting. Careful use of intermediate or long-acting insulins plus a short-acting insulin administered before meals would be an effective strategy.
- Post-*Ramadan* supervision of fasting diabetic.

After the month of *Ramadan* ends, the patients therapeutic regimen should be changed back to its previous schedule. Patients should also be required to get an overall education about the impact of fasting on their physiology.

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Chapter 9

Physical Activity in Ramadan

Altamash Shaikh

Abstract

Despite being of a proven benefit in diabetes, exercise is one of the less implemented tools in clinical practice. The goal is to provide a simple regime to accommodate the needs of fasting in *Ramadan* and to avoid hypoglycemia, hyperglycemia, and hypovolemia. Meals should be also planned accordingly. Risk of thrombosis in high-risk group patients like laborers, elderly and with other risk factors should be addressed specifically, to prevent dehydration and hyper viscosity. However, professional sports have been played and with their training in the late evening hours. Timing of exercise in others can be as per their change of schedule in *Ramadan*. Aerobic and resistance both types of exercise can be prescribed in *Ramadan*.

INTRODUCTION

Despite being of a proven benefit in diabetes, exercise is one of the less implemented tools in clinical practice. Exercise in *Ramadan* represents a big challenge to the treating physician/endocrinologist. Regular physical activity is a must for all diabetics who desire the best glycemic control. Exercise improves glycated hemoglobin, lipid profile (triglycerides) and also lowers cardiovascular risk. The need for doing physical activity and the risk involved in excessive exercise need not be over emphasized.

PATHOPHYSIOLOGY OF EXERCISE IN DIABETES AND RAMADAN

There is a defect in functional exercise capacity in both Type 1 and Type 2 diabetes mellitus patients. This is generally manifested as reduction in oxygen uptake, and also in VO_2 peak. Apart from clinical signs, there is increase in hematocrit, hemoglobin and plasma osmolarity as markers of dehydration during fasting in *Ramadan*.[1] Exercise in the post-prandial period, in *Ramadan* reduces the oxidative stress and carbonyl stress, and also decreases average glucose, mean amplitude of glycemic excursion (MAGE), and mean post-prandial glycemic excursion (MPPGE).[2]

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EXERCISE, SPORTSMANSHIP AND RAMADAN

In several Muslim countries, the professional sports and the special *Ramadan* cup tournaments and matches are held 2 to 3 hours post-sunset meal (*Iftar*) or even in the late night.[3] In young collegiate wrestlers, *Ramadan* fasting had positive effects on body composition and lipid profile.[4] In the fasting state, there is a state of carbohydrate "stress", when the muscle promptly utilizes lipid as alternate sources of energy and spares glucose for the brain. The muscle gets adapted to this refeeding/fasting in *Ramadan*, utilizing lipids and is stronger if exercise is continued in *Ramadan*.[5]

GOALS: EXERCISE AND RAMADAN

The simple goal of exercise in *Ramadan* is to provide a regimen suiting the daily needs as well as the metabolic demands of patient. Also, utmost care should be taken to avoid hypovolemia, hypoglycemia and hyperglycemia to give a flexible adjustment of daily schedule for the patient in *Ramadan*. This will also help the treating doctor, to continuously help the patients to understand and realize the importance of exercise in the management of diabetes.

PRE-EXERCISE EVALUATION AND RAMADAN

Every diabetic individual should undergo pre-exercise evaluation. This includes assessment of glucose control, enquiry of hypoglycemia (recurrent or unawareness), review of medications (oral or insulin regimen), and also evaluate for complications (cardiac, neuropathy, retinopathy, and/or nephropathy). Generally stress test is done to document the safety, however, with the exception of young patient with low cardiovascular risk profile. The exercise prescription can be broadly divided as frequency, intensity, type and timing of exercise during *Ramadan*.

EXERCISE TYPE/TIME IN DIABETES AND RAMADAN

In *Ramadan* there is tendency towards decreased physical activity both in Type1 and Type 2 diabetes patients, as shown in EPIDIAR study.[6] American Diabetes Association (ADA) recommends aerobic and resistance exercise for diabetes. Although, it should be individualized, certain principles need to be followed. It is important to monitor the patient during start of a new exercise plan including blood glucose monitoring. Aerobic exercise should focus on large muscle and non-weight bearing, e.g. walking or cycling. This improves glycemic control and insulin sensitivity. If type of exercise chosen is accessible and does not alter the daily schedule in *Ramadan*, patients' adherence to exercise also improves. This should also be done, keeping in mind the attitude of patients and family members towards diabetes and exercise.[7]

In general patients can do moderate intensity exercise depending on their changed pattern of eating, working and sleeping. This can be post-sunset meal (*Iftar*), or post-*Tarawih* prayers or even after midnight (*Tahajjud*) prayers [prior to sunrise meal (*Suhur*)]. Exercise time should be adjusted also in polar regions as the duration of fast may be too long or short.

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EXERCISE, HYPOGLYCEMIA AND RAMADAN

Prevention of hypoglycemia is the mainstay of treatment in diabetic patients in *Ramadan*. Extreme care must be taken while advising any form of physical activity to prevent hypoglycemia. It is noted in clinical practice that intense or excessive exercise leads to high chances of hypoglycemia. Also, in patients with severe hypoglycemia, physical activity changes were important factor in EPIDIAR study. At all levels of prescription, exercise should not be advocated in the hours before sunset meal (*Iftar*) irrespective of patients on diet, oral or insulin regimen. Should hypoglycemia be detected or impending, fast should be broken (details in Insulin in Type 2 diabetes chapter).

EXERCISE, DIET CONTROLLED DIABETES AND RAMADAN

This group of diabetic patients would always want to fast in *Ramadan* as they feel just diet restriction will not hamper the glycemic control. In them, their normal physical activity should be maintained as part of exercise prescription. Nevertheless, if they indulge in overeating their meals should be divided in smaller frequent portions post-sunset meal (*Iftar*) to avoid hyperglycemia. This can be accomplished by rescheduling the frequency and intensity of exercise regime.

EXERCISE, TARAWIH PRAYER AND RAMADAN

Prayer (*Namaz*) involves movements like bending, bowing, kneeling, and rising in repeated cycles. One to two hours after sunset meal (*Iftar*) is the daily night (*Isha*) prayer immediately followed by special *Ramadan* prayer called as *Tarawih* prayer. If performed, this is considered as a part of daily exercise program for the individual.[8] However, depending on other comorbidities, this may not suffice for the daily exercise program.

Exercise in the form of *Tarawih* prayer, can mitigate the harmful effects of hyperglycemia. In a recent study, prayer movements were shown to reduce the MPPGE due to its effect on GLUT4 and hence, glucose transport.[2]

The mean blood glucose at fasting was lower even in pregnant patients those had less calories as a part of fasting and who performed *Tarawih* prayer, as a part of daily exercise in *Ramadan*.[9]

EXERCISE, HYPERGLYCEMIA AND RAMADAN

Not only in some poorly controlled Type 1 diabetes, but also in some Type 2 diabetes mellitus (T2DM) patients, there can be exercise induced hyperglycemia. High intensity exercise in Type 2 diabetes can inflict a hyperglycemic response due to intense counter regulatory response of glucagon and epinephrine, whereas with long duration of Type 2 diabetes, the insulin response is reduced, thus also leading to exercise induced hyperglycemia. So, when initiating a new exercise plan during *Ramadan*, the blood glucose should be checked before during and postexercise. The management plan must be highly individualized, to watch for any exercise-induced hyperglycemia and avoid iatrogenic complications.

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ROLE OF PHYSICAL ACTIVITY, WEIGHT AND RAMADAN

Diabetes patients report weight gain in *Ramadan* attributable to physical inactivity,[10] this is generally due to fear of hypoglycemia, that the patient wants to avoid and becomes inactive. However, there is beneficial effect on weight and body composition in body builders whether they do exercise while fasting or post-sunset meal (*Iftar*).[11]

EXERCISE, PHYSICAL LABOR AND RAMADAN

Patients with diabetes who are physical laborers and fast during *Ramadan* belong to very high-risk group. Fluid restriction at the time of fast, especially in hot climatic conditions and in regions of extreme summer season increases the risk of dehydration and is more in patient who do laborious work.

EXERCISE, DEHYDRATION AND RAMADAN

Diabetic patients who fast in *Ramadan* are at increased risk of developing thrombosis due to fluid restriction, consequent to volume depletion during the fasting hours; and the excessive perspiration.[12] This could lead to thrombotic events in diabetic patients with risk factors, hence antiplatelets may be started in such patients. If blood glucose is uncontrolled, it may further add to electrolyte imbalance and osmotic disturbances. Thus, extreme climate, physical labor and prolonged fasting hours must be specifically looked into while managing such patients. Adequate hydration must be assessed and addressed at each visit whether pre-*Ramadan* or if need be during *Ramadan*. Dose and or the type of antihypertensive medication must be adjusted, to avoid hypovolumia and hypotension especially in summer season. With specific avoidance of diuretics in *Ramadan* for some patients, others may be used in *Ramadan*.

BENEFITS OF PHYSICAL ACTIVITY AND RAMADAN

- Provides a dialect between patients and physician
- Better chance of diabetes education
- Improves insulin sensitivity
- Blood glucose and glycated hemoglobin improves
- Improvement in MAGE and MPPGE
- Lipid utilization while exercise training, better lipid profile
- Body weight and composition improves
- Improved mobility.

RECOMMENDATIONS FOR PHYSICAL ACTIVITY IN RAMADAN

See **Table 1.**

DISCLAIMER

The authors received no funding and report no conflict of interest.

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Table 1: Physical activity recommendations during *Ramadan*	
Before Ramadan	*During Ramadan*
On diet and exercise control	Modifying frequency and intensity of physical activity; e.g. 2 hours post-sunset meal (*Iftar*); ensure adequate fluid intake
T2DM: oral or insulin regimen	Avoid exercise pre-sunset meal (*Iftar*); ensure adequate fluid intake
T1DM	Highly individualized; avoid intense exercise
Glucose monitoring	Pre- and post-exercise in susceptible patients
Fluid intake timing	Plenty of fluids during and after sunset meal (*Iftar*) to avoid dehydration and its consequences
Preferable mode of exercise	Maintain normal daily routine, walking, stationary cycling If performed *Tarawih* prayers
Exercise timing (depending on the work pattern during *Ramadan*)	After sunset meal (*Iftar*) After night (*Isha*) prayer After midnight (*Tahajjud*) prayer
Dehydration and *Ramadan*	Reduce dose/adjust antihypertensives Avoid diuretics May consider antiplatelets

Abbreviations: T1DM—Type 1 diabetes mellitus; T2DM—Type 2 diabetes mellitus

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Chapter 10

Stress Management and Diabetes in Ramadan

Altamash Shaikh

Abstract

Low quality of life and poor glycemic status arises from stress in diabetes. Stress may be present in patients in both, those who are diabetic and fast; and those who are diabetic and do not fast in *Ramadan*. From dietary indiscretion to altered sleep due to modern *Ramadan* practices; and the changing treatment regimen also add to stressfulness in patients. This chapter describes stress management in four prongs; patient, physician, peer and folk level. Directly diabetes-related distress can influence healthy status of patients, while indirectly it demotivates them to pursue further control. To overcome the distress of stress counseling has to be provided at all levels to all patients in need. The treating physician should impart technical details of coping up as illustrated and be tactical so that it is implemented by the patient in manner that it not only helps in *Ramadan*, but also in post-*Ramadan*.

INTRODUCTION

Stress is present in diabetic patients in both, those who are diabetic and fast; and those who are diabetic and do not fast in *Ramadan*. Also, mood disorder, anxiety, depression, etc. are few psychological problems in diabetics, well known. Stress is inevitable in a diabetic patients life, hence a common simple approach to offset these stresses should be made. This approach should take into consideration of the biopsychosocial model including the patients, psychological and social (friends and family) of managing stress as discussed further. The various stressors and destressors in *Ramadan* are discussed in this chapter.

WHY MANAGE STRESS IN DIABETES?

Despite all efforts, the number of diabetic population is increasing at a rapid pace and more number of subjects would be fasting in *Ramadan*. The comorbid distress in diabetes is part and parcel of many factors as described below. Stress in diabetes *per se* is due to the following: emotional distress due to diabetes itself, social and

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environmental factors, stress related to control, treatment and monitoring of diabetes; and also the stress due to long-term complications of diabetes. Added with these are newer sleep and feeding behavior in *Ramadan*.

MECHANISM

Cortisol and Sleep

Stress leads to increased catecholamines and hypercortisolism, with consequent hyperglycemia. Hypercortisolemia is one factor in the setting of chronic stress, confirmed by salivary cortisol, as observed in *Ramadan* fasting. Also, lack of sleep contributes to stress in addition due to altered hypothalamo-pituitary-adrenal axis. Owing to benefits of modern lifestyle, long waking hours and sedentary profile, these two factors add further to dysmetabolic status of individuals and increase in insulin resistance.[1]

Causes of Stress in Ramadan

Lifestyle Changes

Former fasting in *Ramadan* did not affect lifestyle majorly. Indirectly the change in present day practices in diet, exercise, may lead to stress in some patients and may affect the self management capacity of diabetes care. This is due to the change in waking and working hours; and also diet and exercise patterns in *Ramadan*.

Altered Sleep

In some patients night may be spent in praying or socializing in some or just waiting till sunrise meal (*Suhur*) in some. This affects the quantity as well as quality of sleep. This is also important in countries, e.g. polar regions with long fasting hours and less sleep hours in summer season and vice versa.

Treatment Regimen

The changed and the changing regimen, in management of diabetes in *Ramadan* can affect a patients control over various aspects of diabetes. With stress and its consequent hyperglycemia, further demands of increase in dosages of insulin may be needed for glycemic control in some patients.

Anxiety and/or ability for fasting and awareness of the disease problem in some patients also effects in *Ramadan*.

However, by understanding the difficulties of an individual patient and with proper counseling and stress management these can be alleviated.

PSYCHOSOCIAL ADVANTAGES OF RAMADAN FASTING

Ramadan month itself acts as a destressor for all patients and also diabetic patients who fast. There is positive benefit and conditioning on mind, body and soul. There is a sense of improved inner well-being, and peace.

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PRE-RAMADAN COUNSELING AND STRESS

Of note, pre-*Ramadan* counseling should not only be limited to patients who fast, but also to diabetic patients who do not fast. Although not fasting, but some patients do still indulge in feasting causing hyperglycemia and leads to stress to patients and relatives. (Details in chapter on pre-*Ramadan* counseling).

THE SOLUTION

At Patients Level

Self-management forms the main basis of diabetes stress management, irrespective of the patients' literacy levels. This also depends on the treating physician or his team by the time given to individual patients in daily practice. At the patients levels the following four aspects should be taken care:

Meals

Following the diet as per individual requirement brings patients closer to targets and reduces stress. Although, The Prophet Muhammad (peace be upon him) use to break the fast with dates and water, the modern style has changed considerably into feasting at sunset meal (*Iftar*) and leading to the constellation of chronic stressful disorders due to dysmetabolism.[1] Patients should be advised to avoid carbohydrate rich and foods high in saturated fats.

Medications

Patients taking their tablets/insulin by themselves on time. Adding anxiolytics during *Ramadan* may not be acceptable to patients if it increases their sleep or hampers daily activity, as patients would like to be alert during *Ramadan*. Patients on multiple medications including insulin (*see* chapter on Insulin and Type 2 Diabetes Mellitus) may find it stressful if not implemented in a patient centered way.

Meditation and Exercise

Reading religious books or performing rites and rituals may provide spiritual benefit and reduce stress. Exercise as prescribed by the doctor in *Ramadan* and *per se* the effect of exercise reduces stress (for details see chapter on Physical Activity in *Ramadan*).

Highly anxious patients may not benefit with progressive muscle relaxation, abdominal breathing, imagery, biofeedback; but various combinations of techniques at all levels as described may be needed.

Monitoring

Self-monitoring of blood glucose is the best immediate incentive the patients gets and helps them adjust the meals and treatment dosages as advised by the physician. While

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in *Ramadan* frequency of testing can be decreased after first few days once control is evident by the changed meals and medication (tablet or insulin).[2] Improved glycemic control positively affects quality of life by reducing lethargy and cognitive distress.[3]

At Physician Level

Recheck

Diet tracking allows us to know dietary indiscretions and reinforce on patients. This along with exercise rechecks, further helps in reducing various components of metabolic syndrome.

Reassess

Diabetes status overtime should be reassessed to know any impending emergency or complication, so that prompt action may be taken even before *Ramadan*. Thus, managing these will decrease the mental burden to patients.

Restress

Motivation should be a part of every visit subject to patients willingness to maintain various parameters as normal as possible. Repeat when required in subsequent fasting years in *Ramadan*, as in the long-term, effectiveness of counseling reduces overtime.

Receive

Physicians should receive training to enquire role of religion and spirituality to enhance patients' coping and better self-management of diabetes.[4]

At Peer Level

Group Discussions

They create awareness about realities that there are others with similar issues and stops the why me attitude of some patients. This can be done by physician or cultural and religious leaders.[4]

Group Visits

Patients of the same family[5] or area can be called for a group visit as a part of stress management session. This reduces the stress and strain of traveling alone and gives a better platform for understanding towards their problem in *Ramadan*.

At Folk Level

Family therapy[5] forms the most important prong in the stress management of diabetes, also in *Ramadan*. Family education is important and regular sessions with them change the outlook of diabetes patients and their family. It can be done in the following way:

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Perishing Stress

Parents of young adults need to be counseled along with patients to cope up in a positive way. Financial stress and stressful moments in life of patients and family needs to be dealt tenderly, for at times the young may be supporting an elderly/old diabetic or vice versa. Healthy coping is stressed upon, for better outcomes in diabetes management. Patients and families at polar regions with long fasting hours may benefit with healthy coping in reducing stress.

Putting it Down

All sorts of conflict within the family has to be solved assertively to improve patients metabolic profile and family's adjustment towards patients. This helps the maximum, in the management of diabetes and involves improvement in all viz. physical, mental and social aspects of life. Always ascertain that patients' family knows about the diet, exercise and treatment regimen prescribed during *Ramadan*.

STRESS, DISTRESS AND DESTRESS

Often there exists an overlap between depression and distress due to diabetes.

Directly diabetes-related distress can influence healthy status of patients, while indirectly it demotivates them to pursue further control. However, when diabetes patients take a short a nap in the afternoon time it is shown to give appropriate rest and covers up for any lack or shortage of sleep at night. For most patients combination of strategies as above may be needed for successful de-stressing in *Ramadan*. Having this done we can make a safe and secure fasting for diabetic patients in *Ramadan*, starting well before in advance when the patients are making cognitive plans for fasting.

CLINICAL IMPLICATIONS

Stress management in *Ramadan* gives a chance to clear out the negative perceptions about the diabetes.

Stressing upon the belief and attitude of patients can bring about reduction in stress levels and better diabetes management.

This also improves quality of life during *Ramadan* and fewer complications.

With proper stress management, even intensive treatment regimens can be implemented easily, subject to time spent with the patient.

Ongoing stress management is a must in a diabetic patients' life, not only for *Ramadan*, but also otherwise to achieve long-term goals for diabetes.

When stress management is taken care, patients do well and all religious obligations can be carried out in a happy and healthy mode, and consequently diabetes outcomes. The treating physician/endocrinologist should impart technical details of coping up and be tactical so that it is implemented by the patient in manner that it not only helps in *Ramadan*, but also post-*Ramadan*.

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Table 1: Stress management in diabetics during *Ramadan*	
Awareness	Make patients aware their responsibility in success of management
Stress free	Monitoring the patients' pre, during and post-Ramadan for stress free fasting
Sleep stress	Sleep adequacy may be a short nap in the afternoon time during Ramadan
Safety	All strategies should ultimately lead towards safety prior, during and post-*Ramadan*
Modernization stress	Patients should be reminded of yesteryears fasting practices, to alleviate the effects of stress of fasting on food quality or sound sleep, in diabetes management in *Ramadan*
Dietary stress	Avoid use of carbohydrate rich and fat (saturated) foods in *Ramadan*
At patients level	Managing meals, medication, meditation and monitoring of glucose
At physician level	Diet tracking and motivation
At peer level	Group discussion, group visits
At family level	Coping strategies and solving conflicts

This multipronged approach will help the doctor to reduce stress levels pre, during and post-*Ramadan*.

RECOMMENDATIONS

See **Table 1**.

DISCLAIMER

The authors received no funding and report no conflict of interest.

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Section 3

Pharmacological Management

CHAPTERS

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Chapter 11

Traditional Oral Antidiabetic Drugs in Ramadan

Shariq Rashid Masoodi

Abstract

The Holy *Ramadan* is a month of fasting and feasting. The *Ramadan* fast is observed by a large section of Muslims with diabetes mellitus; more than 50 million people with diabetes are estimated to fast during *Ramadan* globally. In general, oral hypoglycemic agents that act by decreasing peripheral insulin resistance, like metformin are preferred because of their low hypoglycemic potential. The older, long acting SUs like glibenclamide should be avoided because of the increased risk of hypoglycemia, whereas the newer SUs like gliclazide MR or glimepiride can be safely used during *Ramadan*. Given their widespread use and relatively low cost, these newer generation SUs may be used, albeit with caution. To lessen the complications faced by diabetic patients who fast during *Ramadan*, health professionals should aim to educate them about safe fasting, not only before and during *Ramadan*, but also at follow-up.

INTRODUCTION

The Holy *Ramadan* is a month of fasting and feasting.[1] The *Ramadan* fasting is observed by a large section of Muslims with diabetes mellitus. Of the 1.6 billion world's Muslim population, more than 50 million people with diabetes are estimated to fast during *Ramadan* globally.[2] By these estimates, one could imagine that in India alone, around 3–4 million diabetic patients will be observing *Ramadan* fasting. Though fasting has the potential of posing certain health risks to diabetic patients, it is generally safe in low-risk groups. Those at low-risk may fast without healthcare advice, but many patients with diabetes insist on fasting during *Ramadan* despite the medical advice not to do so.[3] The physician's role is to help out the devoted individual to *Ramadan* fasting in categorizing the risk involved, and by raising awareness of lifestyle and dietary rules, daily self-monitoring, and a fresh adjustment of treatment.[4]

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TREATMENT MODALITIES DURING RAMADAN

A variety of treatment modalities exist for people with Type 2 diabetes mellitus (T2DM). The therapeutic options for management of T2DM have expanded with the introduction of new antidiabetic drugs like amylin analogs, incretin hormone mimetics and dipeptidyl peptidase 4 (DPP-4) inhibitors. Apart from insulin and its analogs, the traditional oral antidiabetic drugs (OADs) include sulfonylureas (SU), biguanides, thiazolidinediones (TZDs), meglitinides and α-glucosidase inhibitors. In this chapter, the role of these traditional oral antidiabetic drugs (TOADs) in *Ramadan* is being discussed; other modalities like diet, exercise, DPP-4 inhibitors and insulin are being discussed elsewhere in the book. Each of these TOADs is being discussed separately followed by some general guidelines on how to adjust oral diabetic medications during *Ramadan*.

Insulin Secretagogues

Insulin secretagogues are substances that stimulate or trigger a secretion or release of insulin from pancreatic β-cells. There are two classes of oral hypoglycemic agents (OHAs) which stimulate release of insulin from β-cells: the SU and meglitinides.

Sulfonylureas

Sulfonylureas are the oldest class of oral hypoglycemic agents and are in use for more than 70 years. They were accidentally discovered by Marcel Janbon during World War II, when he encountered some unexplained deaths in typhoid patients, who would present with hypoglycemic symptoms and seizures after receiving sulphonamides.[5] Their discovery was further confirmed by French physiologist, Auguste Loubatières who observed that repeated oral administration of sulfonamide, 2254RP caused hypoglycemia and convulsions in experimental animals. These hypoglycemic sulfonamides were later named as SU.

Pharmacology

The mechanism of SU remained unclear till 1968 when it was shown that SU depolarize the pancreatic β-cell and stimulate electrical activity.[6] Later on it was shown that SU receptor is a component of the adenosine triphosphate (ATP)-sensitive potassium (K^+ATP) channel in the pancreatic β-cell and their binding leads to inhibition of K^+ATP channels; the ensuing cell depolarization leads to calcium influx and stimulation of insulin secretion.[7] Sulfonylureas act independent of blood glucose levels but as expected, are useful only in patients having some β-cell function. Wide presence of SU receptor in various tissues suggests that SU could be having extrapancreatic effects as well, but the clinical importance of these effects is negligible.[8]

For several decades, after their introduction into clinical practice, SUs have been the mainstay of the pharmacologic management of T2DM. In fact, SU are among the most widely used drugs for the treatment of T2DM. Older SU like acetohexamide, chlorpropamide and tolbutamide are called first generation SU, whereas so called

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Table 1: Traditional oral antidiabetic drugs

OAD	*Elimination Half-life (h)*	*Route of elimination*	*Usual daily dose (mg)*	*Dosing per day*
First generation SU				
• Chlorpropamide	36 (24–72)*	Urine, 80–90%	250–500	Once
• Tolbutamide	4.5 (14–16)	Urine, 75–85%	1,000–2,000	Once or divided
Second generation SU				
• Glipizide	2.5 (14–16)	Urine, 80%	2.5–10	Once or divided
• Glibenclamide (Glyburide)	10 (20–24+)	Bile, 50% Urine, 50%	2.5–10	Once
• Gliclazide	10.4 (24)		40–240	Once or divided
• Glimepiride	9.2 (24+)	Urine, 60% Feces, 40%	2.0–4.0	Once
Meglitinides				
• Repaglinide	1.0 (3.0–3.5)	Feces, 90%	0.5–4.0	Before each meal
• Nateglinide	1.5 (4.0)	Urine, 83%	60–120	Before each meal
Biguanides				
• Metformin	6.2 (24+)	Urine, 100%	1,000–2,500	Once or divided
Thiazolidinediones				
• Pioglitazone	3-7 (24+)	Urine, 15–30% Bile	15.0–30.0	Once or divided
α-Glucosidase Inhibitors				
• Acarbose	2.0	Feces, 51% Urine, 34%	25–100	Before each meal

* Figures in parenthesis show duration of biological effect.

Abbreviations: OADs—Oral antidiabetic drugs; SU—Sulfonylureas

second generation SU include glipizide, glibenclamide (glyburide), gliclazide and glimepiride. The latter have structural characteristics that make them effective in much lower doses than the first-generation SU. Though all SU are effective in lowering blood glucose levels, there are differences in pharmacokinetics and pharmacodynamics, as well as in the effective dose of individual SU **(Table 1)**.[9]

Adverse Reactions

Sulfonylureas are generally well tolerated, their main adverse effects being hypoglycemia and weight gain. Because of their potential for causing β-cell exhaustion in the long run, and concerns regarding their cardiovascular safety (especially of older agents like glibenclamide), the use of SU has fallen considerably with time. The continued introduction of newer, safer, and effective classes of antidiabetic drugs has further added to decline. However, in real terms, very few episodes of major

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hypoglycemia were observed in a large retrospective study of 14,000 elderly patients with T2DM.[10] Given their less expense and wide availability, SU continue to be used in many parts of the world as first-line agents in the treatment of T2DM.

Meglitinides

The meglitinides, repaglinide and nateglinide, are short-acting glucose-lowering drugs for therapy of patients with T2DM or in combination with insulin sensitizers like metformin. Though structurally different than SU, their action is similar to SUs, i.e. by regulating ATP-dependent potassium channels in pancreatic β-cells, thereby increasing insulin secretion. However, meglitinides exert their effects via different receptors. Their clinical efficacy and side effect profile is similar to that of the SU. The usual daily dose of meglitinides is shown in **Table 1.**

Sulfonylureas and Meglitinides in Ramadan

Because they have been widely available for a long time, there is considerable experience with use of insulin secretagogues especially SU in *Ramadan*. As expected, the use of chlorpropamide is contraindicated during *Ramadan* because of possibility of prolonged hypoglycemia. Initial reports suggested that use of glibenclamide was safe during *Ramadan* fasting.[11] Subsequent reports, however, suggested that glibenclamide may be associated with higher risk of hypoglycemia than other SU of same class like glimepiride, gliclazide and glipizide.[12,13] Particularly, gliclazide and glimepiride have been reported to be effective and safe during *Ramadan*.[14] A study on 136 nonobese Asian men with previously well-controlled Type 2 diabetes, did not show any significant alteration in glycemic control during *Ramadan* when gliclazide (60 mg, modified release, monotherapy) was administered in the evening at *Iftar* (fast breaking) time.[15] More importantly, there were few hypoglycemic events and no significant weight gain was observed. Similar findings were reported in a Moroccan study on 122 patients (62 women, 58 men), aged 48–60 years with well-controlled diabetes who were treated with modified release gliclazide.[16]

In last decade, some studies were done to evaluate the effect of different therapy models on clinical and metabolic status in Type 2 diabetic patients during *Ramadan* on TOADs like gliclazide and glimepiride.[14,17] One of such early studies was GLIRA[17]—an open-label, prospective, observational study carried out in 33 centers in Algeria, Egypt, Indonesia, Jordan, Lebanon, and Malaysia. The study was undertaken to assess the effect of the changes in nutritional habits and drug administration schedule during *Ramadan* in well-controlled Type 2 diabetes patients. The reported incidence of hypoglycemic episodes was 3 percent in newly diagnosed and 3.7 percent in already-treated patients on glimepiride. The authors concluded that when the time of administration of glimepiride is changed from the morning to the evening, the efficacy and safety of glimepiride in T2DM patients is not altered during *Ramadan* fasting.[17]

One of the main concerns of using insulin secretagogues during *Ramadan* fasting is hypoglycemia, especially when the fasting period lasts 16 to 18 hours during summer time. Understandably, an OAD with quick onset and offset of action would be preferred in this setting. In this regard, role of meglitinides especially repaglinide

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has been subject of many studies during *Ramadan*. In one of the earliest such studies conducted in Malaysia, 235 sulfonylurea treated patients were randomized to receive either repaglinide or glibenclamide 6 weeks before *Ramadan* till 4 weeks after *Ramadan*.[18] During *Ramadan*, patients changed their eating pattern to two meals daily, repaglinide twice day (pre-prandial), and glibenclamide, once or twice daily. Though both treatments were equally well-tolerated, the authors observed that hypoglycemic events were significantly lower in the repaglinide group than the glibenclamide group (2.8% vs. 7.9%; $P < 0.001$). Besides lesser hypoglycemias, blood glucose levels were also better in repaglinide group with significant improvement in mean serum fructosamine concentration, compared to glibenclamide group.[18] Subsequent studies also showed that repaglinide was safe and effective during *Ramadan* fasting.[14,19,20]

Some studies have tried to compare safety and efficacy of various OADs in general, though there have not been any large head-to-head trials during *Ramadan*. In the GUIDE study, a double-blind comparison of once daily gliclazide MR and glimepiride in T2DM patients, gliclazide MR was found to cause fewer confirmed hypoglycemic episodes as compared to glimepiride (3.7% versus 8.9%).[21] In another study, conducted to compare the treatment efficacy between repaglinide and glimepiride during *Ramadan* fasting, 41 patients were randomized to receive either repaglinide or glimepiride.[22] No statistically significant difference in the incidence of hypoglycemia or glycemic variability was observed in the two groups, and the authors concluded that glimepiride may offer an advantage over repaglinide during the *Ramadan* fasting because of its longer duration of action.[22] Meglitinides, the short acting insulin secretagogues (repaglinide and nateglinide) have short duration of action and as such are useful in patients with Type 2 diabetes during *Ramadan* fasting. In the above mentioned study by Mafauzy et al.[18] the use of repaglinide was associated with a lower risk of hypoglycemia; 0.03 hypoglycemic events per patient per month were observed within repaglinide group compared to 0.05 events per patient per month in the glibenclamide group.

Biguanides

Biguanides (Metformin), the only bigaunide presently available for use, is the most widely prescribed medication in the pharmacological management of T2DM. Though its main metabolic action appears to be upon the liver, the therapeutic use of metformin has been ignited by the identification of its pleiotropic actions on several tissues, which are affected by insulin resistance.[23] The scientific utilization of "formin sisters" (phenformin, metformin and buformin) became well-known in the 1950s, but the so called association of biguanides with lactic acidosis in the 70s pulled them down and they were wrenched from the industry.[24] Though metformin was accepted for the therapy of hyperglycemia in Europe (England) as early as 1958, it was not established in the United States until 1995.

Pharmacology

Metformin is an insulin sensitizer. Though not very clear, the main action of metformin lies in activating AMP-activated protein kinase (AMPK)—an important enzyme

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that plays essential role in body's energy balance.[25] Metformin acts by decreasing hepatic glucose production and intestinal glucose absorption, and improves insulin sensitivity. The usual dose of metformin is 1000–2500 mg/day. It has a half-life is 6.2-hour (plasma); it is not metabolized and is excreted unchanged in urine **(Table 1)**.

Adverse Reactions

Common reactions to metformin are mainly gastrointestinal, like, anorexia, nausea/vomiting, indigestion, flatulence, abdominal discomfort and diarrhea. Other side effects include headache, metallic taste in mouth, and megaloblastic anemia. Lactic acidosis is often related to metformin, though there is no evidence at present that metformin is associated with an increased risk for lactic acidosis when prescribed under the study conditions.[26] However, the drug is contraindicated in patients with renal dysfunction with serum creatinine > 1.4 mg/dL (women) or 1.5 (men). Other contraindications to metformin use include conditions predisposing to lactic acidosis like hypoxia, dehydration, sepsis, surgery, congestive heart failure (CHF), metabolic acidosis, diabetic ketoacidosis or chronic liver disease.

Use of Metformin in Ramadan

Given its efficacy, low-price and low hypoglycemic potential, metformin is certainly the first therapeutic choice for T2DM patients during *Ramadan* as well. In routine practice, hypoglycemia has been accounted zero to 20 percent of nonfasting patients taking metformin.[27] However, major hypoglycemia, needing third-party assistance has not been reported with metformin use unless given in combination with other hypoglycemic agents. An observational pilot study from Iran showed a significant increase in number of hypoglycemic events in patients who took sulfonylurea compared with those who took only metformin during *Ramadan*.[28] However, in most studies conducted during *Ramadan*, SU and other OADs have been used as add-on to metformin, it is difficult to assess the efficacy and safety of metformin per se in *Ramadan*.

Thiazolidinediones

The TZDs, also known as glitazones, were introduced in the late 1990s. Troglitazone, the first drug in this class to be marketed, was withdrawn from the market due to an increased incidence of drug-induced hepatitis. Another TZD, Rosiglitazone was also withdrawn from the market due to an increased risk of cardiovascular events, though it is available in United States under selling restrictions. Pioglitazone, the only available TZD in India, is also under debate due to several potential side effects.

Pharmacology

The insulin-sensitizing TZDs, are selective ligands of the nuclear transcription factor peroxisome-proliferator–activated receptor γ (PPARγ).[29] The mechanism by which TZDs exert their effect is not fully understood, but they act on adipose tissue, muscle,

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and liver to increase glucose utilization and decrease glucose production. The efficacy of the TZDs as monotherapy for the treatment of Type 2 diabetes is similar to that of metformin; their cost and side effects make them less appealing as initial therapy. Though one can give up to 45 mg of pioglitazone per day, the usual daily dose is 15–30 mg **(Table 1)**.

Adverse Effects

Common reactions to TZDs are include headache, edema, weight gain and dilutional anemia. However, the serious adverse effects that are of concern include CHF, hepatotoxicity, diabetic macular edema, fractures (in female patients) and bladder cancer (with prolonged use). Although TZDs seem to improve many cardiovascular risk factors, the data demonstrating their ability to decrease cardiovascular events are unimpressive. As far the risk of hypoglycemia is concerned, TZDs are not independently associated with hypoglycemia, though they can increase the hypoglycemic effects of other hypoglycemic drugs.

Use of Pioglitazone in Ramadan

Used alone or in combination with other OADs, pioglitazone has been found to be safe and effective in lowering blood glucose levels during *Ramadan* fasting. In his multicenter, double-blind randomized controlled trial on 86 fasting Muslim subjects, Vasan et al.[30] observed that pioglitazone was tolerated well by subjects in the study. Though pioglitazone was efficacious in lowering blood glucose in combination with conventional OADs, there was no reduction in the number of hypoglycemic events as compared to conventional therapy without pioglitazone. An average weight gain of 3.02 kg was observed in the pioglitazone group.[30]

Alpha-Glucosidase Inhibitors (AGIs)

This oral class of drugs lower blood glucose by modifying the intestinal absorption of carbohydrates. There are three drugs in this group, acarbose, miglitol and voglibose, though most of the available studies are on acarbose.[31] Taken orally, they inhibit the upper gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides in a dose-dependent fashion, thus slowing the absorption of glucose. They can be of potential benefit in both Type 1 and Type 2 diabetes because of their ability to dampen prandial glucose excursions. As a group, they are not that effective and hence are mostly used in combination with other OADs.

Adverse Effects

Alpha-glucosidase inhibitors are not associated with any systemic adverse effects but cause frequent mild to moderate GI side effects particularly flatulence. The risk of hypoglycemia with AGIs is very low.[32]

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Table 2: Recommended changes to treatment regimen in OAD treated patients with Type 2 diabetes who fast during *Ramadan*

Before Ramadan	*During Ramadan**
• Patients on diet and lifestyle measures	No change needed Modifying the time and intensity of physical activity should be discussed with the patient
• Metformin 500 mg, thrice daily	Metformin, 1,000 mg at *Iftar* (sunset); 500 mg at the *Sehri* (predawn meal)
• TZDs or AGIs at breakfast	No change needed; same dose before *Iftar*
• Sulfonylureas—once daily glimepiride, gliclazide or gliclazide MR	Same dose, but before *Iftar*
• Sulfonylureas—twice daily gliclazide	Full morning dose at *Iftar* time and half the evening dose at *Sehri*
• Sulfonylureas—glibenclamide, once or twice daily.	Consider changing to a SU with less risk of hypoglycemia like gliclazide MR If on once daily dose, use same dose before *Iftar*; If on twice daily give full morning dose with *Iftar* and half the evening dose with *Sehri* Consider omitting pre-*Sehri* dose

* For all patients fasting during *Ramadan*, ensure adequate fluid intake.

Abbreviations: AGI—α-glucosidase inhibitor; OADs—Oral antidiabetic drugs; SU—Sulfonylureas; TZD—Thiazolidinedione

Source: Adapted from Suliman M, Abdu T, Elhadd T, et al. Diabetes and fasting in *Ramadan*: Can we provide evidence-based advice to patients? Sudan Med J. 2010:46(1):4-14.

DIABETIC MEDICATION ADJUSTMENT DURING RAMADAN

Before going for adjustment of medications, it is important to assess the degree of risk with *Ramadan* fasting for the individual patient, and determine whether fasting is advisable.[33] If the patient makes a decision to fast, one needs to find how best the individual can be helped. Guidelines for adjusting therapy during *Ramadan* fasting in patients with Type 2 diabetes are shown in **Table 2.**[34] Many patients may be able to carry on with their *Ramadan* fasting without needing any change in their treatment regimen. Only one-fourth of patients in EPIDIAR study treated with OADs needed to change their treatment dose.[35] In general, oral hypoglycemic agents that act by decreasing peripheral insulin resistance, like metformin or pioglitazone are preferred because of their low hypoglycemic potential. The older, long acting SUs like glibenclamide should be avoided because of the increased risk of hypoglycemia, whereas the newer SUs like gliclazide MR or glimepiride can be safely used during *Ramadan*. Given their widespread use and relatively low cost, these newer generation SUs may be used, albeit with caution. If the patient's glycemic control before *Ramadan* is stable, clinicians recommend changing the timing of once daily dose of SU from the usual morning dose to before the sunset meal (*Iftar*); those taking twice daily SU are advised to take half their usual evening dose with the predawn meal (*Sehri*) and

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the usual morning dose with the *Iftar*. Slow release or extended release metformin formulations (SR/XR) are usually well tolerated. These may be a better choice in fasting diabetic patients who are controlled on metformin and can be taken once daily after the *Sehri*. For those on AGIs like acarbose or voglibose, it is good enough to continue with the prescribed doses of these drugs. To lessen the complications faced by diabetic patients who fast during *Ramadan*, health professionals should aim to educate them about safe fasting, not only before and during *Ramadan*, but also at follow-up.

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Chapter 12

Incretin-based Therapies and Fasting during Ramadan

Mahdi Kamoun, Mouna Feki Mnif, Ines Slim

Abstract

Incretin hormones are intestinally derived peptides that play major role in the normal regulation of glucose homeostasis. Incretin effect is impaired in Type 2 diabetes, leading to development of new therapeutic strategies aimed at redressing this abnormality. These strategies include administration of inhibitors of dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for of rapid endogenous incretin degradation, and the use of glucagon-like peptide-1 (GLP-1) receptor analogues. Hypoglycemia is a well-known risk associated with the daytime fasting required during *Ramadan*, especially for individuals with Type 2 diabetes. DPP-4 inhibitors and GLP-1 analogues stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner and carry no intrinsic risk of hypoglycemia. Therefore, such therapies may be suitable for Type 2 diabetic patients who fast *Ramadan*. However, few current data related to the use of DPP-4 inhibitors during *Ramadan* are available. In addition, there are no published studies on the use of GLP-1 analogs during *Ramadan*. Although preliminary clinical studies provide clear and interesting benefits of the use of incretin-based therapies during *Ramadan*, further and larger studies are needed to draw firm conclusions.

INTRODUCTION

The concept of incretin was first hypothesized to exist when it was noted that ingested glucose elicits a larger and longer-lasting insulin response compared with intravenous glucose, suggesting that a mechanism existed within the gut that enhanced insulin release in response to meals.[1,2] This augmentation of glucose-stimulated insulin secretion by oral glucose is defined as incretin effect and is mediated by two intestinally-derived peptides, the glucose-dependent insulinotropic polypeptide (GIP) and the glucagon-like peptide-1 (GLP-1). Both of these incretin play an important role in the normal regulation of glucose homeostasis; but in Type 2 diabetes, only GLP-1 acts to increase glucose-induced insulin secretion.[3,4] Incretin hormones are rapidly degraded by endogenous proteases, dipeptidyl peptidase-4

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(DPP-4). Thus, the glucose-lowering activity of GLP-1 is relatively short lived, with a circulating half-life of less than 2 minutes.[5]

The therapeutic arsenal in Type 2 diabetes has expanded in recent years with the addition of incretin-based antidiabetic agents. Two approaches have thus emerged to increase incretin action: administration of injectable GLP-1 mimetics or analogs, consisting in molecules that are DPP-4 resistant, or administration of inhibitors of DPP-4, able to enhance endogenous GLP-1 and GIP.[6] Major similarities and points of distinction between the two classes of incretin-based therapies are summarized in **Table 1.**[7]

During the holy month of *Ramadan*, Muslims observe a daytime fast and abstain from eating and drinking. Both the act of fasting and the use of antihyperglycemic therapy may increase the risk of hypoglycemia. The EPIDAR (Epidemiology of Diabetes and *Ramadan*) study noted a 7.5-fold increase in the incidence of severe hypoglycemia during *Ramadan* in patients with Type 2 diabetes.[8] To minimize

Table 1: Comparison of GLP-1 analogs and DPP-4 inhibitors[7]

Feature	*GLP-1 analogs*	*DPP-4 inhibitors*
Mode of action	GLP-1 receptor agonist, resistant to degradation by DPP-4	Inhibits degradation of GLP-1, increases endogenous GLP-1 level
Usage	Combination with metformin ± SU ± TZD	Combination with metformin ± SU ± TZD
Administration	Sc injection (pen)	Oral (tablet)
Reduction in HbA_{1c}	~1–1.5%	~0.5–1%
Beta-cell function	Possibly improved	Possibly improved
Extraglycemic benefits	↓ BP, ↓ cholesterol, ↓ LDL, ↓ TG, ↑ HDL, ↑ Left ventricular function, ↑ arterial vasodilatation	↓ BP, ↓ cholesterol, ↓ LDL, ↓ TG, ↑ HDL
Hypoglycemia	Very low-risk	Very low-risk
Weight	Reduction	Neutral
GI adverse effects	Frequent (~35–50%, dose-dependant and usually self-limited)	Uncommon
Gastric emptying	Slowed (most intensive effect with exenatide)	No effect
Other adverse effects	Pancreatitis	Nasopharyngitis, upper respiratory tract infection, headache, elevated liver enzymes (vildagliptin)

Abbreviations: BP—Blood pressure; GI—Gastrointestinal; HDL—High-density lipoprotein; LDL—Low-density lipoprotein; GLP-1—Glucagon-like peptide 1; DPP-4—Dipeptidyl peptidase-4; TG—Triglycerides; TZD—Thiazolidinediones; Sc—Subcutaneous; SU—Sulfonylurea

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such complications, guidelines recommend a pre-*Ramadan* medical assessment of diabetic patients specifically addressing lifestyle as well as timing and dose changes to antidiabetic medication.[9]

Dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists act in a glucose-dependent manner and are associated with less hypoglycemia when compared with conventional treatments, and hence may be suitable for use during *Ramadan*.[10]

This paper summarizes current data about incretin-based agents use during *Ramadan*. We firstly provide a short description of physiological effects of incretin.

PHYSIOLOGICAL EFFECTS OF THE INCRETIN HORMONES GLP-1

Glucagon-like peptide-1 is synthesized in L-cells primarily found in the distal small bowel and colon. It is now recognized that the physiological effects of GLP-1 comprise not only an effect on insulin secreting cells, but also on other pancreatic cells, as well as effects on several extra-pancreatic sites.[4] GLP-1 acts via receptors that are ubiquitously expressed and has been detected in islet cells as well as many other areas such as gastrointestinal tract, heart, vasculature, macrophages, liver, kidney and brain.[4]

Glucagon-like peptide-1 has numerous pleiotropic effects[11] **(Figure 1)**. It stimulates glucose-induced insulin secretion. The effect of GLP-1 on insulin secretion is strictly glucose-dependant and there is no effect of GLP-1 on insulin secretion at low blood glucose concentrations. GLP-1 stimulates not only insulin release, but also insulin biosynthesis and gene expression.[12] GLP-1 is able to suppress glucagon secretion possibly via a paracrine mechanism involving somatostatin, and therefore, it reduces hepatic glucose output.[13] Interestingly, this inhibitory effect on glucagon secretion is also glucose-dependant, meaning that the glucagon counter-regulatory response hypoglycemia is preserved during fasting with no apparent increased risk of hypoglycemic episodes.[14]

Glucagon-like peptide-1 exerts inhibitory effects on gastrointestinal secretion and motility, particularly on gastric emptying. GLP-1 can improve endothelial dysfunction induced by high-fat meals or by hyperglycemia.[15] *In vitro* and preliminary clinical studies also indicate that GLP-1 or GLP-1 agonists can improve endothelial function by direct action on endothelium and can improve left ventricular function following myocardial infarction.[15-17] GLP-1 inhibits intestinal lipoprotein secretion and may lower postprandial hyperlipidemia.[18,19] It can also inhibit muscle glucose utilization while favoring hepatic glycogen stores.[20] GLP-1 has central effects, as it has been shown to preserve neuronal cells, influence neurobehavioral changes (enhanced learning, cognitive performance, spatial memory), reduce caloric intake, and enhance the sensation of satiety.[4,21] Finally, GLP-1 is supposed to improve the function of pancreatic β-cells by promoting neogenesis and proliferation, and by decreasing apoptosis signals.[22,23] Therefore, the incretin may have the potential to improve β-cell function. Indeed, in cultured β-cells and in a rodent model of diabetes, GLP-1 receptor agonists have been shown to cause an increase in β-cell mass.[24]

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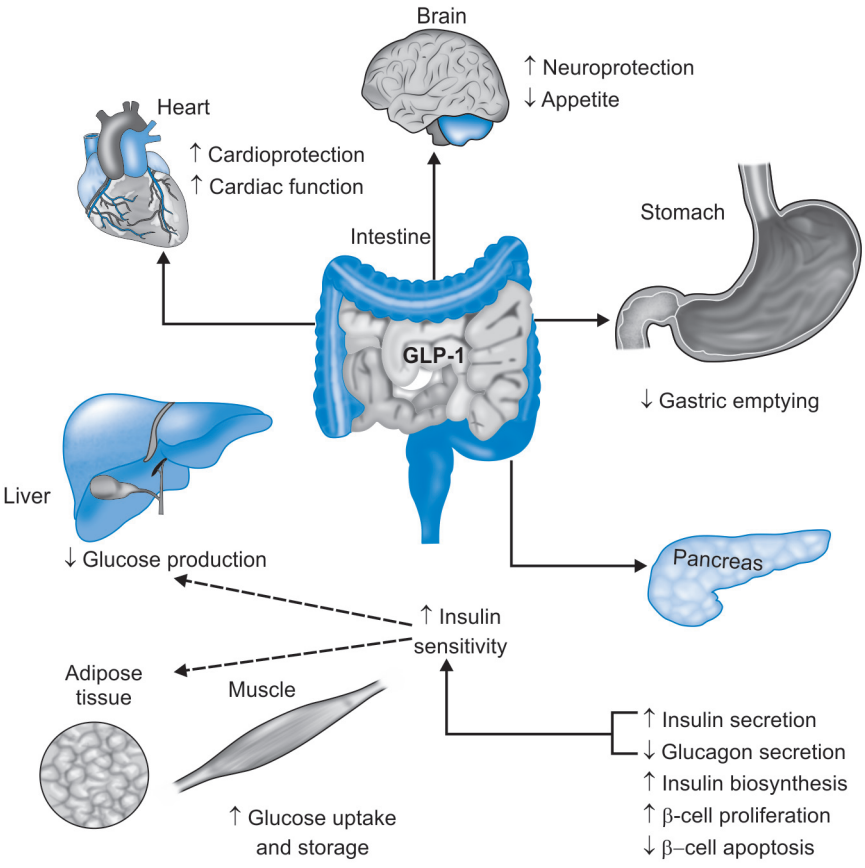

Figure 1: Physiological effects of the incretin hormone GLP-1. GLP-1 administration exerts diverse biological actions on a number of human target organs, such as the pancreas, heart, brain, liver, stomach, muscle and adipose tissue. The actions of GLP-1 in liver, fat, and muscle most likely occur through indirect mechanisms (dotted arrows)[11]

Abbreviation: GLP-1—Glucagon-like peptide-1

DIPEPTIDYL PEPTIDASE-4 INHIBITORS AND RAMADAN FASTING

Dipeptidyl peptidase-4 inhibitors are taken orally. They block DPP-4 activity and thereby increase the free levels of GLP-1. DPP-4 inhibitors have been reported to cause a 0.5–1 percent glycated hemoglobin (HbA_{1c}) reduction.[18,25] Theses agents can reduce HbA_{1c} to a greater extent in patients with higher baseline levels.[26] Also, they can reduced appetite and are not associated with hypoglycemia or weight gain.[7] DPP-4 inhibitors are formulated to allow once daily dosing and the pharmacokinetics are not affected by age, gender, ethnicity or body mass index. Also, no significant drug interactions have been documented.[27]

Current data on the use of DPP-4 inhibitors during *Ramadan* relate to two drugs: vildagliptin (Galvus®, Novartis) and sitagliptin (Januvia®, Merck and Co.).

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Vildagliptin and Ramadan Fasting

In an observational study conducted at northwest London, the authors aimed at evaluating hypoglycemic events (blood glucose < 3.5 mmol/L with or without symptoms), HbA_{1c} and weight change in 52 Muslim patients with Type 2 diabetes who fasted *Ramadan*. These patients were insufficiently controlled before *Ramadan* on metformin 2 g daily alone. Participants were randomized to the addition of either vildagliptin 50 mg daily (26 individuals) or gliclazide 160 mg twice daily (26 individuals). Fewer patients experienced hypoglycemia with vildagliptin plus metformin during *Ramadan* than those taking sulfonylurea (SU) plus metformin (7.7% vs. 61.5% of patients, respectively; $p < 0.001$). The total numbers of hypoglycemic events (HEs) were two with vildagliptin, and 24 with gliclazide. There was one severe case of hypoglycemia in the gliclazide arm and none in the vildagliptin arm. Vildagliptin also reduced the incidence of HEs versus before *Ramadan*, whereas the incidence increased for patients taking gliclazide. Vildagliptin was also associated with a reduction in the mean number of HEs during *Ramadan* compared with before *Ramadan* (on metformin monotherapy), whereas gliclazide was associated with an increase. Both gliclazide and vildagliptin were associated with similar reductions in HbA_{1c} (1.26% in the vildagliptin group and 1.23% in the gliclazide group). There was a small but nonsignificant, increase in weight in both groups (0.12 kg with vildagliptin and 0.38 kg with gliclazide).[28]

More recently, a prospective, observational, noninterventional VECTOR (Vildagliptin Experience Compared To gliclazide Observed during *Ramadan*) study was conducted in the UK. Fifty-nine Muslim patients with Type 2 diabetes were enrolled. These patients were already prescribed vildagliptin (50 mg twice daily; n = 23) or gliclazide (80 mg gliclazide daily; n = 36) add-on to metformin 2 g daily. After enrolment, patients were prescribed the same pre-study regimens. During *Ramadan*, there were no HEs or severe HEs (patient required third-party assistance) with vildagliptin, compared with 34 HEs (in 15 patients) and one severe HE with gliclazide. In the subset of vildagliptin, patients who had pre- and post-*Ramadan* assessments (n = 20), mean HbA_{1c} reduced from 7.7 percent at baseline to 7.2 percent post-*Ramadan* ($p = 0.0594$). This compares with a small (nonsignificant) increase in HbA_{1c} from 7.2 percent at baseline to 7.3 percent post-*Ramadan* in the equivalent subset receiving SU (n = 32). The mean between-group difference for the change from baseline (vildagliptin cohort minus gliclazide cohort) was significant (-0.5%; $p = 0.02$) **(Figure 2)**. Vildagliptin was more tolerated and adhered than gliclazide. Body weight remained unchanged in both groups.[29]

Sitagliptin and Ramadan Fasting

In a large, prospective, randomized, multicenter study, 1,021 patients with Type 2 diabetes and who observed the fast during *Ramadan* were recruited from six Middle East countries. These patients were treated with a stable dose of SU (SU: glimepiride, gliclazide or glibenclamide) with or without metformin for at least the last 3 months prior to enrolment in the study and had HbA_{1c} less than 10 percent at the screening visit. Mean HbA_{1c} at baseline was 7.5 percent. Participants were randomized to either

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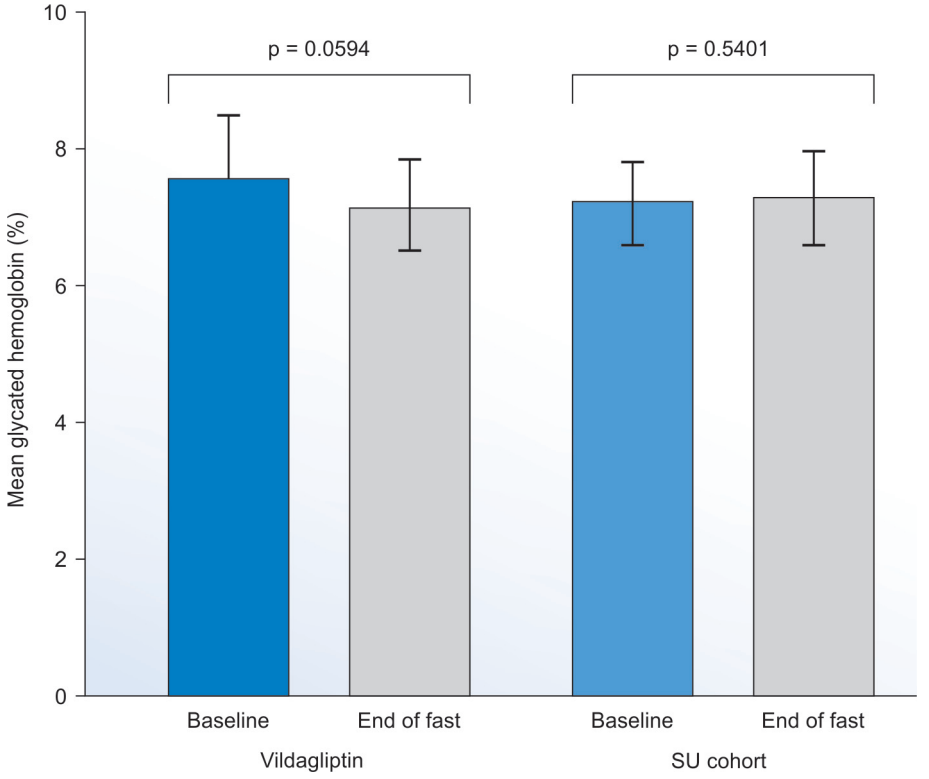

Figure 2: Mean (SD) glycated hemoglobin (HbA_{1c}) at baseline and following *Ramadan* fasting in vildagliptin group (n = 20) and SU (n = 32) group. Mean between-group difference (vildagliptin cohort minus SU cohort) in HbA_{1c} change from baseline was - 0.5% (p= 0.02)[28].

Abbreviation: SU—Sulfonylurea

switch to sitagliptin 100 mg or to remain on their prestudy SU. The proportion of patients who recorded one or more symptomatic hypoglycemia (blood glucose ≤ 3.9 mmol/L with reported symptoms) during *Ramadan* was significantly lower in the sitagliptin group (6.7%) compared with the SU group (13.2%, p < 0.001; **Figure 3**). The proportion of patients with either symptomatic or asymptomatic HEs was 8.5 percent in the sitagliptin group and 17.9 percent in the SU group (p < 0.001). In both groups, there were no reports of severe hypoglycemia, and no reports of patients requiring medical assistance due to a hypoglycemic event.[30]

A similarly designed study was conducted in India and Malaysia and involved 870 patients. The proportion of patients who recorded at least one symptomatic hypoglycemic event during *Ramadan* was lower with sitagliptin (3.8%) compared to SU (7.3%). The total proportion of symptomatic or asymptomatic HEs was 4.8 percent in the sitagliptin group and 9.6 percent in the SU group. No patient discontinued treatment due to a hypoglycemic event. One patient on sitagliptin and seven on SU had an event that required nonmedical assistance. No events requiring medical assistance were noted. Both treatments were generally well-tolerated during *Ramadan*.[31]

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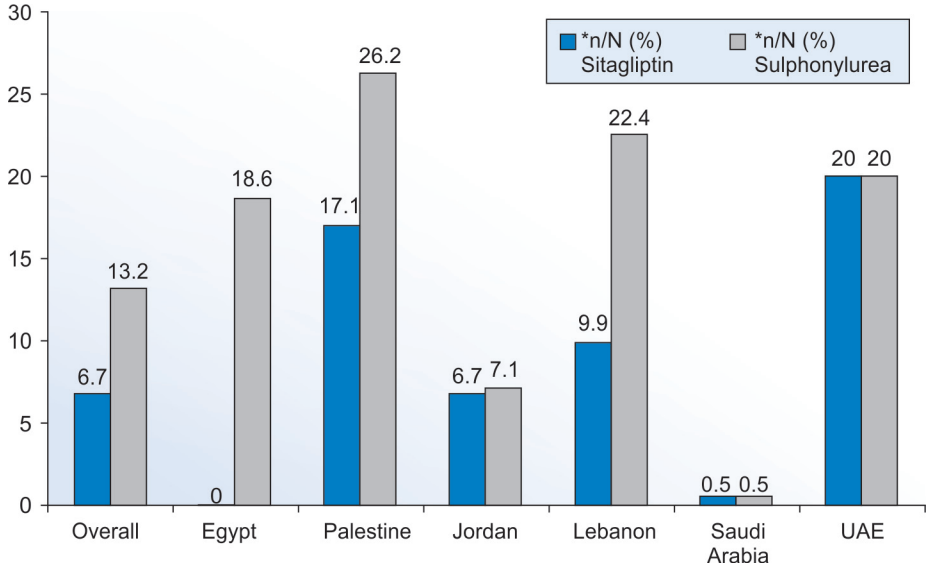

Figure 3: Proportion of patients reporting symptomatic hypoglycemia during *Ramadan* overall and by country[29]

*Number of patients experiencing event/number of patients overall or in each country by treatment (%)

In conclusion, both studies on sitagliptin use during *Ramadan* showed a nearly 50 percent reduction in the risk of symptomatic or asymptomatic HEs with sitagliptin relative to SU treatment.

GLP1 RECEPTOR ANALOGS AND RAMADAN FASTING

By mimicking the effects of GLP-1, GLP-1 receptor analogs inhibit glucagon and stimulate insulin secretion in a glucose-dependent manner, reduce the gastric emptying rate, and suppress appetite leading to a weight loss.[32] These analogs, which are administered by subcutaneous injection, include the short-acting (half-life 2 hours) exenatide (Byetta®; Eli Lilly) and once-daily liraglutide (Victoza®; Novo Nordisk). Long-acting formulations are in development.

Exenatide can be dosed before the two main meals and is not associated with significant effects on fasting glucose. In a recent large randomized trial, the authors have showed that exenatide twice daily as add on to metformin reduced worsening of glycemic control and rate of hypoglycemia compared with add-on glimepiride in patients with Type 2 diabetes inadequately controlled by metformin alone.[33]

Liraglutide is a once-daily formulation that can be taken independently of meal times, and has significant antiglycemic effects with fasting.[34] In a randomized, double-blind, active controlled, double-dummy, parallel-group study, liraglutide as monotherapy provided better glycemic control with fewer HEs than did glimepiride in patients with early Type 2 diabetes previously treated with either diet and exercise or oral antidiabetic monotherapy.[35]

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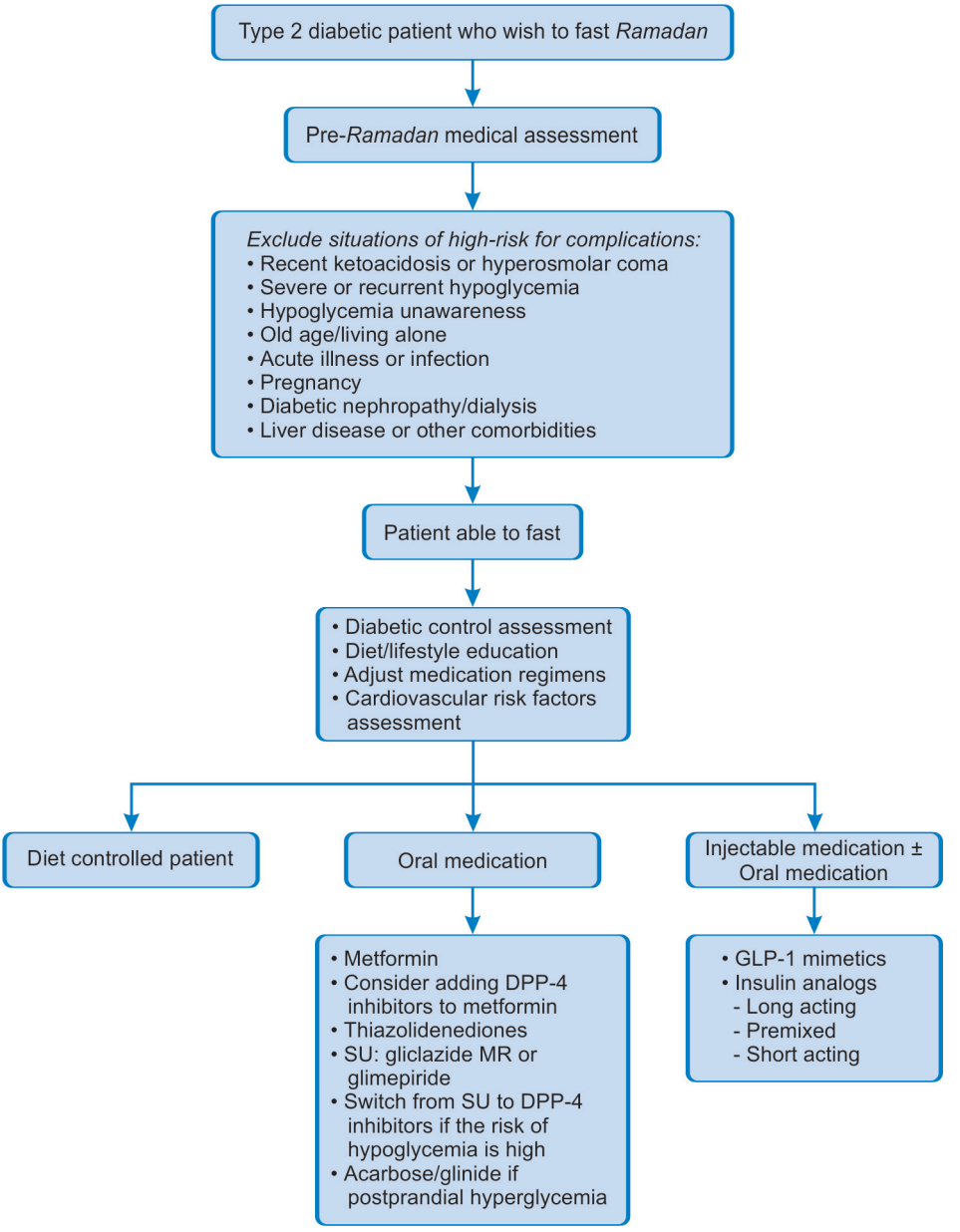
Flow chart 1: Suggested role of incretin-based therapies in the management of type 2 diabetic patients who wish to fast *Ramadan*



Abbreviations: GLP-1—Glucagon-like peptide 1; DPP-4—Dipeptidyl peptidase-4; SU—Sulfonylurea; MR—Modified release

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Exenatide and liraglutide injections have a potential for safe use during *Ramadan*, primarily because their reduced risk of hypoglycemia. This low-risk of hypoglycemia may offer advantages regarding medication adherence during *Ramadan*; as hypoglycemia is a major problem for antidiabetic medication adherence. However, hypoglycemia can still occur when GLP-1 receptor agonist therapy is combined with an insulin secretagogue such as a SU. Therefore, insulin secretagogue dose should be adjusted when it is combined with a GLP-1 analog.[36]

In a head-to-head comparison of liraglutide and exenatide in combination with metformin and/or SU, liraglutide reduced HbA_{1c} by significantly more than exenatide (1.12 ± 0.08% vs. 0.79 ± 0.08%, $p < 0.0001$).[37] Others studies have also shown that liraglutide is associated with less pronounced gastrointestinal side effects compared with exenatide.[38,39] As yet, there are no published reports on the use of GLP-1 analogs during *Ramadan*.

CONCLUSION

Current data indicates that incretin-based antidiabetic agents may have a role to play in the management of Muslim patients with diabetes during *Ramadan*, particularly to reduce their risk of hypoglycemia during the long daytime fasting periods. Furthermore, patients who fasted showed very good adherence to these drugs making them an attractive therapeutic option for the safe management of fasting. Suggested role of incretin-based therapies in the management of Type 2 diabetic patients during *Ramadan* is provided in **Flow chart 1**. Further and larger studies are needed to draw firm conclusions.

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Chapter 13

Type 1 Diabetes Mellitus and Fasting during Ramadan

Rakesh Sahay, V Sri Nagesh

Abstract

Fasting during *Ramadan* is fraught with multiple medical problems for patients with T1DM. The risks of fasting include hypoglycemia, hyperglycemia, DKA, and dehydration. The *Ramadan* fast typically consists of a fasting period which can extend up to 12 hours in summer and 8–9 hours in winter. Once the fast is broken, it is followed by a heavy evening meal. The meals are also traditionally rich in fats and carbohydrates. In patients with T1DM, the normal metabolic mechanisms become modified by various factors like hypoglycemia unawareness and autonomic neuropathy leading to lack of epinephrine rise during episodes of hypoglycemia and failure of glucagon secretion to increase, during hypoglycemia. Excessive decrease of insulin dose during fasting can precipitate hyperglycemia and diabetic ketoacidosis (DKA) and a relatively higher dose can lead to hypoglycemia. However, fasting during *Ramadan* for patients with T1DM is feasible, provided good pre-*Ramadan* glycemic control is initiated, appropriate education and preparation for the fasting period is imparted and coordination is maintained between the health care provider and the patient is maintained throughout the fasting period and also subsequently.

INTRODUCTION

Ramadan, the 9th month of the Islamic calendar, is synonymous worldwide, as the month of fasting. During this month, a majority of the more than 1 billion Muslims worldwide observe an absolute fast from dawn to dusk without intake of any food or drink. People whose health can be negatively impacted by fasting are exempt from it, but many people still insist on fasting, because the *Ramadan* fast is one of the five pillars of Islam. Data from the *EPIDIAR*[1] study, which was conducted across 13 countries in 2004 and included 12,243 participants, who fasted during the month of *Ramadan*, indicated that 42.8 percent of patients with Type 1 diabetes reported fasting at least 15 days during *Ramadan*. The *Ramadan* fast typically consists of a fasting period which can extend up to 12 hours in summer and 8–9 hours in winter. Once the fast is broken, it is followed by a heavy evening meal *Iftar* and a lighter meal *Saher*, before sunrise, interspersed with snacks. The meals are also traditionally rich in fats and carbohydrates. The International Consensus Meeting[2] held in Morocco in

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1995 defined suitable criteria for fasting and exempted people with Type 1 diabetes from fasting. However, a sense of appreciation of their religious responsibilities and a desire to fast along with other adherents of the faith has ensured that a large majority of Muslims with Type 1 diabetes mellitus (T1DM) continue to fast during *Ramadan*.

ALTERED PATHOPHYSIOLOGY DURING FASTING

While fasting, circulating glucose levels decrease, leading to decreased secretion of insulin and increase in levels of counter regulatory hormones and increasing glycogenolysis and gluconeogenesis. Further prolonged fasting leads to adipose tissue breakdown and ketogenesis. Normally, the body has enough glycogen stores to support fasting for up to 10–12 hours, before gluconeogenesis and ketogenesis become predominant. In patients with T1DM, these mechanisms become modified by various factors like hypoglycemia unawareness and autonomic neuropathy, leading to lack of epinephrine rise during episodes of hypoglycemia and failure of glucagon secretion to increase during hypoglycemia. Excessive decrease of insulin dose during fasting can precipitate hyperglycemia and diabetic ketoacidosis (DKA) due to unfettered glycogen breakdown and increased gluconeogenesis and ketogenesis. Other studies have demonstrated a rise in high-density lipoprotein (HDL) levels and a fall in triglycerides during fasting, while blood pressure remained unchanged.[3]

COMPLICATIONS OF FASTING

Fasting during *Ramadan* is fraught with multiple medical problems for patients with T1DM. The risks of fasting include hypoglycemia, hyperglycemia, DKA and dehydration.[4]

Hyperglycemia

Hyperglycemia is one of the most common problems observed during this month. A fear of hypoglycemia on part of both the doctors and the patients, coupled with carbohydrate and calorie-rich meals, associated with an abrupt change in meal times and use of insulin contributes to this hyperglycemia. Water is also proscribed during the fast throughout this month. While fasting, eating and drinking are exclusively at night. Further, the management of children with diabetes who choose to fast during *Ramadan*, also poses a challenge, as the majority of guidelines and data on safety and metabolic impact of fasting are based on practice and studies on adult population. The EPIDIAR (Epidemiology of Diabetes and *Ramadan*) study[1] reported a five-fold increase in the incidence of severe hyperglycemia (requiring hospitalization) and an approximate three-fold increase in the incidence of severe hyperglycemia with or without ketoacidosis in patients with Type 1 diabetes. However, there is no information linking yearly episodes of a month long fast and diabetes-related complications.

Diabetic Ketoacidosis

Patients with Type 1 diabetes, who fast during *Ramadan* are at a greater risk for developing DKA. This is plausible in the setting of pre-fast poor control and compliance,

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carbohydrate-rich meals, the tendency to reduce insulin doses for fear of hypoglycemia and in the setting of infection. However, data which supports the increased incidence of DKA during the *Ramadan* fasting is scarce. In fact, studies by Kadika[5], Abusreiwil[6] and Rafik[7] have reported rates of incidence of DKA during *Ramadan* fasting, which are similar to the general population incidence rates. However, given the increased risk factors for DKA during fasting and the high morbidity and mortality associated with DKA, appropriate education about recognizing DKA and vigilance for its symptoms must be strictly enforced during *Ramadan* fasting.

Dehydration

Multiple factors are responsible for dehydration during fasting, including a restriction on fluid intake while fasting, osmotic diuresis due to hyperglycemia, fasting during summer and increased physical activity and associated sweating. Dehydration, especially when severe, can manifest as postural dizziness, orthostatic hypotension leading to falls and fractures, especially in the older people, and the most dreaded complication of thrombosis. Dehydration precipitates a hypercoagulable state due to contraction of intravascular volume and increase in the viscosity of blood. Diabetes itself is a prothrombotic state due to decreased fibrinolysis and endogenous anti-coagulants and the rise in a few clotting factors. This thrombotic state can manifest as a cerebrovascular accident, myocardial infarction or even as retinal vein occlusion.

Hypoglycemia

Fasting can precipitate hypoglycemia due to a reduction in oral intake. The impact of fasting during *Ramadan* on incidence of hypoglycemia and mortality is not well known. The EPIDIAR study[1] found that the change in eating patterns during *Ramadan* increased the risk of severe hypoglycemia 4.7-fold (from 3 to 14 events per 100 people per month) in Type 1 diabetes. Further, severe hypoglycemia was probably under-reported in this study, because only episodes requiring hospitalization were considered. Another study by Loke SC et al.[8] found that relative risk (RR) of hypoglycemia of 1.60 during *Ramadan* fasting, compared with a non-fasting period of equivalent length. Good metabolic control [glycated hemoglobin (HbA_{1C}) < 8 percent)] and old age (> 60 years) increased RR more than twice, while taking breakfast prior to fasting reduces RR to less than half. These RR are lower than what have been reported by EPIDIAR.[1] Hypoglycemia is of special concern in children and adolescents due to its neurocognitive impact. Some of the factors which can influence the severity of hypoglycemia while fasting are: the age of patient with T1DM, duration of diabetes, prior glycemic control, level of diabetes education and the type of insulin being used. In a study by Kadiri et al.[9] when lispro was compared with regular insulin in T1DM patients on a *Ramadan* fast incidence of hypoglycemia (15 episodes for lispro vs. 31 for regular insulin), frequency of hypoglycemia (0.7 ± 0.19 episodes for lispro vs. 2.26 ± 0.36 episodes/patient/30 days for regular insulin) and nocturnal hypoglycemia (5 episodes for lispro vs. 27 for regular insulin) were lower with lispro, while compliance with recommended time of insulin injection was better, thus underlining the advantages of rapid acting analogs over regular insulin in fasting patients with T1DM.

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Data about impact of *Ramadan* fasting on chronic complications of diabetes is very sparse.

PRE-RAMADAN MEDICAL ASSESSMENT

Patients with T1DM who plan to fast during *Ramadan* should undergo a medical assessment 2–3 months prior to fasting. This assessment should include evaluation of HbA1C, lipids, blood glucose values and other parameters **(Table 1)**. Patients should also be apprised of the risks of fasting, as also the exemptions granted to patients who are not suited to fasting **(Table 2)**. Necessary changes in diet and exercise regimen should also be initiated at this point of time.[10]

Table 1: Prior screening for fasting (2–3 months prior to *Ramadan*)
• Diet and lifestyle history
• Diabetes education status and awareness of complications of diabetes
• History of medication, diet and medication compliance
• Blood pressure record
• Body mass index (BMI)
• HbA_{1C}
• Fasting, pre-lunch and pre-dinner sugar chart
• Fasting lipid profile
• Liver and renal function tests
• Evaluation for retinopathy and nephropathy (if T1DM duration > 3 years)
• Evaluation for macrovascular complications (if T1DM duration > 3 years)

Abbreviations: HbA_{1C}—Glycated hemoglobin; T1DM—Type 1 diabetes mellitus

Table 2: T1DM patients for whom fasting is not advisable
• Children under 8 years of age
• Pregnant women with T1DM
• HbA_{1C} less than 10 percent
• Poor compliance with diet and insulin
• Diabetic nephropathy and severe retinopathy
• Vascular disease, uncontrolled hypertension or urolithiasis
• At least one episode of diabetic ketoacidosis or severe hyperglycemia requiring hospitalization in the past 2 months
• Four episodes of minor hypoglycemia or two episodes of major hypoglycemia in the past 2 months
• Elderly patients with T1DM

Abbreviations: HbA_{1C}—Glycated hemoglobin; T1DM—Type 1 diabetes mellitus

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STRUCTURED DIABETES EDUCATION

A structured *Ramadan*-focused diabetes education program, is perhaps the single most important intervention for a successful *Ramadan* fast in diabetic patients. Unfortunately such programs are hampered by lack of awareness among patients, health care providers and religious leaders. Hence, to ensure success, such programs should involve an awareness campaign about fasting in patients with diabetes focusing on the mosques and community centers. Health care professionals should also be made aware of the recent guidelines on this subject and requisite training imparted, to deliver necessary health care. Religious leaders should also be involved in these campaigns.

Components of this program include:

- Importance of self-monitoring of blood glucose (SMBG)
- Appropriate meal choices
- Recognition of DKA, hyperglycemia and hypoglycemia
- Avoiding excessive physical activity and dehydration promoting behavior
- Cessation of fasting whenever required.

This education should be imparted in the vernacular, either singly or as group discussions at mosques, community or health care centers or as brief lectures over mass media or social networks. The benefits of a well delivered diabetes education program can extend well beyond the period of fast and can lead to a positive impact on glycemic control of patients with T1DM. In an observational study by Bravis et al.[11] patients who fasted during Ramadan without the benefit of a structured educational program suffered a 400 percent rise in hypoglycemic events, whereas those who attended an education program showed a significant decline in hypoglycemic events.

MANAGEMENT (FLOW CHART 1)

Diet

Diet should be similar to the diet being taken prior to *Ramadan*. Simple carbohydrate and fats should be curtailed. Rather than taking a large quantity of food in the evening meal, the evening meal could be broken down into a medium sized lower calorie meal followed by a snack. Liberal intake of fluids during the night should be encouraged. The evening meal should have more simple carbohydrates to ensure normalization of blood glucose levels, while the predawn meal should comprise more of complex carbohydrates and foods like maize which release calories slowly throughout the day. The predawn meal should also be taken as close to sunrise, as is feasible.

Exercise

While some physical activity during the day is encouraged, it should not be overdone, especially in the late afternoon, as it can precipitate hypoglycemia and also lead to dehydration. Physical activity during the prayers should also be factored into the quantum of total daily exercise.

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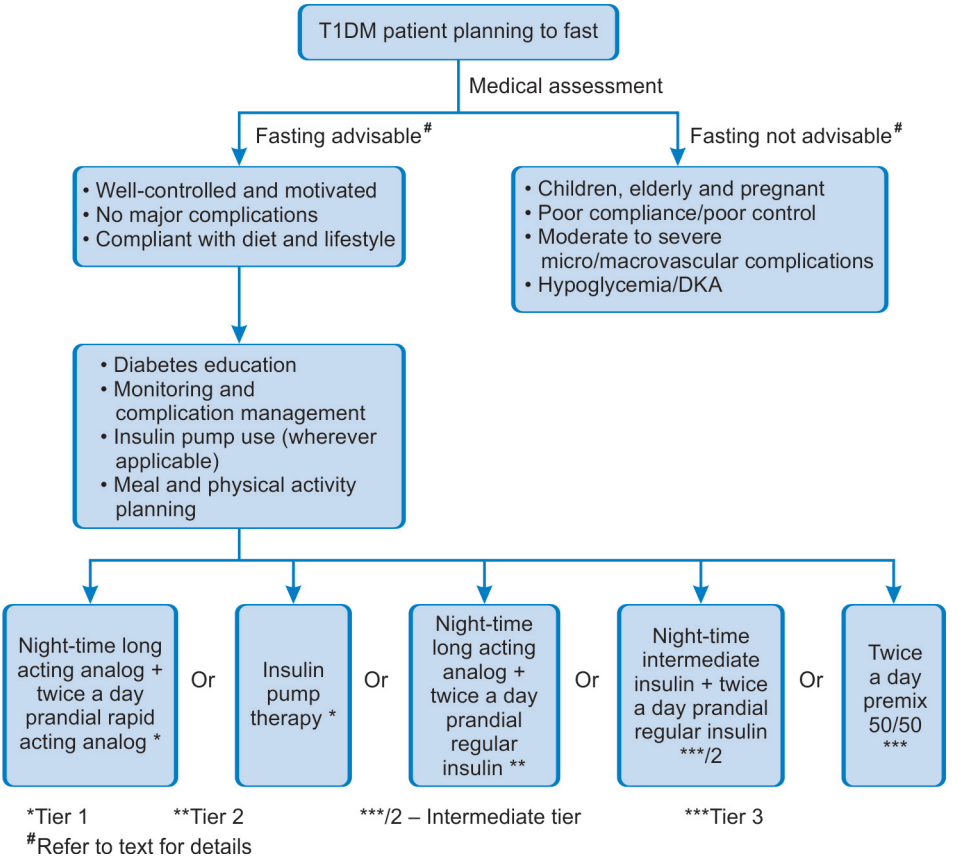
Flow chart 1: Approach to a Type 1 diabetes mellitus patient planning for *Ramadan* fast



Abbreviations: T1DM—Type 1 diabetes mellitus; DKA— Diabetic ketoacidosis

Insulin Regimens

Several insulin regimens have been proposed by various studies and guidelines. When prescribing a regimen, a balance should be sought between safety, efficacy, cost of therapy and patient acceptability. Individualization of regimens based on the pre-*Ramadan* glycemic record can be helpful. Some of the regimens which can be used are mentioned in **Table 3** and a few caveats regarding insulin therapy in **Table 4**.[12,13]

Insulin Pumps

The increasing availability and rising affordability of insulin pumps have provided a new option for managing T1DM during *Ramadan*. While studies about pump therapy are limited, a few studies have been published in the past 2–3 years, all of

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Table 3: Insulin regimens

*Basal-bolus analog**	*Basal-bolus conventional***/2*	*Twice daily regimen****	*LA analog + Regular insulin***	*Insulin pump**
Single dose of long-acting analog in late evening with two doses of prandial short-acting analog. Correcting doses of short-acting analog as required, based on SMBG	Single dose of NPH in late evening with 2 doses of prandial regular insulin.	To use morning dose of premix /split mix regimen before evening meal and use only short-acting insulin at 0.1–0.2 u/kg before pre-dawn meal	Single dose of long-acting analog in late evening with two doses of prandial regular insulin. Useful when early morning hypoglycemia is to be avoided and affordability precludes short acting analog	Reduce basal infusion rate and increase bolus dose prior to evening and morning meals.

*Tier 1—Most preferred

**Tier 2—Less preferred

***/2-tier intermediate—Less preferred—cost cutting measure

***Tier 3—Least preferred

Abbreviation: SMBG—Self-monitoring of blood glucose

Table 4: Caveats regarding insulin therapy and SMBG during *Ramadan* fast[13]

- Basal insulin should be reduced by up to 20 percent of pre-dose
- If using premix, 50/50 can be used instead of 30/70 to avoid post-prandial hyperglycemia
- As a starting point, transfer morning pre-meal dose to evening and take half of pre-dinner dose before the dawn meal. Titrate according to SMBG
- Adjust insulin doses every 3 days or more frequently, if required
- Insulin therapy should be supported by frequent SMBG
- Blood glucose levels should be monitored half an hour before and 2 hours after evening meal, 2 hours after pre-dawn meal, at mid-day and whenever symptoms suggestive of hypoglycemia or hyperglycemia occur
- End fast if blood glucose < 60 mg/dL or > 300 mg/dL
- Avoid fasting on sick days
- Use of carbohydrate counting and correction doses of short acting insulin as required

Abbreviation: SMBG—Self-monitoring of blood glucose

which have endorsed the efficacy and safety of insulin pumps during *Ramadan*. A pump is very useful in balancing the risk of hypoglycemia while fasting and the hyperglycemia which can set in after the heavy evening meal, by timely adjustments of basal and prandial insulin delivery through pump. In a study by Al Baker et al.[14] T1DM patients on insulin pump, when compared to patients on multiple daily insulin

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injections (MDII) or premix insulin, were able to fasting period able to complete their fasting with minimal episodes of mild hypoglycemia (two episodes per patient), no episodes of hypoglycemia requiring assistance and no emergency room (ER) visits. They also had better biochemical profiles than patients on premix insulin and profiles comparable to patients on MDII. In another study by Khalil et al.[15] patients on pump had no change in basal insulin requirements from the pre-fasting period, had very few episodes of minor hypoglycemia which were easily managed by titration of doses and no episodes of major hypoglycemia, thus underlining the advantages of pump therapy. However, to use a pump during *Ramadan*, the patient needs to be educated about the pump, motivated to monitor blood glucose frequently and should also be able to afford pump therapy. If these limitations are overcome, insulin pumps seem to provide the best possible solution for control of sugars during *Ramadan* fasting with minimal complications.

FUTURE PERSPECTIVES

Smart Insulins

These comprise a new type of insulin delivery system, based on nanotechnology. These glucose-responsive controlled insulin delivery systems are based on the agglomerated vesicle technology (AVT), which is a chemically cross-linked agglomerate of liposomes loaded with insulin.[16] The break-up of these chemical cross links can be initiated by high blood glucose levels, thus releasing insulin from the agglomerate and restoration of blood glucose to normal levels. The quantity of insulin released is proportional to the blood glucose level and thus, the hypoglycemia generally associated with insulin use can be avoided. Initially, a lectin, cancavalin–A was used as a cross-linker,[16] but due to its toxicity and inflammatory effects, it was discarded and boronic acids are now being explored. In addition, to being non-toxic and noninflammatory, more so when conjugated with lipid polyethylene glycol (PEG), boronic acids[17] have also been found to have a basal untriggered release of insulin, a property not found with concavalin-A. This helps to avoid a build-up of cross-linked insulin in the body and also ensures a basal insulin release. These insulins are at least a decade away from commercial development, but have the potential to be useful for treatment while fasting during *Ramadan* and in avoiding hypoglycemia.

Dipeptidyl Peptidase-4 Inhibitors and Alpha Glucosidase Inhibitors

Postprandial hyperglycemia, especially after the evening meal is one of the major concerns of the *Ramadan* fast. This can be countered by increasing the insulin dose, but sometimes, postprandial hypoglycemia can be precipitated, especially in T1DM patients with autonomic neuropathy or nephropathy. Recently a few studies have explored DPP-4 inhibitors in T1DM. In a study by Hari Kumar et al.[18] T1DM patients who used insulin and sitagliptin had lower insulin requirements, lower body mass index (BMIs) and HbA_{1C} and a nonsignificant decrease in the incidence of hypoglycemia when compared to users of insulin alone. Another study by Ellis et al.[19] showed improved measures of glycemic control, including mean blood glucose and time in euglycemic range when sitagliptin was used along with insulin. Another study

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by P. Sharifi et al.[20] demonstrated lower HbA_{1C}, fasting and post-prandial glycemic values along with reductions in total cholesterol and triglycerides, when acarbose was used along with insulin. While none of these studies were conducted during *Ramadan* fasting, these studies do seem to suggest DPP-4 inhibitors and alpha-glucosidase inhibitors (AGIs) as viable add-ons to insulin therapy in T1DM patients on a *Ramadan* fast.

In conclusion, fasting during *Ramadan* for patients with T1DM is feasible, provided good pre-*Ramadan* glycemic control is initiated, appropriate education and preparation for the fasting period is imparted and coordination is maintained between the health care provider and the patient, throughout the fasting period and also subsequently. Appropriate selection of patients for the fast is also mandatory.

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Chapter 14

Insulin in Type 2 Diabetes Mellitus

Altamash Shaikh, Manoj Chadha

Abstract

A significant proportion of diabetes patients fast in *Ramadan* and are either already on insulin or may be started (naive), presenting a challenge for the management to the health care providers. This chapter emphasizes on the importance of prerequisite of insulin, its strategies, and role of insulin in special populations like the pregnant lady and the elderly. Implementing insulin in management through patients and their family members will provide a successful path towards the unbroken barriers and complications of diabetes. Prevention of hypoglycemia is mainstay of diabetes management in *Ramadan*. Monitoring of blood glucose for dose adjustment and prevention of glycemic excursions are dealt with. Insulin regimens should be tailored to meet individual needs of a patient in *Ramadan*.

INTRODUCTION

With the advent of insulin, life in various situations has become easy for the diabetic patient. One such situation is the change in lifestyle for people, who fast during *Ramadan*. Although, diabetics are exempt from fasting in *Ramadan*, some people yet insist on fasting. This requires a special session with patient, the pre-*Ramadan* counseling. The treating physician should explain the changes that occur while fasting in a diabetic. With the increasing prevalence of diabetes and more physician's will be facing the challenge of management of diabetic patients who wish to fast. Nevertheless, insulin treatment holds the biggest challenge for patients and physicians due to unbroken barriers and unwanted complications. This chapter will focus on various aspects of insulin therapy in patients fasting in *Ramadan*.

WHY INSULIN IN RAMADAN?

In 78.7 percent of Muslim patients with Type 2 diabetes fast during *Ramadan*, as revealed by the population-based Epidemiology of Diabetes and *Ramadan*, (EPIDIAR) study.[1]

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The very aim of giving insulin in fasting patients in *Ramadan* is to supplement basal insulin to reduce the relative insulin deficiency and also to reduce the insulin resistance. This reduces the hepatic glucose output, which happens due to glucagon and other counter-regulatory hormones during the fasting hours.[2]

The treating physician must keep in mind these alteration in normal metabolism while managing a diabetic patient in *Ramadan*.

Insulin effectively controls the progressive nature of Type 2 diabetes. It directly influences quality of life by achieving euglycemia and indirectly by reducing the fear of development of secondary complications.

With the change in pattern of life in *Ramadan*, and poorly controlled patients insulin stands the best for these patients, willing to fast.

PREREQUISITES FOR INSULIN IN RAMADAN

Patient's lifestyle, pattern of meals (content and timing), comorbidities, cost and affordability must be considered before insulin therapy. Foods and fluids are allowed between sunset and sunrise. However, some people have only two meals, but few also have dinner depending on the content of sunset meal (*Iftar*). Knowing the dietary pattern is of vital importance in deciding the insulin regimen.

The duration of fast changes with season and geographic area of residence and may range up to 20 hours a day. *Ramadan* can coincide with any month of the English calendar as there is a season to season variation of the lunar. Patient and next of kin must be taught how to recognize hypoglycemia, hyperglycemia, dehydration and ketosis. Total calorie intake should be kept as far as possible, the same as in pre-*Ramadan* days.

The possible risks involved in fasting have to be told to each individual patient.

Therapeutic inertia to start insulin must be tackled to obtain euglycemia. Physician must plan effectively and decide on whether the patient will be able to cope with the fast, and accordingly prescribe various insulin regimens to cater to the need of their patients. It is also imperative for the physician to emphasize the need for self-monitoring of blood glucose (SMBG) in *Ramadan*.

Also, assess control of metabolic parameters like blood glucose, blood pressure, glycated hemoglobin, electrolytes, renal, hepatic, lipid status.

The overall wellbeing of the patient should be addressed with utmost care.

STRATIFICATION[2] BEFORE RAMADAN INSULIN INITIATION

Very High-Risk

- Severe hypoglycemia within the 3 months prior to *Ramadan*
- A history of recurrent hypoglycemia
- Hypoglycemia unawareness
- Sustained poor glycemic control
- Ketoacidosis within 3 months prior to *Ramadan*
- Type 1 diabetes mellitus
- Acute illness

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- Hyperosmolar hyperglycemic coma within the previous 3 months
- Performing intense physical labor
- Pregnancy
- Chronic dialysis.

High-Risk

- Moderate hyperglycemia (average blood glucose 150–300 mg/dL or A1C 7.5–9.0%)
- Renal insufficiency
- Advanced macrovascular complications
- Living alone and treated with insulin or sulfonylureas
- Patients with comorbid conditions that present additional risk factors
- Old age with ill health
- Treatment with drugs that may affect mentation.

Moderate Risk

Well-controlled diabetes treated with short-acting insulin secretagogues.

Low-Risk

Well-controlled diabetes treated with lifestyle therapy, metformin, acarbose, thiazolidinediones, and/or incretin-based therapies in otherwise healthy patients.

INSULIN, COUNSELING AND RAMADAN

Counseling forms the integral part of management of diabetes. One Indian study[3] has shown that only the one-third of patients receive counseling about fast during *Ramadan*. As a result, there are more number of hypoglycemic episodes and hyperglycemic excursions. In this study, patients' attitude towards *Ramadan* and fasting was assessed, emphasizing the importance of counseling regarding insulin, diet and lifestyle. Apart from this, physician must also educate about when to break a fast in emergency, by providing details of symptoms of hypoglycemia and hyperglycemia and home monitoring of blood glucose. Patients with previous experience of fasting, who receive counseling, do better than new patients in terms of outcomes during successive *Ramadan*.

INSULIN INDIVIDUALIZATION AND RAMADAN

The special needs of a diabetic patient in *Ramadan* need to be addressed on a one to one basis. This with its outcomes, strengthens patient and physician bond. Individualization is the most crucial concern while treating a diabetic, especially so when in *Ramadan*.[2] It should be always remembered that glycemic control may alter as fasting days approach, while in some it may happen, also during or even post-*Ramadan*. The same patient may have different requirements of insulin at different time. Hence, there is a need for individualization. It can be achieved by

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physician-related and patient-related educational program for *Ramadan*. A dietary plan to adjust metabolic and nutritional needs should be made for the patient on an individual basis.[4] Only after considering the meal, activity, complications of diabetes, etc. can be individualized at it best.

INSULIN INITIATION (INSULIN NAÏVE PATIENTS) AND RAMADAN

Ramadan offers a very good opportunity for a direct discussion for lifestyle changes and insulin initiation. Patients become more disciplined as a part of worship and fasting may prove beneficial for various aspects of diabetes management. One point that differentiates Type 1 from Type 2 diabetics in *Ramadan* is the lesser incidence of hypoglycemia.[2] This can further be reduced by selecting the type and pattern of dosage of insulin. One of the simplest regimen is to get the fasting glucose values under control, by starting on a basal insulin.

Let us start by this patient example who wishes to fast but has hypoglycemic events due to his present oral regimen, weight gain, uncontrolled hyperglycemia. Insulin is to be initiated, after pre-*Ramadan* counseling for better control of metabolic parameters. For this kind of individuals, we generally would start on single daily basal insulin. This basal insulin would give a long-lasting cover for the glucose fluctuations and make smoother control, while performing fast. Also, analogs have proven to be better than conventional long-acting insulin. As a rule, the pre-sunset meal (*Iftar*) and pre-sunrise meal (*Suhur*) glucose values provide good information on initiation of basal insulin. Basal insulin can be given just after or before the sunset meal (*Iftar*) or in some patients it can be given at bedtime or pre-dinner if the person has that meal.

Another scenario where insulin initiation succeeds is by giving a flexible regime of premixed insulin once then if required twice daily, but with careful dosing. By just inverting the dosage pattern that we start in clinical practice. Hence, in *Ramadan*, we can give two-thirds of the dose in evening and half of the evening dose at dawn (*Suhur*). This regimen is the most acceptable to patients as seen in clinical practice. Insulin initiated this way is safer for the patient giving better control and avoids metabolic complications. The shifting of patients from conventional insulin to analogs may not be justifiable in metabolically well-controlled patients.

Unlike the earlier belief, insulin initiation is associated with biochemical, physical social and psychological wellbeing **(Table 1).**

INSULIN CONTINUATION AND RAMADAN

Another set of patients, who wish to fast and are already on insulin needs to be dealt differently. If the patient is only on a basal insulin, reducing the dosage by around 30 percent suffices the glycemic need for the patient. Any further insulin adjustment should be done in the light of glucose monitoring. Example: pre-*Ramadan* 30 units, in *Ramadan* 21 units.

If the patient is on single premix insulin dose, reducing it by 20 percent, and taking at sunset meal (*Iftar*) gives a better evening glycemic control. Example: pre-*Ramadan* 40 units, in *Ramadan* 32 units.

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Table 1: Insulin initiation (naïve patients) and *Ramadan*	
Recommendation	*Insulin initiation*
Pre-*Ramadan*	During *Ramadan*
Basal (NPH, glargine, detemir)	Bedtime only Titrate fasting glucose
Basal (NPH, detemir)	Twice daily if uncontrolled
Premix conventional or analogs	
Premix once daily	Sunset meal (*Iftar*)
Premix twice daily	Sunset meal (*Iftar*) and sunrise meal (*Suhur*)
Titrate doses as per control, move to continuation phase as required	

If the patient is on two premix insulin dose, 100 percent of the pre-*Ramadan* morning dose of 2.33 premixed insulin may be given at *Iftar* and 50 percent of the usual evening dose at *Suhur*, i.e. if patient is on 30 units in morning and 20 units at dinner then give full 30 units at sunset meal (*Iftar*) and 10 units at sunrise meal (*Suhur*) or If the patient is on basal bolus therapy, and takes two meals only in *Ramadan*. Then this can be switched to basal plus regimen. To give one basal at evening meal, and a short acting post-dawn meal (*Suhur*). Example: Basal insulin at sunset meal (*Iftar*) and short acting at sunrise meal (*Suhur*).

If the patient is on basal bolus therapy, and takes three meals, i.e. dinner in addition to above two meals, then an extra shot of rapid acting insulin is a must predinner to avoid premorning hyperglycemia. Example: 20 percent reduced dose of basal insulin at 10 pm, three short-acting insulin: First at sunset meal (*Iftar*), second dose at dinner and third dose (50% of dinner dose) at sunrise meal (*Suhur*).

Few patients already on a premixed regimen, who choose to fast, should have their regimen inversed. This is accomplished by giving the full morning dose at pre-sunset meal. The usual evening dose in this category of patients can be reduced by half and given at the pre-sunrise meal. Continuation of insulin this way has given better clinical outcome in clinical practice **(Table 2)**.

INSULIN OPTIMIZATION AND RAMADAN

There is another group of patients who are on insulin and are uncontrolled for various reasons. Optimal control of glucose is crucial in disease process and achieved by optimization of insulin therapy which is of utmost importance in patients while fasting **(Table 3)**. This provides a good platform for emphasizing the need for a better control of glucose and complications. There is a large number of patients in the clinical practice who need simple optimization of their regime to achieve their goals. This starts by noting the premeals value of the patient. There may be a need to increase the morning dose marginally in case the pre-evening blood glucose values are high. Owing to the changes in dietary habits during *Ramadan* which results in extreme postprandial glucose rises and there is a big question for glucose control in patients taking twice daily insulin. Therefore, if the sunset meal (*Iftar*) values are lower than the sunrise meal (*Suhur*) insulin dose needs to be lowered in morning.

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Table 2: Insulin continuation and *Ramadan*	
Recommendation	*Insulin continuation*
Pre-*Ramadan*	During *Ramadan*
On basal insulin	Reduce dose by 30%
Single premix night dose	Reduce by 20% give at *Suhur*
Two premix insulin dose morning dose evening dose	 Same dose at *Suhur* 50% dose at *Iftar*
Basal bolus takes three meals	
Basal	20% dose reduction at bed time
Bolus: Morning dose Lunch dose Dinner dose	At *Iftar* At dinner Half the dose at *Suhur*
Basal bolus to basal plus (add/titrate bolus as per control)	
Takes two meal	Basal at *Iftar* + bolus at *Suhur*
Titrate doses as per control, move to optimization phase as required	

Table 3: Insulin optimization and *Ramadan*	
Recommendation	*Insulin optimization*
Pre-*Ramadan*	During *Ramadan*
Premix 30 twice daily	Premix 50 at sunset meal (*Iftar*) and premix 30 at sunrise meal (*Suhur*)
Premix 30 twice daily	Increase the sunset meal (*Iftar*) premix dose to cover the post-meal excursion
Basal plus regime: Basal Bolus	70% of pre-*Ramadan* dose 60% as basal insulin in the evening 40% as 2 bolus doses: at *Suhur* and *Iftar*
If on split mix regime twice daily (Short-acting + Intermediate)	
Morning dose RI + 0 + RI NPH + 0+NPH	RI + 0 + ½ RI NPH + 0 + ½ NPH
Evening dose	Give both insulin in 50% dose at *Suhur*
If basal insulin is detemir	
Evening dose	Same dose at sunset meal (*Iftar*)
Morning dose	50% dose at sunrise meal (*Suhur*)
Titrate doses as per control, move to intensification phase as required	

Abbreviation: RI—Regular insulin

In daily practice, as a part of optimization, patients on premix 30 twice daily when converted to premix 50 at sunset meal (*Iftar*) and keeping same dose of premix 30 at sunrise meal (*Suhur*) maintains euglycemia.

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Another way for optimization for patients on premix 30 twice daily, is to further increase the sunset meal (*Iftar*) premix dose to cover the expectant postmeal glucose excursion. This is due to the fact that sunset meal (*Iftar*) may be high in carbohydrate content and may also be larger in quantity in some patients.

This reduces the chances of hypoglycemia and better yields glycated hemoglobin. Example: Out of the 70 percent of the pre-*Ramadan* insulin dose: 60 percent as 1 daily injection of basal insulin in the evening and 40 percent as short-acting insulin given in 2 doses, 1 at *Suhur* and 1 at *Iftar*.

If on split insulin therapy,[4] with short-acting and intermediate acting insulin twice daily then morning doses of both can be given at sunset meal (*Iftar*) and dinner doses of both should be made into half and given at sunrise meal (*Suhur*).

INSULIN INTENSIFICATION AND RAMADAN

This holds true for most of the patients on insulin pre-*Ramadan*. Intensification may be done in a highly motivated patient willing to fast and also to check his/her blood glucose values at regular intervals.

Patient on basal insulin and uncontrolled may be changed to premix daily. This can be either conventional or analog premix. Intensification should start well in advance before *Ramadan* and should be done stepwise. From basal insulin we can start shifting to premix daily once, then twice depending upon the glycemic targets. Titration should be done by fasting glucose values. Compliance and cost are positively influenced by satisfaction of intensification of insulin. Hence, intensive patient counseling is also a must. Premix insulin provide benefit in both pre- and postmeal glucose values.

And those on premix with complications may need a regime like basal plus, or a basal bolus regimen. If on split insulin therapy with short-acting and intermediate acting: Split with three time short-acting and NPH at dinner—Morning short-acting insulin to be transferred as full dose at *Iftar*, Lunch short-acting insulin to be transferred as full dose at dinner if taken and Dinner short-acting insulin to be transferred half dose at *Suhur*. Intermediate acting insulin give half dose at *Suhur* **(Table 4)**.

One limitation of intensification is that, it may require too frequent glucose monitoring in uncontrolled patients.

INSULIN AND OAD (ORAL ANTIDIABETIC DRUGS) IN RAMADAN

Patients on oral therapy as well as insulin pose a different scenario in the management during *Ramadan* **(Table 5)**.

Either intensifies short-acting oral therapy with a basal insulin once a day generally. Another way to deal with this, is to start on a premixed either once or twice daily, but always start with a single dose of premixed then titrate upwards for control.

Long-acting insulin analog like insulin glargine[5] mimics basal insulin secretion and does not have peaking profile.

INSULIN, GLUCAGON-LIKE PEPTIDE-1 AND RAMADAN

There is least evidence of using glucagon-like peptide-1 (GLP-1) analogs in practice **(Table 6)**. However, pre-*Ramadan* assessment stands the same across all therapeutic

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Table 4: Insulin intensification and *Ramadan*	
Recommendation	*Insulin Intensification*
Before *Ramadan*	During *Ramadan*
If on split mix regimen thrice daily	
Short-acting + Intermediate	*Iftar* Dinner *Suhur*
RI + RI + RI + NPH	M-RI + L-RI + N-½RI + ½ NPH
If on basal bolus regime	
Bolus portion	
Morning dose	Transfer full dose at *Iftar*
Lunch dose	If patient takes dinner, transfer the full dose at dinner
Evening dose	Transfer ½ dose at *Suhur*
Basal portion	
If patient is on NPH	50% dose at *Suhur*
If patient is on basal analog	Same dose at bed time
Titrate doses as per control, move to intensification phase as required	

Abbreviation: RI—Regular insulin; M—Morning; L—Lunch; N—Night

Table 5: Insulin and OAD (oral antidiabetic drugs) in *Ramadan*	
Before Ramadan	*During Ramadan*
If on biphasic insulin (BIAsp 30 or BIL is 25 or BHI 30) + Metformin	
Breakfast dose	Sunset meal (*Iftar*)
Metformin	Sunrise meal (*Suhur*)
If mid-day blood sugar control not good	Add insulin at *Suhur* (around 50% of the normal evening dose)
Titrate doses as per control, move to another phase as required	

Table 6: Insulin, GLP-1 and *Ramadan* **GLP-1 analogs plus insulin**	
Pre-Ramadan	*During Ramadan*
Exenatide twice daily + insulin	Sunrise meal (*Suhur*) and sunset meal (*Iftar*) Insulin timing same
Liraglutide + insulin	Liraglutide at sunset meal (*Iftar*) Basal insulin in at bed time
Exenatide once weekly + insulin	No change in timing of doses
Titrate doses as per glucose monitoring	

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options. Exenatide twice daily dosage can be given pre-sunrise meal (*Suhur*) and pre-sunset meal (*Iftar*). Long-acting exenatide once weekly doses can be given as usual dose as prior to *Ramadan*. However, liraglutide once daily should be given at sunset meal (*Iftar*) preferably without any change in dose.[6] And insulin when basal, can be given preferably at bedtime, whereas timing of other insulin regimen (twice daily, basal plus, basal bolus, split-mixed regimen) can remain same, presently till more evidence on their use is available.

As there are exceedingly rare chances of hypoglycemia with GLP-1 analog combinations, frequent checking of blood glucose may be relaxed. This class of drug can be used with renal or hepatic impairment, but gastrointestinal side effects does exist.

Studies with the aim of investigating the use of GLP-1 analogs during *Ramadan* are needed.

CONVENTIONAL INSULIN VERSUS ANALOGS IN RAMADAN

Insulin analogs whether short- or long-acting have several advantages over conventional insulin in relation to the fasting in *Ramadan*.

Firstly, the pharmacokinetics and pharmacodynamics of analogs are better compared to conventional. In one study[7] comparing premix insulin lispro 25/75 and premix regular 30/70 during *Ramadan*, the control of blood glucose before and 2 hours after sunset meal (*Iftar*) was better with analog.

Also, there were less chances of hypoglycemia with analog, as the late peak of regular insulin starts 2 hours postinjection and further increases risk of hypoglycemia while fasting.

Some patients have unusually large meal contributing to post-sunset meal (*Iftar*) hyperglycemia. This can be very detrimental in patients with diabetes with several cardiovascular risk factors, and may increasingly put the patient at risk for a cardiac event. Increase platelet aggregation and enhancement of atherosclerosis is present with acute hyperglycemia. Thus, the pharmacokinetic profile of analogs allows us to reduce cardiovascular risk in such patients.

More, meal time flexibility is provided with analogs, as they can be injected just before or after meals in *Ramadan*.

Analogs like aspart or lispro are safer in renal and hepatic impairment and pregnancy.

INSULIN, PREGNANCY AND RAMADAN

Pregnancy is a special condition, a different metabolic stage in the life of a diabetic lady. Although, pregnancy is exempted from fasting still some women insist on observing fast. This is generally against advice of patient's family and physician. During pregnancy there is increase in insulin resistance and insulin secretion and also reduced hepatic insulin extraction.[2] However, some women seek advise on insulin regimen and dietary pattern to be able for them to fast.

Pre-*Ramadan* evaluation is important to provide guidance on time and type of meal, insulin regime and importance of blood glucose monitoring.[8] These women

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should be managed in high-risk clinics and require intense education, monitoring and insulin dosage change.

In clinical practice, basal plus regime stands the best for pregnant ladies with diabetes. But, however, some women are fairly well controlled with three doses of short-acting insulin.

There is a study on diabetes and pregnancy during *Ramadan* which discusses the use of NPH insulin[9] either once or twice daily. NPH was safe and pregnant women achieved good glycemic control after fasting. It is interesting to note that there were no fetal or maternal complications in this study.

Another recent study,[8] had two groups type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM). Short-acting insulin was used in this study at sunrise meal (*Suhur*) and sunset meal (*Iftar*) and basal insulin was added only if glycemic control deteriorated. Fasting was easier in second trimester, as the nausea of hyperemesis in first trimester and excess metabolic demand of third trimester may be more demanding in some women **(Table 7)**.

INSULIN, ELDERLY AND RAMADAN

With rising prevalence of diabetes in the elderly more patients of this group would bring challenge to the treating physician. Elderly patients with Type 2 diabetes fall into high-risk category as per the stratification.[2]

Especially hypoglycemia is of a major concern in elderly, as they have macrovascular complications more frequently than their younger counterparts. Thus, it is recommended that elderly Type 2 diabetes patients reduce their insulin doses to prevent hypoglycemia at all times. Frail elderly people with morbidities are exempt from fasting. However, it is observed that some of the elderly patients fast.

INSULIN PUMPS AND RAMADAN

An insulin pump is another new technique of insulin delivery continuously over 24 hours with basal infusion rate and is individualized. Theoretically, hypoglycemia and hyperglycemia in *Ramadan* can be better managed by insulin pump–based regimen than by multiple dose insulin-injection therapy. It is self administered by the patients. Short-acting insulin allows better control and great precision. Frequent glucose

Table 7: Insulin, pregnancy and *Ramadan*

Recommendation	*Insulin, pregnancy and Ramadan*
Pre-*Ramadan*	During *Ramadan*
NPH twice daily	Sunrise meal (*Suhur*) and sunset meal (*Iftar*)
Prandial insulin thrice (pre-meal bolus)	*Iftar*, Dinner (if taken) and *Suhur*
Basal plus	Bolus *Suhur* and *Iftar*
	Basal bedtime only if uncontrolled
Titrate doses as per control, move to intensification phase as required	

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monitoring is required. One limitation is the failure of pump or the infusion site with resultant loss of glycemic control over just few hours.

Basal rate of pump needs to be adjusted in evening hours, and boluses more at sunrise meal (*Suhur*) and sunset meal (*Iftar*). There is decrease in basal insulin up to 20 percent in day time. Pre-*Ramadan* evaluation, counseling, monitoring need not be re-emphasized, even while using pumps.

INSULIN, WEIGHT AND RAMADAN

Patients with Type 2 diabetes have alterations in their weight during *Ramadan*. There is a noticeable gain[1,2] in weight as a result of large evening meals mainly carbohydrate and fat rich. Also, there is decrease in physical activity in patients due to fasting condition and the impending fear of hypoglycemia itself. Moreover, immediately post-*Ramadan* there is feasting of sugary delicacies. This duration may depend on culture and various geographic regions. Hypoglycemia in *Ramadan* may inadvertently lead to weight gain if not kept in check.

INSULIN, HYPERGLYCEMIA AND RAMADAN

In the EPIDIAR study, the incidence of severe hyperglycemia in fasting patients who needed hospitalization, reduced to 4 percent in Type 2 diabetes patients, compared to 9 percent in the previous *Ramadan*. Prevention of catabolic effects of hyperglycemia and its osmotic symptoms (polyuria, polydipsia) remains important given the state of fasting for a diabetic patient. Excess or large meal may trigger hyperglycemia subject to patient education and appropriate insulin adjustment. This would avoid unwanted hospitalization and other hyperglycemic emergencies. Excessive reduction in insulin dosages may increase the risk of Diabetic ketoacidosis (DKA). This risk further increases if pre-*Ramadan* glucose values are high and associated with diabetic complications.[10]

INSULIN, HYPOGLYCEMIA AND RAMADAN

In the EPIDIAR study,[1] the largest study on *Ramadan* and diabetes revealed 7.5-fold increase in the incidence of hypoglycemia in patients with Type 2 diabetes. The change in insulin dose and extreme life style changes were responsible for hypoglycemia in this study.

Structured education program is important in the management of *Ramadan* and Type 2 diabetes as it decreases risk of hypoglycemia significantly whereas those who did not receive education had four-fold increase in hypoglycemia[11] and this risk of hypoglycemia further increases in patients on insulin and or oral antidiabetic agents. Thus, it is important to titrate insulin dosages as per the individual requirement to prevent the ensuing hypoglycemia and complications.

BREAKING THE FAST[2]

If blood glucose value reaches below 70 mg/dL (3.9 mmol/L) in the first few hours after the start of the fast, especially on insulin, (also sulfonylurea drugs, or meglitinide are taken at predawn), then fast should be broken.

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All patients should understand that they must always and immediately end their fast if hypoglycemia (blood glucose of < 60 mg/dL [3.3 mmol/L]) occurs, since there is no guarantee that their blood glucose will not drop further if they wait or delay treatment.

The fast should be broken if blood glucose exceeds 300 mg/dL (16.7 mmol/L), and urine ketones should be checked.[4] However, in clinical practice if regular checking is not done and; as hyperglycemia may be asymptomatic in some patients, this may not be picked up. Patients should also avoid fasting on "sick days."

INSULIN, FAMILY THERAPY AND RAMADAN

Family holds center position in the management of diabetes. Preferably family should be involved in making such decisions. This would also give them sufficient to make arrangements for *Ramadan*. In the authors experience,[12] family therapy is important in the management of diabetes in *Ramadan*. It gives opportunity to understand the problems faced by the patients and family members and to solve it with expertise for a better outcome.

FUTURE INSULIN AND RAMADAN

Once in two days (degludec) and weekly insulin are the matter of talk with all healthcare providers treating patients with diabetes. These would also be used in the near future. Nevertheless, dosage of such long acting insulin would not be changed in reference to fasting during *Ramadan*.

INSULIN AND BLOOD GLUCOSE MONITORING DURING RAMADAN

Monitoring forms the basis on which generally the doses of treatment are adjusted. This also helps us to take any action depending on the glucose readings during *Ramadan*. A simple way to monitor blood glucose for dosage adjustment and recognition of hypoglycemia or hyperglycemia is shown in **Tables 8 and 9** respectively.

SUMMARY

Fasting should be encouraged but with medical supervision. More counseling for patients and more training for healthcare providers should be imparted, to strengthen

Table 8: Insulin and blood glucose monitoring during *Ramadan*

Monitoring	*Action*
Adjust insulin dose at 3 days' interval	
Pre-*Iftar*	Adjust basal insulin dose at *Suhur*
2 hours post-*Iftar*	Adjust *Iftar* bolus insulin dose
2 hours post-dinner	Adjust dinner bolus insulin dose
2 hours post-sunrise meal (*Suhur*)	Adjust *Suhur* bolus insulin dose

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Table 9: Blood glucose level monitoring during fasting to recognize subclinical hypoglycemia and hyperglycemia

Monitor	*Benefit*
2 hours post (*Suhur*) meal (*Iftar*) and 1/2 hour pre-*Iftar*	To pick subclinical hypoglycemia
2 hours post-*Iftar*/dinner	To pick subclinical hyperglycemia

the patient-physician relationship. Insulin regimens should be tailored to meet individual needs of a patient in *Ramadan*. Counseling must be provided at all levels of insulin therapy. Care should be taken to avoid hypoglycemia throughout, with special emphasis to iatrogenic hypoglycemia.

Monitoring of glucose to be encouraged as it would help in titrating insulin dose accurately. The aim of insulin therapy is to prevent hypoglycemia while fasting and also post-meal glycemic excursions.

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Section 4

Special Situation in Ramadan

CHAPTERS

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Chapter 15

Ramadan Fasting in Children and Adolescents

Anish Ahamed

Abstract

The holy month of *Ramadan* is one of the five main pillars of being a Muslim. Many experts have opined that patients with Type 1 diabetes who fast during *Ramadan* are at a very high risk of developing complications, if the pattern and amount of their meal and fluid intake are markedly altered. However, some experienced physicians believe that fasting during *Ramadan* is safe for patients with Type 1 diabetes mellitus (T1DM) also, including adolescents and older children, if their glycemic control is good. The factors which are important for healthy children above 12 years who wish to fast during *Ramadan* are individualization, frequent monitoring of blood sugar during fast, nutrition, exercise, breaking the fast if necessary, pre-*Ramadan* medical assessment and *Ramadan*-focused patient education. Insulin-pump therapy may help in controlling blood glucose during fasting and continuous insulin infusion can be modified and adjusted instantaneously to avoid hypoglycemia and the necessity to break the fast.

INTRODUCTION

According to a 2009 demographic study, Islam has 1.57 billion followers, making up 23 percent of the world population of 6.8 billion, and is growing by 3 percent per year.[1] Fasting during *Ramadan*, the 9th month of Islamic lunar calendar, is compulsory for all healthy adult Muslims and children above the age of 12 years. It has been shown that about 43 percent of Muslims with Type 1 diabetes and 79 percent with Type 2 diabetes fast during *Ramadan*.[2] This implies that about 40–50 million people with diabetes worldwide fast during *Ramadan*.

Ramadan, which is a lunar-based month, has between 29 and 30 days. Muslims fast from early dawn (*Sohur*/*Sehri*) till sunset (*Iftar*). They have to abstain from eating, drinking, sexual intercourse, smoking and use of oral medications during this period. There are no restrictions on food or fluid intake between sunset and dawn. Most of them usually consume only two meals per day during this month, one after sunset and the other before dawn.[3]

Islam has exempted many categories of people from fasting like travelers, the sick, the elderly, and pregnant and lactating women. Children are not required to fast till

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they reach adolescence. However, they should be encouraged as much as possible while they are still young to practice fasting by gradually expanding the time that they can observe it.

Although Muslims with diabetes may be exempted from fasting, most of them prefer not to accept this exemption. They wish to fast and be able to follow their religious convictions just as the other members of their community. Unfortunately, many diabetics fast without any medical guidelines and hence end up with serious complications.[4]

Many experts have opined that patients with Type 1 diabetes who fast during *Ramadan* are at a very high risk of developing complications, if the pattern and amount of their meal and fluid intake are markedly altered. However, some experienced physicians believe that fasting during *Ramadan* is safe for patients with T1DM also, including adolescents and older children, if their glycemic control is good.[5]

This article highlights the potential risks to children and adolescents who fast during *Ramadan*, and discusses the various methods of overcoming these.

Major risks associated with fasting in patients with diabetes are given in the **Box 1**.

PATHOPHYSIOLOGY OF FASTING

Fasting during *Ramadan* is not meant to cause excessive hardship on Muslims. Nevertheless, many patients with diabetes insist on fasting during *Ramadan*. This, in turn, creates a medical challenge for not only themselves, but also their health care providers. It is very important for medical professionals to be aware of the potential risks associated with fasting during *Ramadan* as well as the approaches to overcome them.[3]

Feeding stimulates insulin secretion in healthy individuals and promotes the storage of glucose in liver and muscle as glycogen. Fasting leads to hypoglycemia and decreased secretion of insulin. It also leads to increased secretion of counter-regulatory hormones like glucagon and catecholamines resulting in glycogenolysis and gluconeogenesis.[6] Prolonged fasting depletes glycogen stores resulting in hypoinsulinemia, the first defence against hypoglycemia. This releases fatty acids from adipocytes, which are oxidized to ketones. These can be used as fuel by the liver, kidney, skeletal muscle, cardiac muscle, and adipose tissue. This is a vital step as it ensures that brain and erythrocytes continue to get glucose for their metabolism.

In nondiabetic patients, the above processes are regulated by a delicate balance between circulating levels of insulin and counter regulatory hormones that help to maintain glucose concentrations in the physiological range. However, in diabetic patients, insulin secretion is altered by the underlying pathophysiology and the various antidiabetic drugs, to enhance or supplement insulin secretion.

Box 1: Risks associated with fasting in diabetic patients

- Hypoglycemia
- Hyperglycemia
- Diabetic ketoacidosis
- Dehydration and thrombosis

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In patients with Type 1 diabetes, the secretions of both glucagon and epinephrine are defective in response to hypoglycemia, due to a combination of autonomic neuropathy and defects associated with recurrent hypoglycemia.[6]

In patients with severe insulin deficiency, a prolonged fast in the absence of adequate insulin can lead to excessive glycogenolysis and increased gluconeogenesis and ketogenesis, resulting in hyperglycemia and ketoacidosis. Similar problems may ensue in patients with Type 2 diabetes also in response to a prolonged fast; however, ketoacidosis is uncommon, and the severity of hyperglycemia depends on the extent of insulin resistance and/or deficiency.[6]

The transition from a fed state to a fasted state may be divided into three stages:[7]

1. The postabsorptive phase, 6–24 hours after beginning fasting
2. The gluconeogenic phase, from 2–10 days of fasting
3. The protein conservation phase, beyond 10 days of fasting.

Although *Ramadan* fasts do not exceed 24 hours, the variability of the duration of every phase may lead to different physiological responses to fasting. This variability may explain the feasibility of prolonged fast even in subjects with Type 1 diabetes in some studies.[8]

The average rate of glucose utilization by a healthy man is about 7 g/hour after an overnight fast. The liver of a normal person contains about 80 g of glycogen which can supply glucose to the brain and peripheral tissues for about 12 hours.[9]

Diabetic patients who fast during *Ramadan* are prone to develop various complications, if they have the following risk factors and should avoid fasting since they are at high risk of complications.

- Type 1 diabetes mellitus especially brittle
- Ketoacidosis, severe hypoglycemia or hyperosmolar hyperglycemic coma within the 3 months prior to *Ramadan*
- A history of recurrent hypoglycemia
- Hypoglycemia unawareness
- *Sustained poor glycemic control*: Glycated hemoglobin [HbA1C (7.5–9%)]
- Any acute illness
- Performing intense physical labor
- Pregnancy
- Chronic dialysis

The following factors are important for healthy children above 12 years who wish to fast during *Ramadan*.

RAMADAN-FOCUSED PATIENT EDUCATION[10,11]

The role of structured education is well-established in the management of diabetes. This should be extended to *Ramadan*-focused diabetes education. The following advice may be given:

- Blood sugar should be monitored by the patient at home.
- The etiology and the methods of early detection of hypoglycemia, hyperglycemia, dehydration and impending diabetic ketoacidosis should be explained in a simple way. The emergency management of these conditions should also be explained.
- Meal planning and dietary advice.

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- Timing and intensity of physical activity should be stressed.
- The importance of compliance to medications should also be stressed.

PRE-RAMADAN MEDICAL ASSESSMENT

- This should be done at least 1–2 months before the onset of *Ramadan*.
- Physical status, glycemic status and appropriate blood investigations should be done.
- Any acute and chronic complications should be excluded.
- Children who are not fit to fast should be identified and not allowed to fast.

NUTRITIONAL ADVICE

- Children should be advised to take food containing complex, fiber-rich carbohydrates rather than refined foods before beginning of fasting. This helps because they are slow-digesting foods that last up to 8 hours while refined foods last only 3–4 hours and may cause acute rise in blood sugar. These should be taken as late as possible.
- During breaking of fast (*Iftar*), fat and carbohydrate-rich food should not be consumed in excess. The predawn meal (*Sehari*) may contain complex carbohydrates.
- Low glycemic fruits, vegetables, lentils, yogurt and cereals like puffed rice should be included in the diet.
- The importance of drinking liberal amounts of fluids during nonfasting hours should be stressed.

PHYSICAL ACTIVITY

- Normal level of physical activity should be maintained.
- Strenuous exercise during fasting hours should be avoided.
- *Tarawih* prayer (multiple prayers after the sunset meal which may last hours) should be considered a part of the daily exercise program.

CHECKING GLYCEMIC STATUS

- There is a wrong notion amongst some Muslims that blood tests and administration of parenteral drugs including insulin are forbidden during *Ramadan* fasting. Muslim scholars are of the opinion that blood tests for glucose monitoring and insulin injection do not invalidate *Ramadan* fasting.
- The importance of frequent home monitoring of glycemic status should be stressed to patients and their parents.
- If blood glucose is more than 270 mg/dL (15 mmol/L), urine should be checked for ketone bodies.

WHEN SHOULD YOU ADVISE THE CHILD TO BREAK THE FAST?

- It should be stressed that all patients should immediately end their fast if hypoglycemia occurs (blood glucose of 60 mg/dL or 3.3 mmol/L), since there is

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no guarantee that their blood glucose will not drop further if they wait or delay treatment. The fast should also be broken if blood glucose reaches 70 mg/dL (3.9 mmol/L) in the first few hours after the start of the fast, especially if insulin, sulfonylurea drugs or meglitinide are taken at predawn. Finally, the fast should also be broken if blood glucose exceeds 300 mg/dL (16.7 mmol/L).

- Fast should be terminated if child develops clinical features suggestive of hypoglycemia.
- A child who is sick should not be allowed to fast.

INSULIN IN TYPE 1 DIABETES

The risk of developing hypoglycemia is more if a patient is on soluble insulin compared to insulin analogs like lispro or aspart.[10] Hypoglycemia is more with twice daily insulin regimens, compared to long-acting synthetic analogs like insulin deltemir or insulin glargine.[12]

Recommendations for Children with T1DM on Basal–Bolus Insulin

- To use carbohydrate counting for meals to match the insulin dose.
- To use rapid acting analogs like aspart with meal
- Reduce basal insulin like glargine by 10–20 percent and more if needed.
- If glucose rises above 270 mg/dL (15 mmol/L), a correcting dose of rapid-acting insulin should be given.
- If long and rapid-acting insulin analogs are not available, intermediate and short-acting insulin may be used instead.[13]

Two-dose Insulin Regimen

Children who are on twice daily insulin regimens due to financial constraints, should change their dosage such that they take combined short- and intermediate-acting insulin before *Iftar* (sunset meal), which is their usual morning dose, and only short-acting insulin before *Sehri* (pre-dawn meal) at a dose of 0.1–0.2 U/kg.[13] The practical approach will be changing to long-acting or intermediate insulin in the evening and short or rapid-acting insulin with meals; take usual dose at sunset meal and half usual dose at predawn meal.[3]

Insulin Pump Therapy

Insulin pump therapy may help in controlling blood glucose during fasting and continuous insulin infusion can be modified and adjusted instantaneously to avoid hypoglycemia and the necessity to break the fast. The ability to lower the basal insulin infusion rate in insulin pump or even suspend it, may help diabetics to avoid major hypoglycemic attacks during fasting. Patients may be able to complete fasting by controlling and adjusting the basal rate. Eating during the period of fasting in *Ramadan* may have a negative psychological effect on patients especially adolescents, who may feel embarrassed to break their fast even if they develop symptoms of hypoglycemia. Insulin-pump therapy may help them to feel more satisfied and confident.[14,15]

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TYPE 2 DM IN CHILDREN AND ADOLESCENTS

Oral Hypoglycemic Agents

- Choice of treatment should be individualized.
- DPP-4 inhibitors, rapid acting insulin secretagogues and thiazolidinedione may be used at meal time without adjustment.
- Sulfonylurea requires dose adjustment.

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Chapter 16

Ramadan Fasting in Women

Sarita Bajaj

Abstract

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*. Although the sick, menstruating, pregnant and nursing women may be exempted, many still choose to fast while others are more careful in practicing it. The research to date regarding effects of *Ramadan* fasting in pregnancy and lactation seems generally reassuring. However, there is inadequate evidence to conclude fasting during these periods is completely safe. Many of the existing studies are small or methodologically flawed. Imbedded in the clinical and medical implications of fasting in these women is a very complex social, religious and spiritual context that influences the health beliefs and practices of Muslim women, especially in *Ramadan*. Doctors and health workers need to understand the religious obligations of a Muslim towards fasting during *Ramadan* and strike a balance between the religious and health concerns of women. Only through this can a healthcare provider adequately counsel Muslim patients and allow informed decision with regards to fasting.

INTRODUCTION

Ramadan, the 9th month on the Islamic calendar, is the month of fasting for Muslims. Fasting is compulsory as it forms one of the five fundamental obligations of a Muslim. Every healthy Muslim adult, man and woman is responsible for fulfilling this fundamental obligation. Fasting during *Ramadan* causes a radical change in lifestyle for the period of one lunar month. The quality of ingested nutrients can also differ during *Ramadan* compared with the rest of the year. The fasting period per day may vary depending on the geographical location of the country and the season of the year, and can be as long as 18 hours/day in the summer. Furthermore, a decrease in meal frequency and sleep duration, together with reduction in daily physical activities during *Ramadan*, has been reported.[1]

However, certain groups of people are exempted from fasting. They include prepubertal children, the frail elderly, the acutely unwell, travelers who journey more

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than 50 miles, menstruating women, pregnant and nursing women who are worried about their health and/or pregnancy, and those with learning difficulties or mental retardation such that they are unable to comprehend the nature and purpose of the fast.[2] This flexibility offered by the religion may not be reflected in the attitudes of observers of Islam. It has been shown that a significant proportion of those who are ill and/or on special diets will fast, thereby not taking their medication or stopping their diets.[3]

The holy month of *Ramadan* is an important time for Muslim women, but healthcare providers taking care of Muslim women face the difficult task of advising them about the safety of fasting during pregnancy and breastfeeding. Providing this advice and counsel requires that the healthcare providers understand and respect beliefs and practices during this time to be able to provide appropriate and sensitive care. This article discusses health beliefs and practices of Muslim women during the fasting month of *Ramadan* as well as provides recommendations to healthcare providers.[4]

PREGNANCY AND RAMADAN

A pregnant woman is exempted from fasting if she has reasons to believe that her health or that of her fetus is in any way compromised through doing so. However, in a survey conducted by Joosoph et al.[2] on 182 pregnant Muslim women, it was observed that most respondents fasted during their last pregnancy. Eighty-seven percent of them fasted at least a day and 74 percent successfully completed at least 20 days of *Ramadan*. Positive encouragement from their spouses and families was observed in more than 90 percent of respondents. Other reasons include the convenience and camaraderie of fasting as a family unit during *Ramadan*, the difficulties of fasting outside the *Ramadan* when no one else is fasting, and the social pressure exerted from outside the family.[2] This high prevalence of fasting in pregnancy was also observed among women in Birmingham, where more than 75 percent of women fasted during their pregnancies.[5]

Research about *Ramadan* fasting during pregnancy has not demonstrated any effect on maternal oxidative stress,[6] amniotic fluid volume, materno-fetal circulation,[7] birthweight,[8,9] Apgar scores, gestational age at delivery, or infant wellbeing.[10] In contrast, in Saudi Arabia, the ratio of low birthweight babies born during the festival months of *Ramadan* and *Hajj* was found significantly higher than in the nonfestival months.[11] Nonstress tests are more likely to be nonreactive during the period of fasting, but return to reactivity after dinner.[10] Stable gestational persons with diabetes who fast experience no increase in hypoglycemic symptoms and have improved glucose control.[12] However, a reduction in energy or fluid intake by the pregnant mother may produce detrimental effects on fetal growth. Evidence of increased metabolic stress in pregnant women undergoing the *Ramadan* fast has been recorded.[13] Women in late pregnancy showed the phenomenon of "accelerated starvation" during *Ramadan*, characterized by low serum levels of glucose and alanine, and especially high levels of free fatty acids and beta-hydroxybutyrate. The additional metabolic stress of *Ramadan* fasting in pregnancy has the potential to cause retardation of fetal growth and development.[14]

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Ramadan fasting in the second or third trimester of gestation has been associated with reduced mean placental weight and a reduced ratio of placental weight to birthweight. However birthweight does not seem to be affected, which suggests that the placentas are able to maintain levels of activity despite their reduced size. Changes in placental growth during *Ramadan* could be associated with altered fetal programming, and may therefore have long-term implications for the health of the next generation.[15]

Although the research to date is generally reassuring, there is inadequate evidence to conclude that prenatal fasting is safe. Hence, healthcare givers face the daunting task of providing accurate and appropriate medical advice to women who wish to fast during their pregnancies **(Table 1)**. On the one hand, the doctor has to determine the

Table 1: Recommendations for intervention for *Ramadan* fasting in women

Ask pregnant Muslim patients if they plan to fast during *Ramadan*	• Explore what influences her decision • Inquire reasons she might decide not to fast • Discuss perceived disadvantages of not fasting • Assess plan to ensure adequate nutrition and fluids
Assess for risk factors that might preclude fasting safely	• Insulin-dependent diabetes • Any condition that requires medications during the day • History of renal stones, preterm delivery, poor obstetrics outcome • Peptic ulcer disease • Malnutrition • Strenuous physical activity • *Ramadan* occurring in summer months
Provide information about how to fast safely	• Diet: – Stop caffeine and cigarettes gradually in advance – Get up for *Suhur* (AM meal) – Eat high fiber, whole grains, fruits, vegetables, nuts – Avoid excess salt, sugar and caffeine – Drink water, milk and juice just before dawn – Breakfast with water and dates (this is a tradition) – Balanced, nutritious evening meal and plenty of fluids – Bedtime snack including water or juice, protein and fruit

Contd…

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Contd…

	• Activity: avoid strenuous physical activity; get adequate sleep • Stay cool during day
Discuss warning signs	• Decrease fetal movement at night • Irritability, headache, excessive hunger or thirst • Nausea/vomiting • Dysuria, fever, flanks pain • Weakness, fatigue, lightheadedness, dizziness • Preterm contractions
Increase prenatal supervision	• Schedule visits to allow maximum rest • Offer written information • Refer to nutritionist and/or community-based nurse • Encourage keeping diet history including fluids • Follow-up at each visit during *Ramadan* • Urinalysis and culture weekly or semi-weekly • Have women test for ketones in afternoons
If there is a medical reason not to fast	• Carefully explain why it may be harmful • Explore what not fasting would be like for her • Encourage other ways to observe *Ramadan* • Prayers at home and at mosque; reading *Quran* • Charitable activities; cooking for others • Encourage consultation with religious leader and family • Consider a short trial of fasting with close monitoring • Follow-up and explore how not fasting is affecting her

Source: Adapted from Robinson T, Raisler J. 'Each one is a doctor for herself.' Ramadan fasting among Muslim women in the United States. Ethn Dis. 2005;15(Suppl 1):S1-99-103.

general good health of the mother, the unborn baby, and the pregnancy prior to and during the fast. In the presence of coexisting medical conditions, the doctor also has to ensure that the medical condition and medication schedule will not be compromised by the fast. On the other hand, the doctor has to be sensitive to the patient's wish to fulfill her religious obligation. It is far better that the patient fasts with the knowledge of her doctor and hence, closer monitoring by her doctor may be instituted than if she fasts against medical advice and returns to consult the doctor only when the whole *Ramadan* is over. Therefore, it is important that the doctor provides a careful

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explanation and counseling which will allow a Muslim woman to make an informed decision whether to start and/or continue her fast during pregnancy.[2]

LACTATION AND RAMADAN

As in pregnancy, it is observed that a significant number of lactating women fast during *Ramadan*. In a Turkish study on mothers of infants aged 1 year or younger, interviewed consecutively during the last 10 days of *Ramadan* in a university-based well-child care clinic and a health station, it was observed that 69 percent of breastfeeding mothers attending the health station and 42 percent of those attending the university clinic were fasting during *Ramadan*. In the same study 22 percent of breastfeeding mothers perceived a decrease in their breast milk production and 40 percent, 47 percent and 66 percent of infants 2 months, 3 months and 6 months of age, respectively, were receiving supplements.[16] In the developing world, decreased breast milk, early supplementation and weaning are inappropriate nutrition for infants, and the consequences are possible malnutrition and anemia.[17]

In 10 lactating Gambian women, the total breast milk output during *Ramadan* was not different from that during a comparable period before or after *Ramadan*. However, fasting caused changes in milk osmolality, and lactose and potassium concentrations indicative of a marked disturbance of milk synthesis.[18] However, a study conducted on 26 lactating women in the UAE found no significant differences in the contents of major nutrients of milk taken during and after *Ramadan*. There was a slight increase in triglycerides and a slight decrease in cholesterol concentration after the end of *Ramadan*, although these changes were also not significant.[19] *Ramadan* fasting has no significant impact on the infants' growth parameters.[20]

The practice of fasting during *Ramadan* by mothers of infants and young children should not be viewed solely from the perspective of feeding and nutrition. It is well-established that breastfeeding of infants is associated with their better biological, psychological and intellectual development. Research has shown that fasting during *Ramadan* changes circadian rhythms, causes more daytime sleepiness, loss of concentration and irritability. Increases in accidents have been reported. The development of the infant depends most on interactions and relationships with his/her mother. The effects of fasting on mother-child interactions and rates of accidents experienced by infants and toddlers need to be investigated.[16]

SICKNESS AND MEDICATION

According to the Islamic Law, a sick person is exempt from fasting from 1 day or for all of 30 days depending on her condition. A sick person is expected to make up the missed fasting days. Despite this clear exemption, some Muslims who are ill and/or on a special diet choose to fast regardless of the medical advice and their health status.

Diabetes is the most commonly studied disease in *Ramadan* due to the complicated management of this disease while fasting. A large epidemiological study of Muslims with diabetes in 13 Muslim countries (n = 12,914)—the EPIDIAR study—showed that 43 percent of patients with Type 1 and 79 percent of those with Type 2 diabetes fasted during *Ramadan*.[21]

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Fasting, especially among patients with Type 1 diabetes with poor glycemic control, is associated with multiple risks. The major potential risks associated with fasting in patients with diabetes are hypoglycemia, hyperglycemia, diabetic ketoacidosis and dehydration and thrombosis. Fasting for patients with diabetes represents an important personal decision that should be made in light of guidelines for religious exemptions and after careful consideration of the associated risks following ample discussion with the treating physician.

In general, women with pregestational or gestational diabetes should be strongly advised to not fast during *Ramadan*. However, if they insist on fasting, then special attention should be given to their care. Pre-*Ramadan* evaluation of their medical condition is essential. This includes preconception care with emphasis on achieving near-normal blood glucose and A1C values, counseling about maternal and fetal complications associated with poor glycemic control, and education focused on self-management skills. Ideally, patients should be managed in high-risk clinics. The management of pregnant patients during *Ramadan* is based on an appropriate diet and intensive insulin therapy with more frequent monitoring and insulin dose adjustment.[22]

Medication noncompliance has been related to fasting; some Muslims believe that using oral medications, injections, or inhalers during the fasting hours breaks their fast. Others believe that using only oral and intravenous medications would break their fast. Nose drops, creams and ointments, suppositories, and patches are considered religiously proper to use during the fasting hours. As a result, depending on type of medication being used during *Ramadan*, patients may change the way they take their medication arbitrarily, which could lead to serious medication interaction and adverse outcomes.[4]

CONCLUSION

The religion of Islam values life. Although fasting during *Ramadan* is one of the obligations of the religion, flexibility exists. Islam has enabled the sick, pregnant and nursing mothers not to fast during *Ramadan*, and states that one is permitted not to fast or to break fast to save a life. Furthermore, those who may harm others by fasting may stop fasting. Health care providers need to be knowledgeable about religious and cultural phenomena, conduct research to investigate the effects of *Ramadan* fasting, and form links with the teachings of Islam to find religiously and culturally acceptable methods to combat the possible unfavorable effects for women, infants and children.[16]

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Chapter 17

Ramadan Fasting in Elderly

Jamal Ahmad

Abstract

The holy month of *Ramadan* is one of the five pillars of being a Muslim. Although the *Quran* exempts sick people, the elderly and the travelers from the duty of fasting, many Muslims with diabetes may not perceive themselves as sick and are keen to fast. Further, the elderly patients often have multiple co-morbid conditions putting them at increased risk of hypoglycemia, hyperglycemia, dehydration and thrombosis. No specific recommendations for the management of diabetes in elderly individuals have been published because of lack of clinical trials. The incretin mimetics are potentially safer during *Ramadan* and provide effective and safe therapeutic options, administered either alone or in combination with metformin or sulfonylurea. Among the sulfonylurea, gliclazide MR (modified release) and glimepiride can be safely used during *Ramadan*, but glibenclamide should be avoided particularly in elderly due to the associated risk of hypoglycemia. In selected patients with Type 2 diabetes mellitus (T2DM), the long-acting insulin analogs glargine and detemir, as well as the pre-mixed insulin analogs, can be used with minimal risk of metabolic derangement or hypoglycemia. Pre-*Ramadan* assessment, counseling, meal planning, frequent glucose monitoring, appropriate physical activity, dosages and time of medication should be provided at least 30–60 days before *Ramadan* to the elderly patients who insist on fasting. Further, clinical trials are needed to evaluate the safety and efficacy of new antidiabetic agents and new diabetes-related technologies in elderly patients during *Ramadan*.

INTRODUCTION

There are about 1.57 billion Muslims in the world comprising 23 percent of the World's populations of 6.8 billion according to a 2009 demographic study, and is growing by ~ 3 percent per year.[1] One of the five pillars of Muslim faith is fasting during the month of *Ramadan* (the 9th month of the Islamic calendar) which is obligatory for all healthy Muslim adults. Muslims who fast during *Ramadan* abstain from food and drinks (including use of oral medications and smoking) from predawn to dusk. The duration of fasting may range from a few or more than 20 hours depending the geographic locations and the season of the year. The populations based Epidemiology of Diabetes

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and *Ramadan* (EPIDIAR) Study conducted in 13 Islamic countries showed that about 43 percent and 79 percent respectively of Muslims with Type 1 and Type 2 diabetes fast during *Ramadan* meaning that more than 50 million individuals with diabetes fast during *Ramadan*.[2]

ISLAMIC RULING ON FASTING FOR ELDERLY

Religious fasting is meant to inculcate discipline in an individual and not meant to impose excessive hardship; in fact, the holy *Quran* specifically exempts the sick person from the obligations of fasting if fasting might have an adverse effect on the individual. People with diabetes mellitus falling in this category are exempted from fasting because marked departures from the usual amount and pattern of food and fluid intake required during *Ramadan* fasting carries the risk of acute metabolic decompensation. Certain groups are exempted from fasting temporarily or permanently—the sick, the elderly, the travelers and the expecting and nursing mothers.[3] Old people, men and women in late years of life for whom fasting is harmful and difficult, can break the prescribed fast, but are required to give a substitute by feeding a needy person for each prescribed fast day omitted.

The very elderly who have lost their strength and are getting weaker everyday as death approaches, do not have to fast, and they are allowed not to fast so long as fasting would be too difficult for them. *Ibn Abbas* (may Allah be pleased with him), used to say, concerning the *aayas* (interpretation of meaning), "And as for those who can fast with difficulty (e.g. an old man, etc.), they have (a choice either to fast or) to feed a poor person (for every day)" [*al-Baqarah* 2:184]:" This has not been abrogated. Those who have become senile and confused, do not have to fast or do anything else, and their family does not have to do anything on their behalf, because such people are no longer counted as responsible. If they are of sound mind sometimes and confused at other times, they have to fast when they are OK and they do not have to fast when they are confused (*See Majaalis Shahr Ramadan* by Ibn Uthyameen, p.28).

There are no published studies which evaluated specific management modalities in elderly diabetic patients and travelers during *Ramadan* fasting. The aim is to present a practical approach to the assessment of diabetic patients before *Ramadan* and provide a guide on how to adjust the lifestyle and medical management appropriately should these patients wish to observe the fast having deemed it to be reasonable safe.

MANAGEMENT OF ELDERLY WITH DIABETES MELLITUS DURING RAMADAN

All diabetic patients desiring to fast during *Ramadan* should be well-prepared to make fasting as safe as possible. Diabetes care department should have comprehensive strategy meeting a few months before *Ramadan*. Many patients would have developed their own opinions and established their practice of amending their diabetes care management plans from previous personal experience. Patients attending diabetic clinic should be encouraged to seek advice before considering fasting in the month of *Ramadan*.[4] However, poor knowledge about *Ramadan* and fasting and its

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management have been described among some health care professionals.[5] Special classes may need to consider enhancing self-management during this month.[6] Expert doctors should take the time to give interviews preferably jointly with *Imams* to offer clear and authoritative views and respond to all commonly asked questions. In the clinical settings, doctors should have a clear understanding of the religious ruling on fasting to give their advice with confidence.

Pre-Ramadan Medical Assessment

This should take place 30–60 days before *Ramadan* and focus specifically on the patient's overall wellbeings and control of blood sugar, hypertension, and dyslipidemia. There are two questions that need to be answered. Firstly, when to advise against fasting? And secondly, what is the optimal therapeutic regimen? Individual's assessment for each patient is essential particularly with co-morbidities, commonly associated in elderly patients and emphasis should be on preventing the occurrence of hypoglycemic events. Appropriate investigations should be carried out to document complication status, and necessary changes in lifestyle and diet. Any changes in medication if required should be instituted at this stage, so as to establish a safe and effective antidiabetic regimen and provide a stable glycemic control prior to start of *Ramadan* fast. Risk stratification of diabetic patients who are planning to fast is recommended based on the presence of various risk factors.[7]

Education Counseling

Each individual needs to be counseled about the essential elements necessary to render fasting safer. These include the importance of glucose monitoring during fasting and nonfasting hours, when to stop the fast, meal planning to avoid hypoglycemia and dehydration during prolonged fasting hours, and the appropriate meal choice to avoid postprandial hyperglycemia. The educational program should include advice on the timing and intensity of physical activity during fasting as well.

Breaking the Fast

Patients must break their fast if hypoglycemia (blood glucose < 60 mg/dL) occurs at any time during the fast or if blood glucose exceeds 300 mg/dL. In case the blood glucose drops to less than 70 mg/dL in early hours of the fast, particularly if sulfonylurea or insulin have been taken at predawn, the fast should be terminated. Fasting should be avoided on sick days.

Diet-controlled Patients

The risk associated with fasting is low. However, there is still a potential risk for occurrence of postprandial hyperglycemia after the predawn and sunset meals in patients over-indulge in eating. Distribution of calories over two to three smaller meals during the nonfasting interval may help prevent excessive postprandial hyperglycemia.

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Patients Treated with Oral Agents

The therapeutic options for management of T2DM have been expanded with the introduction of new oral hypoglycemic agents (OHA). Some of these have been used during *Ramadan* and have strong potential therapeutic benefit, although no studies are available regarding their safety in elderly patients. In general, agents that act by increasing insulin sensitivity are associated with a significantly lower risk of hypoglycemia than compounds that act by increasingly insulin secretion.

Metformin: Patients treated with metformin alone may safely fast because the possibility of severe hypoglycemia is minimal. However, perhaps the timing of the dose should be modified to provide two-thirds of the total daily dose with the sunset meal and the other third before the predawn meal.

Glitazones: The PPARγ agonist are not independently associated with hypoglycemia, but can increase the hypoglycemic effects of others hypoglycemic agents. The adverse effect includes weight gain, macular edema, and increased frequency of bone fractures in postmenopausal women. Long-standing concern regarding cardiovascular safety caused by the increased frequency of heart failure continues despite greater understanding that the mechanism of this adverse effect seems to be related to renal tubular sodium and water reabsorption and not to an intrinsic effect on cardiac contractility. The controversy regarding cardiovascular safety of rosiglitazones has resulted in a more cautious approach to its use as advocated by Food and Drug Administration (FDA). Pioglitazones has been found to be safe and efficacious in lowering blood glucose during *Ramadan* in combination with others OHAS. A randomized controlled in patients (not elderly patients) already taking other OHAs did not find any increase in hypoglycemic events during *Ramadan* fasting with pioglitazones 30 mg once daily compared to placebo,[8] mean weight gain of 3.02 kg was observed in the placebo group. Al-Arouj et al. writing for American Diabetes Association (ADA) on recommendations for diabetic patients undertaking *Ramadan* fast recommended that patients controlled on pioglitazone along or with other treatments continue with their usual pioglitazone dose.[7]

Sulfonylurea: It has been suggested that this group of drugs is unsuitable for the use during fasting because of the inherited risk of hypoglycemia. However, severe or fatal hypoglycemia is relatively rare complications of sulfonylurea use. Nevertheless, the risk of hypoglycemia, weight gain, and concerns surrounding the cardiovascular safety of these drugs especially the older agents like glibenclamide, together with continued introduction of newer, safer, and effective classes of antibiotics medications, some of which hold the promise (unproven) of altering the course of diabetes, has led to a progressive decline in use of sulfonylurea. Glibenclamide use was claimed to be safe during *Ramadan* fasting.[9] However subsequently, it has been suggested that glibenclamide may be associated with higher risk of hypoglycemia than other second generation sulfonylureas like glipizide, gliclazide, and glimepiride.[10,11] Higher number of hypoglycemic events has been reported to occur with glibenclamide as compared to short-acting insulin secretogogue repaglinide among fasting patients during *Ramadan*.[12] Several studies have shown that glimepiride and gliclazide to be effective and safe during *Ramadan* particularly the use of gliclazide MR-60 as monotherapy.[10,13]

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Additional studies on the use of sulfonylurea in elderly patients of Type 2 diabetes who fast during *Ramadan* are needed before strong recommendations on their utility can be made. Nevertheless, because of their worldwide use and relatively low cost, these agents may be used in elderly patients in *Ramadan*, though with caution.

Short-Acting Insulin Secretagogues

Members of this group (repaglinide and nateglinide) are useful because of their short duration of action. They could be taken twice daily before the sunset and predawn meals. Nateglinide has the short duration of action and therefore, the lowest risk of severe fasting hypoglycemia among the secretagogues, however, no statins have been carried out in the elderly patients with Type 2 diabetes who insist on fasting in *Ramadan*.

Incretin-based Therapy

Gliptins or dipeptidyl peptidase-IV (DPP IV) inhibitors are new oral hypoglycemic agents which act as selective inhibitors of enzyme DPP-IV to enhance endogenous incretin activity by preventing the rapid degradation of the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These classes of agents are not independently associated with hypoglycemia, though they can increase the hypoglycemic effects of sulfonylurea, glinides and insulin. Gliptins are important addition to the currently available management options for patients with Type 2 diabetes and are among the best tolerated drugs for the treatment of T2DM. They can cause modest A1C reduction and are weight neutral. Many consider DPP-IV as a substitute to sulfonylurea. DPP-IV Is among the best tolerated drugs for the treatment of drugs and importantly vis-a-vis treatment during *Ramadan*, do not require titration. However, there are no specific studies of these agents during periods of fasting in *Ramadan* among elderly patients available.

Alpha-Glucosidase Inhibitors

This group of antidiabetic agents inhibits the action of intestinal brush border enzyme, α-glucosidase, and retards the absorption of carbohydrate when taken with meal. Because they are not associated with an independent risk of hypoglycemia, particularly in the fasting state, they may be particularly useful during *Ramadan*. As a group, these drugs are only moderately effective and do not exert much effect on fasting glucose levels and hence are mostly used in combinations with other anti-diabetic agents. α-glucosidase inhibitors are associated with frequent mild to moderate gastrointestinal effects, particularly flatulence however, no studies of these agents during period of fasting in *Ramadan* among elderly patients are available.

Patients Treated with Insulin

Problems faced by Type 2 diabetics who administered insulin are similar to those faced by Type 1 diabetics, except that the incidence of hypoglycemia is lower. Again, the aim is to maintain necessary levels of basal insulin to prevent fasting

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hyperglycemia. An effective strategy would be judicious use of intermediate or long-acting insulin preparations plus short-acting insulin administered before meals. Although hypoglycemia tends to be less frequent, it is still a risk especially in patients who have required insulin therapy for a number of years or in whom insulin deficiency predominates in the pathophysiology. Very elderly patients with Type 2 diabetes may be at high-risk.

Insulin can be safely used in Type 2 diabetic individuals twice daily premixed insulin such as lispro mix (25/75) and human insulin (30/70) have been used safely during *Ramadan*.[14] It is recommended that the usual morning dose of this regimen be used with the sunset meal and half the usual evening dose be used with the predawn meal.[15] Insulin Glargine is also effective and safe during *Ramadan* and can be given as single injection at 10 pm with or without mealtime short-acting analogs or other oral antidiabetic medications.[16]

CONCLUSION

Fasting during *Ramadan* for patients with diabetes, particularly elderly, individuals carries a risk of an assortment of complications. Elderly patients with Type 2 diabetes additionally will have multiple comorbid conditions that put them at increased risk of hypoglycemia, dehydration and other diabetes related complications. In general, patients with Type 1 diabetes are at very high-risk of life-threatening complications. Hypo- and hyperglycemia may also occur with Type 2 diabetes, but is generally less frequent and has less severe consequences. Patients who insist on fasting should undergo Pre-*Ramadan* assessment and receive appropriate education, counseling and instructions related to physical activity, meal planning, glucose monitoring, and dosage and timing of medication.

Newer pharmacological agents have lesser hypoglycemic potential and may have specific advantages during *Ramadan*, but in general these challenging therapeutic situations have not been adequately addressed in clinical trials particularly elderly patients of T2DM who insist on fasting.

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Section 5

Management of Complications

CHAPTERS

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Chapter 18

Hypoglycemic Emergencies

Intekhab Ahmed

Abstract

Hypoglycemia is potentially a life-threatening complication of diabetes management. In a diabetic person, it is commonly the result of inadvertent over treatment of hyperglycemia or due to mismatch between diabetic medication and food intake, lack of food intake, or excessive physical exertion in the absence of adequate medication adjustment. Patients especially elderly are more prone to hypoglycemia during the month of *Ramadan* if no appropriate adjustment is made in their diabetic medications.

In this chapter, a brief description of definition of hypoglycemia, its symptoms and signs, predisposing factors, and measures how to prevent hypoglycemia and its management is discussed. A thorough understanding of the diabetic disease process, its medications and their side effects especially secretagogues and insulin, and a close interaction between patient and physician is of paramount importance to avoid hypoglycemia.

INTRODUCTION

According to American Diabetes Association (ADA), hypoglycemia is defined as all episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm. It is recommended that people with diabetes become concerned about the possibility of hypoglycemia at a self-monitored blood glucose (SMBG) level ≤ 70 mg/dL (3.9 mmol/L).[1]

Hypoglycemia is an important problem in Type 1 diabetes, especially in patients receiving intensive therapy in which the risk of severe hypoglycemia is increased more than three-fold.[2-3] Less commonly, hypoglycemia also affects patients with Type 2 diabetes who take a sulfonylurea or a meglitinide or who use insulin.

In addition, in the month of *Ramadan*, diabetic patients are at an increased risk of hypoglycemia especially if they are treated with sulfonylureas and insulin due to prolonged fasting.

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CLINICAL MANIFESTATIONS

Symptoms

The symptoms of hypoglycemia in patients with diabetes are nonspecific. Hypoglycemia causes neurogenic (autonomic) and neuroglycopenic symptoms.

- *The neurogenic symptoms*: It includes tremor, palpitations, and anxiety/arousal (catecholamine-mediated, adrenergic) and sweating, hunger, and paresthesias (acetylcholine-mediated, cholinergic). They are largely caused by sympathetic neural, rather than adrenomedullary, activation.[4-5]
- *The neuroglycopenic symptoms*: It includes cognitive impairment, behavioral changes, psychomotor abnormalities and, at lower plasma glucose concentrations, seizure and coma. Although profound prolonged hypoglycemia can cause brain death in the unobserved patient with diabetes, the vast majority of episodes are reversed after the glucose level is raised to normal and the rare fatal episodes are generally thought to be the result of ventricular arrhythmia.[5-6]

It is important to remember that not all the patients experience symptoms of hypoglycemia and the patient may not recognize the symptoms, even though they are evident to an observer.[7] Furthermore, many patients cannot describe their episodes in any detail because of amnesia, so that information should be obtained from a close family member or friend whenever possible.

The symptoms may also be absent because of hypoglycemia unawareness, which is thought to be the result of reduced sympathoadrenal, predominantly sympathetic neural, responses to a given degree of hypoglycemia caused by recent antecedent hypoglycemia, prior exercise or sleep in patients with diabetes.

Signs

Diaphoresis and pallor are common signs of hypoglycemia. Heart rate and systolic blood pressure are raised, but not greatly. Neuroglycopenic manifestations are often observable. Occasionally, transient neurological deficits occur. Permanent neurological damage is rare and, should it occur, it would be more likely in a patient with diabetes and prolonged severe hypoglycemia.[8]

Clinical Classification

The ADA workgroup on hypoglycemia recommends the following classification of hypoglycemia in diabetes:[9]

- *Severe hypoglycemia*: An event requiring the assistance of another person to actively administer carbohydrate/glucagon or other resuscitative actions is classified as a severe hypoglycemic event. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- *Documented symptomatic hypoglycemia*: An event during which typical symptoms of hypoglycemia are accompanied by a measured (typically with a monitor or with a validated glucose sensor) plasma glucose concentration less than

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or equal to 70 mg/dL (3.9 mmol/L) is classified as a documented symptomatic hypoglycemic event.

- *Asymptomatic hypoglycemia*: Asymptomatic hypoglycemia is classified as an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration of less than or equal to 70 mg/dL (3.9 mmol/L).
- *Probable symptomatic hypoglycemia*: Probable symptomatic hypoglycemia is classified as an event during which typical symptoms of hypoglycemia are not accompanied by a plasma glucose determination [but that was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L)].
- *Relative hypoglycemia*: Relative hypoglycemia is classified as an event during which the person with diabetes reports typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration more than 70 mg/dL (3.9 mmol/L). This category reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels more than 70 mg/dL (3.9 mmol/L) as glucose levels decline into the physiological range.

MAGNITUDE OF THE PROBLEM

Frequency

No exact figures of hypoglycemia are available in diabetics who observe *Ramadan*, but the following estimates in diabetics can highlight the significance of the problem.

Type 1 Diabetes

Hypoglycemia occurs frequently in patients with Type 1 diabetes. The average patient suffers up to two episodes of symptomatic hypoglycemia per week, and one episode of temporarily disabling hypoglycemia per year.[10] Severe hypoglycemia events, the most reliable values albeit representing only a small fraction of the total hypoglycemic experience, have been reported to range from 62–170 episodes per 100 patient years in Type 1 diabetes. In the Diabetes Control and Complications Trial (DCCT), a greater proportion of patients in the intensively treated group had at least one episode of severe hypoglycemia (65 vs 35% of patients in the control group), with overall rates of 61 and 19 per 100 patient-years, respectively.[11]

Type 2 Diabetes

Hypoglycemia is less common in Type 2 diabetes. However, because there are a greater number of individuals with Type 2 than Type 1 diabetes, and because most people with Type 2 diabetes ultimately require treatment with insulin, most episodes of iatrogenic hypoglycemia occur in people with Type 2 diabetes.

Among the commonly used insulin secretagogues (sulfonylureas, meglitinides), hypoglycemia is most often reported in patients taking long-acting drugs, such as *glyburide* (glibenclamide).[12]

Hypoglycemia is relatively uncommon during treatment with insulin early in the course of Type 2 diabetes. However, its frequency increases, approaching

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Type 1 diabetes, as patients approach the insulin deficient end of the spectrum of Type 2 diabetes. In contrast to insulin and insulin secretagogues, agents that do not cause unregulated hyperinsulinemia, such as metformin, alpha glucosidase inhibitors (acarbose, miglitol, voglibose), TZDs (pioglitazone, rosiglitazone), glucagon-like peptide-1(GLP-1) receptor agonists (exenatide, liraglutide), and dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, vildagliptin) probably do not cause hypoglycemia. However, they increase the risk if used with insulin or an insulin secretagogue.[13]

Nocturnal Hypoglycemia

A particular problem is nocturnal hypoglycemia, which can lead to disruption of sleep and delays in correction of the hypoglycemia. Night-time is typically the longest period between self-monitoring of plasma glucose, between food ingestion, and the time of maximum sensitivity to insulin. Nocturnal hypoglycemia is less common in individuals using rapid acting insulin analogs (lispro, aspart, glulisine) rather than regular insulin before meals and in individuals using long-acting insulin analogs (glargine, detemir) rather than NPH as the basal insulin.

RISK FACTORS FOR HYPOGLYCEMIA

Hypoglycemia is the result of absolute or relative therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations (defective glucose counterregulation and hypoglycemia unawareness). In clinical practice, insulin excess alone explains only a minority of episodes of hypoglycemia. Impaired counterregulatory defenses resulting in hypoglycemia is the primary risk factor for subsequent hypoglycemia.

Impaired Counterregulatory Responses

The first and second physiological defenses against hypoglycemia, decrements in insulin and increments in glucagon as glucose levels fall in response to therapeutic hyperglycemia, are lost in parallel with beta-cell failure in diabetes. This occurs rapidly in Type 1 diabetes and more gradually in Type 2 diabetes.

The third physiological defense, an increment in epinephrine, is typically attenuated in such patients. In the setting of absent insulin and glucagon responses, the attenuated epinephrine response causes defective glucose counterregulation. In addition, an attenuated epinephrine response is a marker of an attenuated sympathoadrenal, including sympathetic neural, response that causes hypoglycemia unawareness. These are the components of hypoglycemia-associated autonomic failure (HAAF) in diabetes. HAAF can be caused by recent antecedent hypoglycemia, prior exercise, or sleep, but the precise mechanisms are unknown.[14]

Risk factors for HAAF include the following:

- Absolute endogenous insulin deficiency
- A past history of severe hypoglycemia, hypoglycemia unawareness, recent antecedent hypoglycemia, prior exercise or sleep
- Intensive glycemic therapy, i.e. lower A_{1C} levels, stricter glycemic goals or both.

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Insulin Excess

Absolute or relative insulin excess occurs in the following settings:

- Insulin (or insulin secretagogue) doses are excessive, ill-timed or of the wrong type
- Exogenous glucose influx is reduced (e.g. during an overnight fast or following missed meals)
- Insulin-independent glucose utilization is increased (e.g. during and shortly after exercise)
- Sensitivity to insulin is increased (e.g. hours after exercise, in the middle of the night, following improved glycemic control or weight loss)
- Endogenous glucose production is reduced (e.g. following alcohol ingestion)
- Insulin clearance is reduced (e.g. with renal failure).

Elderly Patients

The risk of hypoglycemia is related to the duration of diabetes and appears to be increased in the elderly. Older adults may have more neuroglycopenic manifestations of hypoglycemia (dizziness, weakness, delirium, confusion) compared with adrenergic manifestations (tremors, sweating).[1-4,15]

Severe hypoglycemia has been associated with an increased risk of dementia, even mild episodes of hypoglycemia may result in adverse outcomes in frail elderly; episodes of dizziness or weakness increase the risk of falls and fracture.

Other Risks

Although insulin secretagogues and insulin are the most common drugs associated with hypoglycemia, other drugs that are often prescribed for people with diabetes and that possibly increase the risk of hypoglycemia are angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, and nonselective beta-2-adrenergic antagonists.[16]

Prediction of Risk from Blood Glucose Monitoring

A simpler and more practical approach during intensive insulin therapy is to evaluate the frequency and severity of low blood glucose readings from blood glucose monitoring records kept by the patient.

STRATEGIES TO PREVENT HYPOGLYCEMIA

In General and Especially in Ramadan

The prevention of hypoglycemia involves assessing for risk factors and tailoring treatment regimens to reduce risk. Reducing the risk of hypoglycemia while maintaining or improving glycemic control involves patient education and empowerment, frequent SMBG, flexible and rational insulin (and other drug) regimens, individualized glycemic goals, and ongoing professional guidance and support.

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Regular SMBG is critical to the glycemic management of intensively treated (basal/bolus insulin) Type 2 diabetes as well as that of Type 1 diabetes but may not be practical in the month of *Ramadan* due to religious beliefs.

Glycemic Targets

Target A_{1C} levels in patients with Type 1 and 2 diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycemia. Less stringent treatment goals may be appropriate for the month of *Ramadan* and in patients with a history of severe hypoglycemia, patients with limited life expectancies, very young children or older adults, and individuals with comorbid conditions.

Insulin Regimens

In patients with Type 1 or Type 2 diabetes who use insulin, the use of long-acting insulin analogs (e.g. glargine, detemir) as the basal insulin can be replaced with NPH twice a day and rapid-acting insulin analogs (e.g. lispro, aspart, glulisine) as the pre-meal bolus insulin at *Sehar* and *Iftar* can reduce the risk of hypoglycemia, particularly nocturnal hypoglycemia. Patients on insulin pump should adjust their basal rate to keep their blood sugar between 100 mg dL and 140 mg/dL.[14-17]

Oral Hypoglycemics

All the long acting sulfonylureas (glipizide, gluburide) should be avoided during the fasting month and be replaced with either prandin or DPP 4 inhibitors. Metformin and TZDs use is not known to cause hypoglycemia and are safe choice during the month of *Ramadan*, provided no contraindications exists.

Other Medications

It is important that patient and physicians are aware of all the medications that can mask the symptoms or signs of hypoglycemia (beta blockers) and others that can precipitate hypoglycemia like ACE-inhibitors.

Strong advice about avoidance of strenuous exercise or activity during fasting is a necessity to prevent hypoglycemia.

Behavioral Approaches

Avoidance of severe hypoglycemia requires the recognition of early symptoms and signs by the patient (and by those around them). Using a variety of well-validated behavioral approaches, people can be trained to improve their ability to recognize hypoglycemia. Furthermore, this increase in recognition may be associated with long-term improvement in A_{1C} values and a reduction in the number of severe hypoglycemic events. Blood glucose awareness training involves techniques in which patients are asked to guess their blood glucose concentration, record their symptoms, and then verify the blood glucose values with a glucose meter.[17-20]

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Hypoglycemia Unawareness

If there is a history of hypoglycemia unawareness, a 2–3 weeks period of avoidance of hypoglycemia is advisable since that often restores awareness.[21-22] That can be accomplished by more intensive professional involvement (e.g. by telephone); in practice, it may require higher glycemic goals for the month of *Ramadan*.

TREATMENT OF HYPOGLYCEMIA

Asymptomatic

When SMBG reveals a blood glucose of less than or equal to 70 mg/dL (3.9 mmol/L), it is reasonable for a person with drug-treated diabetes to consider defensive actions. The options include repeating the measurement in the near term, avoiding critical tasks such as driving, ingesting carbohydrates, and adjusting the treatment regimen.[23]

Symptomatic

In order to treat early symptoms of hypoglycemia, patients should be certain that fast-acting carbohydrate (such as glucose tablets, hard candy, or sweetened fruit juice) is available at all times. Fifteen to twenty grams is usually sufficient to raise the blood glucose into a safe range without inducing hyperglycemia. This can be followed by long-acting carbohydrate to prevent recurrent symptoms.

In patients taking insulin or an insulin secretagogue in combination with an alpha-glucosidase inhibitor (acarbose, miglitol, voglibose), only pure glucose (dextrose) should be used to treat symptomatic hypoglycemia.[24] Other forms of carbohydrates, such as table sugar (sucrose), will be less effective in raising blood sugar as alpha-glucosidase inhibitors slow digestion of other carbohydrates.

Severe

When the patient is unconscious or unable to ingest carbohydrate, it is necessary that close friends or relatives be trained to recognize and treat this complication. Dealing with a loved one who is pale, sweaty, acting in a bizarre fashion, or unconscious and convulsing is often a terrifying situation, yet one that can be reversed with an injection of glucagon. Successful glucagon therapy requires that the glucagon kit can be located and that the relative or friend is able to remain calm, and able to inject prefilled glucagon injection. The glucagon kit should be checked regularly and replaced when it is beyond its expiration date.

- A subcutaneous or intramuscular injection of 0.5–1.0 mg of glucagon will usually lead to recovery of consciousness within 10–15 minutes, although it may be followed by marked nausea or even vomiting.[25]
- Patients brought to the hospital can be treated more quickly by giving 25 g of 50 percent glucose (dextrose) intravenously. A subsequent glucose infusion (or food, if patient is able to eat) is often needed, depending upon the cause of the hypoglycemia.[26]

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CONCLUSION

Hypoglycemia in a diabetic person, if unrecognized can be a frightening and fatal event. Most common cause of hypoglycemia in diabetics is a mismatch in insulin and food intake, which is especially common in the setting of fasting. A complete understanding of the diabetes, risk factors for hypoglycemia, its recognition are of utmost importance for the patient in general and particularly in a diabetic patient who is planning to observe the month of *Ramadan* with full religious vigor. A close communication between patient and physician, frequent evaluation of blood sugar readings, and timely adjustments in medications are the corner stone of preventing hypoglycemia. A mild hyperglycemia in the month of *Ramadan* is much better than any episode of hypoglycemia.

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Chapter 19

Hyperglycemic Emergencies in Ramadan

Intekhab Ahmed

Abstract

The two most acute and serious hyperglycemic emergencies are diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar, nonketotic state (HHNK). They are part of the spectrum of hyperglycemia and each represents an extreme in the spectrum. DKA can affect both Type 1 and Type 2 diabetics while HHNK is limited to Type 2 diabetics. Diabetic patients who observe *Ramadan* have to be extremely careful about their diabetic treatment and hydration status (water intake) especially when *Ramadan* falls in summer months to avoid these hyperglycemic events especially elderly Type 2 diabetics as the mortality is up to 5–20 percent with HHNK.

In this chapter, a brief review of etiology, pathophysiology, treatment and steps to avoid DKA and HHNK in general and especially in the month of *Ramadan* are discussed.

INTRODUCTION

Diabetic ketoacidosis and HHNK represent extremes forms of hyperglycemia and differ clinically according to the presence of ketoacidosis and usually the degree of hyperglycemia.[1] The definitions proposed by the American Diabetes Association for DKA and hyperglycemic hyperosmolar syndrome (HHS) are shown in a table, along with criteria for classification of DKA as mild, moderate, or severe, based on the patient's arterial pH, serum bicarbonate, and mental status **(Table 1)**.[2]

- Diabetic ketoacidosis is characterized by the triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia. Metabolic acidosis is often the major finding. The serum glucose concentration is usually greater than 500 mg/dL (27.8 mmol/L) and less than 800 mg/dL (44.4 mmol/L)[3,4] though serum glucose concentrations may exceed 900 mg/dL (50 mmol/L) in patients with DKA who are comatose. In certain instances, such as DKA in the setting of starvation or pregnancy, or treatment with insulin prior to arrival in the emergency department, the glucose may be only mildly elevated.
- In HHNK, there is little or no ketoacid accumulation, the serum glucose concentration frequently exceeds 1,000 mg/dL (56 mmol/L), the plasma

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Table 1: Characteristics of DKA and HHNK states[2]

	DKA			HHNK
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	> 250	> 250	> 250	600
Arterial pH	7.25–7.30	7.0–7.24	< 7.00	> 7.30
Serum bicarbonate	15–18	10–15	< 10	> 18
Urine ketones	Positive	Positive	Positive	Small
Serum ketones	Positive	Positive	Positive	Small
Serum osmolality	Variable	Variable	Variable	> 320
Anion gap	> 10	> 12	> 12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Abbreviations: DKA—Diabetic ketoacidosis; HHNK—Hyperglycemic hyperosmolar nonketotic state

osmolality may reach 380 mosmol/kg and neurologic abnormalities are frequently present especially comatose state. Most patients with HHNK have an admission pH greater than 7.30, a serum bicarbonate greater than 20 mEq/L, a serum glucose greater than 600 mg/dL (33.3 mmol/L), and test negative for ketones in serum and urine, although mild ketonemia may be present.

There is significant overlap between DKA and HHS has been reported in more than one-third of patients.[4,5] The typical total body deficits of water and electrolytes in DKA and HHS are compared in a table **(Table 2)**.[6]

Diabetic ketoacidosis is more common in young (< 65 years) diabetic patients and in women compared to men.[7] Mortality in DKA is primarily due to the underlying precipitating illness and only rarely to the metabolic complications of hyperglycemia or ketoacidosis. The prognosis of DKA is substantially worse at the extremes of age and in the presence of coma and hypotension.[8,9] HHNK is the most commonly seen in individuals older than 65 years with Type 2 diabetes.[10] Mortality attributed to HHNK is higher than that of DKA, with rates ranging from 5 to 20 percent; as in DKA, mortality is most often due to the underlying illness or comorbidity.

PATHOGENESIS

Two hormonal abnormalities are largely responsible for the development of hyperglycemia and ketoacidosis in patients with uncontrolled diabetes:[11]

1. Insulin deficiency and/or resistance.
2. Glucagon excess, which may result from removal of the normal suppressive effect of insulin.[12,13] There is no evidence for defective pancreatic alpha cell function in diabetes, since there is a normal glucagon response to nonhypoglycemic stimuli.[14]

Although glucagon excess contributes to the development of DKA, it is not required. As an example, patients with complete pancreatectomies and who have no

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Table 2: Typical total body deficits of water and electrolytes in diabetic ketoacidosis and hyperosmolar hyperglycemic state[6]

	DKA	HHNK
Total water (L)	6	9
Water (mL/kg)	100	100–200
Na^+ (mEq/kg)	7–10	5–13
Cl^- (mEq/kg)	3–5	5–15
K^+ (mEq/L)	3–5	4–6
PO_4 (mmol/kg)	5–7	3–7
Mg^+ (mEq/kg)	1–2	1–2

Abbreviations: DKA—Diabetic ketoacidosis; HHNK—Hyperglycemic hyperosmolar nonketotic state

pancreatic glucagon will develop DKA if insulin is withheld; however, it takes longer for DKA to develop compared with patients with Type 1 diabetes. In addition to these primary factors, increased secretion of catecholamines and cortisol can contribute to the increases in glucose and ketoacid production.

Spectrum of Hyperglycemic Crises

The basic mechanism underlying both DKA and HHNK is reduction in the net effective action of circulating insulin, with concomitant elevation of counterregulatory hormones, primarily not only glucagon, but also catecholamines, cortisol, and growth hormone.[15,16]

The deficiency in insulin (absolute deficiency, or relative to excess counterregulatory hormones) is more severe in DKA compared with HHNK. The residual insulin secretion in HHS is sufficient to minimize ketosis but does not control hyperglycemia.[17]

Diabetic ketoacidosis and HHNK are two extremes in the spectrum of hyperglycemic crisis and patients can fall anywhere along the disease continuum of diabetic metabolic derangement **(Table 1)**. The serum glucose concentration in HHNK frequently exceeds 1,000 mg/dL (56 mmol/L), but in DKA is generally below 800 mg/dL (44 mmol/L).

At least two factors contribute to the lesser degree of hyperglycemia in DKA:

1. Patients with DKA often present early with symptoms of ketoacidosis (such as shortness of breath and abdominal pain), rather than late with symptoms due to hyperosmolality.
2. Patients with DKA tend to be young and to have a glomerular filtration rate that, at least in the first 5 years of diabetes, may be as much as 50 percent above normal. As a result, they have a much greater capacity to excrete glucose than the usually older patients with HHS, thereby limiting the degree of hyperglycemia.

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Hyperglycemia

Hormonal alterations in DKA and HHNK result in hyperglycemia by their impact on three fundamental processes in glucose metabolism:[18]

- Impaired glucose utilization in peripheral tissues
- Increased gluconeogenesis (both hepatic and renal)
- Increased glycogenolysis.

Insulin deficiency and/or resistance in diabetic patients impair peripheral glucose utilization in skeletal muscle. However, decreased glucose utilization alone will produce only postprandial hyperglycemia; increased gluconeogenesis is required for the often severe fasting hyperglycemia seen in DKA and HHNK.

Insulin deficiency and/or resistance promote hepatic gluconeogenesis by two mechanisms: increased delivery of gluconeogenetic precursors (glycerol and alanine) to the liver due to increased fat and muscle breakdown;[19] and increased secretion of glucagon by removal of the inhibitory effect of insulin on glucagon secretion and the glucagon gene.[20]

The glucosuria associated with DKA and HHNK initially minimizes the rise in serum glucose. However, the osmotic diuresis caused by glucosuria leads to volume depletion and a reduction in glomerular filtration rate that limits further glucose excretion. This effect is more pronounced in HHNK which, as noted above, is usually associated with a higher serum glucose than seen in DKA.

Ketoacidosis

Both insulin deficiency and glucagon excess contribute to the genesis of DKA.[21,22] As noted above, however, glucagon is not required for DKA to occur.

Acetoacetic acid is the initial ketone formed; it may then be reduced to beta-hydroxybutyric acid, which is also an organic acid, or nonenzymatically decarboxylated to acetone, which is chemically neutral.[2] Ketones provide an alternate source of energy when glucose utilization is impaired.

Insulin deficiency and increased catecholamine lead to enhanced lipolysis, thereby increasing free fatty acid delivery to the liver. Normal subjects will convert these free fatty acids primarily into triglycerides. The development of ketoacidosis requires a specific alteration in hepatic metabolism so that free fatty acyl CoA can enter the mitochondria, where conversion to ketones occurs.[22,23]

Mitochondrial entry is regulated by the cytosolic enzyme carnitine palmitoyltransferase I (CPT I), the activity of which varies inversely with malonyl CoA. Glucagon decreases the production of malonyl CoA, thereby increasing CPT I activity and ketogenesis. A concurrent increase in hepatic carnitine content contributes to this process. Insulin does not appear to directly affect hepatic ketogenesis.[24]

In states of insulin deficiency, the combination of increased free fatty acid delivery and glucagon excess promotes ketogenesis.

The factors responsible for the general absence of ketoacidosis in HHNK are incompletely understood. One important factor may be the differential sensitivity of fat and glucose to the effects of insulin. Studies in humans have demonstrated that the concentration of insulin required to suppress lipolysis is only one-tenth that required to promoting glucose utilization. Thus, moderate insulin deficiency, as seen

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in HHNK, might be associated with sufficient insulin to block lipolysis (and therefore ketoacid formation) but not enough to promote glucose utilization and prevent the development of hyperglycemia. More severe insulin deficiency will also be associated with ketoacidosis.[25]

Precipitating Factors

Multiple factors can precipitate onset and progression of DKA and HHNK. The most common cause of DKA in Type 1 diabetics is lack of or insufficient insulin action while the most common cause of HHNK is compromised water intake due to underlying medical conditions in the elderly. Most of the times, more than one factor contributes to the onset of these emergencies.

- *Lack of insulin*: Insufficient amount of insulin or its lack especially in Type 1 diabetic will initiate the cascade resulting in hyperglycemia and ketosis in diabetics.
- *Infection*: Most commonly urinary tract infection or pneumonia can precipitate DKA and HHNK.
- *Infarction/Ischemia*: Ischemia or any infarction of any organ (heart, brain, intestine, etc.) will cause a stress on the body in the form of an inflammatory state and can precipitate DKA or HHNK.
- *Medications*: Drugs that affect carbohydrate metabolism, including glucocorticoids, higher dose thiazide diuretics, sympathomimetic agents (e.g. dobutamine and terbutaline),[26] and second-generation antipsychotic agents.[27] Use of cocaine has been associated with recurrent DKA.
- *Psychological problems* associated with eating disorders and purposeful insulin omission, particularly in young patients with Type 1 diabetes.[28] Factors that may lead to insulin omission in younger patients include fear of weight gain, fear of hypoglycemia, and the stress of chronic disease.

CLINICAL PRESENTATION

Diabetic ketoacidosis usually evolves rapidly, over a 24-hour period while symptoms of HHNK develop more insidiously with polyuria, polydipsia, and weight loss, often persisting for several days before hospital admission.

The earliest symptoms of marked hyperglycemia are polyuria, polydipsia, and weight loss. As the degree or duration of hyperglycemia progresses, neurologic symptoms, including lethargy, focal signs, and obtundation, which can progress to coma in later stages, can be seen. Neurological symptoms are the most common in HHS, while hyperventilation and abdominal pain are primarily limited to patients with DKA.

Initial Evaluation

Both DKA and HHNK are medical emergencies that require prompt recognition and management. An initial history and rapid but careful physical examination should focus on:

- Airway, breathing and circulation (ABC) status
- Mental status

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- Possible precipitating events (e.g. source of infection, myocardial infarction, medications)
- Volume status.

Neurologic Symptoms and Plasma Osmolality

Neurologic deterioration primarily occurs in patients with an *effective* plasma osmolality above 320–330 mosmol/kg. Mental obtundation and coma are more frequent in HHNK than DKA because of the usually greater degree of hyperosmolality in HHNK. In addition, some patients with HHNK have focal neurologic signs (hemiparesis or hemianopsia) and/or seizures. Mental obtundation may occur in patients with DKA, who have lesser degrees of hyperosmolality, when severe acidosis is also present.

In the calculation of effective plasma osmolality, the urea concentration is not taken into account because urea is freely permeable and its accumulation does not induce major changes in intracellular (including brain) volume or the osmotic gradient across the cell membrane.[29]

The effective plasma osmolality (Posm, in mosmol/kg) can be estimated from either of the following equations:

Effective Posm = [2 × Na (mEq/L)] + [glucose (mg/dL) ÷ 18]

Effective Posm = Measured Posm - [BUN (mg/dL) ÷ 28]

Where Na is the serum sodium concentration, the multiple 2 accounts for the osmotic contribution of the anions accompanying sodium (primarily chloride and bicarbonate), and 18 and 28 are conversion factors from units of mg/dL into mmol/L. Where standard units are used, the following equations apply:

Effective Posm = [2 × Na (mmol/L)] + glucose (mmol/L)

Effective Posm = Measured Posm - BUN or blood urea (mmol/L)

Importance of Osmotic Diuresis

The rise in plasma osmolality in DKA and HHNK is only in part due to the rise in serum glucose. The increase in plasma osmolality pulls water out of the cells, which reduces the plasma osmolality toward normal and lowers the serum sodium. The marked hyperosmolality seen in HHNK is primarily due to the glucose osmotic diuresis that causes water loss in excess of sodium and potassium.

It is important to remember that the presence of stupor or coma in diabetic patients with an effective plasma osmolality lower than 320 mosmol/kg demands immediate consideration of other causes of the mental status change.

Abdominal Pain in Diabetic Ketoacidosis

Patients with DKA may present with nausea, vomiting, and abdominal pain; although more common in children, these symptoms can be seen in adults. Abdominal pain is unusual in HHNK. The presence of abdominal pain is associated with the severity of the metabolic acidosis and not with the severity of hyperglycemia or dehydration. Possible causes of abdominal pain include delayed gastric emptying and ileus induced

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by the metabolic acidosis and associated electrolyte abnormalities. Other causes for abdominal pain should be sought when it occurs in the absence of severe metabolic acidosis and when it persists after the resolution of ketoacidosis.[30]

Physical Examination

Signs of volume depletion are common in both DKA and HHNK, including decreased skin turgor, dry axillae and oral mucosa, low jugular venous pressure and, if severe, hypotension. Neurologic findings, noted above, also may be seen, particularly in patients with HHS. Patients with DKA may have a fruity odor (due to exhaled acetone and similar to the odor of nail polish remover), and deep respirations reflecting the compensatory hyperventilation (called Kussmaul respirations).

Fever is rare even in the presence of infection, because of peripheral vasoconstriction due to hypovolemia.

LABORATORY FINDINGS

Hyperglycemia and hyperosmolality are the two primary laboratory findings in patients with DKA or HHNK; patients with DKA also have a high anion gap metabolic acidosis. Most patients also have acute elevations in the blood urea nitrogen (BUN) and serum creatinine concentration, which reflect the reduction in glomerular filtration rate induced by hypovolemia.

The initial laboratory evaluation of a patient with suspected DKA or HHNK should include determination of:

- Serum glucose
- Serum electrolytes (with calculation of the anion gap), BUN and serum creatinine
- Complete blood count with differential
- Urinalysis, and urine ketones by dipstick
- Plasma osmolality
- Serum ketones (if urine ketones are present)
- Arterial blood gas (if urine ketones or anion gap are present)
- Electrocardiogram

Additional testing, such as cultures of urine, sputum, and blood, serum lipase and amylase, and chest X-ray, should be performed on a case-by-case basis.

Measurement of A1C may be useful in determining whether the acute episode is the culmination of an evolutionary process in previously undiagnosed or poorly controlled diabetes or a truly acute episode in an otherwise well-controlled patient.

Serum Ketones

Three ketone bodies are produced in DKA: acetoacetic acid, which is the only true ketoacid; beta-hydroxybutyric acid, a hydroxyacid formed from the reduction of acetoacetic acid; and acetone, which is derived from the decarboxylation of acetic acid. Acetone is a true ketone but is chemically neutral and therefore not an acid. Urine ketone bodies are detected by a dipstick. Testing for serum ketones is performed if urine testing is positive, using nitroprusside (Acetest) tablets or reagent sticks. A 4+ reaction with serum diluted 1:1 is strongly suggestive of ketoacidosis.

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False Negative Tests

Nitroprusside reacts with acetoacetate and acetone, but not with beta-hydroxybutyrate. This is important because beta-hydroxybutyrate is the predominant ketone, particularly in severe DKA. It is therefore possible, although unusual, to have a negative serum nitroprusside reaction in the presence of severe ketosis.

An indirect method to circumvent the masking of ketoacidosis is to add a few drops of hydrogen peroxide to a urine specimen. This will nonenzymatically convert beta-hydroxybutyrate to acetoacetate, which will then be detectable by nitroprusside. An alternative is to directly measure beta-hydroxybutyrate in the blood.

False Positive Tests

Sulfhydryl drugs, such as captopril, penicillamine, and mesna, interact with the nitroprusside reagent and can lead to a false positive ketone test. Thus, a positive nitroprusside test cannot be reliably interpreted in patients treated with these drugs and direct measurement of beta-hydroxybutyrate is recommended. If it is not available, the diagnosis of DKA in this setting should be made on the basis of clinical presentation and an otherwise unexplained high anion gap metabolic acidosis in association with hyperglycemia.

Anion Gap Metabolic Acidosis

The serum bicarbonate concentration in DKA is reduced to a variable degree, ranging from mild to severe. In contrast, the serum bicarbonate concentration is normal or only mildly reduced in HHNK.

The sine qua non of DKA is an elevated anion gap metabolic acidosis, due to the production and accumulation of beta-hydroxybutyrate and acetoacetate. Compensatory hyperventilation results in a fall in the partial pressure of CO_2 that minimizes the fall in arterial pH. The arterial pH in DKA is less than 7.30 and can be lower than 6.90.

The severity of the metabolic acidosis is dependent upon a number of factors including rate of ketoacid production, duration of onset and the rate of excretion in the urine.

The serum anion gap provides an estimate of the quantity of unmeasured anions in the serum, such as albumin and, in DKA, ketoacids. It is calculated by subtracting the major measured anions (chloride and bicarbonate) from the major measured cation (sodium):

Serum anion gap = Serum sodium - (serum chloride + bicarbonate)

Patients with DKA usually present with a serum anion gap greater than 20 mEq/L. However, the increase in anion gap is variable, being determined by two factors: the rate and duration of ketoacid production, and the rate of loss of ketoacid anions in the urine. With respect to ketonuria, excretion of the sodium and potassium salts of beta-hydroxybutyrate and acetoacetate lowers the serum anion gap without affecting the serum bicarbonate concentration and therefore the degree of acidosis.[31]

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Serum Sodium

The measured serum sodium concentration in uncontrolled diabetes mellitus is variable, as factors are present that can both lower and raise the measured value. The final serum sodium concentration will reflect the balance between dilution of sodium due to osmotic water movement out of the cells, and concentration of sodium due to glucosuria-induced osmotic diuresis resulting in water loss in excess of sodium.

Physiologic calculations suggest that the serum sodium concentration should fall by 1 mEq/L for every 62 mg/dL (3.5 mmol/L) rise in the serum concentration of glucose. However, this standard correction factor was not verified experimentally and in the setting of DKA and HHNK, a ratio of 2.4 mEq/L for every 100 mg/dL of glucose rise is more appropriate.[32]

Remember, some patients with uncontrolled diabetes have marked hyperlipidemia and lactescent serum. In this setting, each liter of serum contains less water and therefore less sodium and the measured serum sodium concentration will fall, even though the physiologically important serum water sodium concentration and plasma osmolality are not affected.

Serum Potassium

Patients with DKA or HHNK, at presentation, have a potassium deficit that averages 3–5 mg/kg. A number of factors contribute to this deficit, particularly increased urinary losses due both to the glucose osmotic diuresis and to the need to maintain electroneutrality as ketoacid anions are excreted. Gastrointestinal losses and the loss of potassium from the cells due to glycogenolysis and proteolysis also may play a contributory role.[33]

Despite these potassium losses, the serum potassium concentration is usually normal or, in one-third of patients, elevated on admission. It is thought that hyperosmolality and insulin deficiency are primarily responsible for the relative rise in the serum potassium concentration in this setting. Insulin therapy lowers the potassium concentration and may cause severe hypokalemia, particularly in patients with a normal or low serum potassium concentration at presentation.[34] Thus, careful monitoring and timely administration of potassium supplementation are essential.

Serum Phosphate

Patients with uncontrolled hyperglycemia are typically in negative phosphate balance because of decreased phosphate intake and phosphaturia caused by osmotic diuresis. Despite phosphate depletion, the serum phosphate concentration at presentation is usually normal or even high because both insulin deficiency and metabolic acidosis cause a shift of phosphate out of the cells.[35]

Serum Amylase and Lipase

Serum amylase and lipase are the standard tests to diagnose acute pancreatitis, which may precipitate DKA, but both are often elevated in patients with DKA who do not have pancreatitis. As a result, the diagnosis of pancreatitis in patients with DKA should

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be based upon clinical findings and imaging. The mechanisms for hyperamylasemia and hyperlipasemia in DKA are not well defined.[36]

Leukocytosis

The majority of patients with hyperglycemic emergencies present with leukocytosis, which is proportional to the degree of ketonemia. Leukocytosis unrelated to infection may occur as a result of hypercortisolemia and increased catecholamine secretion. However, a white blood cell count greater than 25,000/microL or a band count greater than 10 percent may designate infection and indicates a need for further work-up.[37]

Lipids

Patients with DKA or HHS may present with marked hyperlipidemia and lactescent serum. In a study of 13 patients with DKA, the mean plasma triglyceride and cholesterol levels on admission were 574 mg/dL (6.5 mol/L) and 212 mg/dL (5.5 mmol/L), respectively. Triglycerides fell below 150 mg/dL (1.7 mmol/L) in 24 hours with insulin therapy.[38]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of metabolic acidosis should include high fat intake, lactic acidosis, alcoholic acidosis, salicylate poisoning and the most important in the month of fasting—fasting ketoacidosis.

Fasting Ketoacidosis

This is the major differential diagnosis to rule out in the fasting patient in *Ramadan*. Mostly ketoacid levels in fasting ketoacidosis do not exceed 10 mEq/L with prolonged fasting alone, which means that the serum bicarbonate concentration is typically above 14 mEq/L.[39]

Anion Gap Acidosis

Diabetic ketoacidosis must also be distinguished from other causes of high anion gap metabolic acidosis including lactic acidosis (which can be induced by Metformin particularly in patients with impaired renal function); ingestion of drugs such as aspirin methanol, and ethylene glycol; and advanced chronic kidney disease. None of these disorders causes ketoacidosis.

TREATMENT

Once the diagnosis of DKA and HHNK is established on the basis of history, physical examination, and laboratory work-up, treatment should be undertaken promptly and in an organized fashion. A flow chart should be made in order to keep track of all treatment steps, blood sugars, and electrolyte balance as under or over treatment can result in devastating consequences.

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AIRWAY, BREATHING AND CIRCULATION, IV ACCESS AND MONITORING

- Stabilize the patient's airway, breathing and circulation.
- Obtain large bore IV (≥ 16 gauge) access; monitor using a cardiac monitor, and pulse oximetry, if possible.
- Monitor serum glucose hourly and basic electrolytes, plasma osmolality, and venous pH every two to four hours until the patient is stable.
- Determine and treat any underlying cause of DKA (e.g. pneumonia or urinary infection, myocardial ischemia).

Replete the Fluid Deficit

- Give several liters of isotonic (0.9%) saline as rapidly as possible to patients with signs of shock.
- Give isotonic saline at 15–20 mL/kg/hour, in the absence of cardiac compromise, for the first few hours to hypovolemic patients without shock.
- After intravascular volume is restored, give one-half isotonic (0.45%) saline at 4 to 14 mL/kg/hour if the corrected serum sodium is normal or elevated; isotonic saline is continued if the corrected serum sodium is reduced.
- Add dextrose to the saline solution when the serum glucose reaches 200 mg/dL (11.1 mmol/L).

Replete Potassium (K^+) Deficits

- Regardless of the initial measured serum potassium, patients with DKA have a large total body potassium deficit.
- If initial serum K^+ is below 3.3 mEq/L, hold insulin and give K^+ 20–30 mEq/hour IV until K^+ concentration is above 3.3 mEq/L.
- If initial serum K^+ is between 3.3 and 5.3 mEq/L, give K^+ 20–30 mEq/liter IV fluid; maintain K^+ between 4 and 5 mEq/L.
- If initial serum K^+ is above 5.3 mEq/L do not give K^+; check K^+ every 2 hours.

Give Insulin

- Do not give insulin if initial serum K^+ is below 3.3 mEq/L; replete K^+ first.
- Give all patients without a serum K^+ below 3.3 mEq/L regular insulin. Either of two regimens can be used: 0.1 units/kg IV bolus, then start a continuous IV infusion 0.1 units/kg/hour; or do not give bolus and start a continuous IV infusion at a rate of 0.14 units/kg/hour.
- Continue insulin infusion until ketoacidosis is resolved, serum glucose is below 200 mg/dL (11.1 mmol/L), and subcutaneous insulin is begun.

Give Sodium Bicarbonate to Patients with pH Below 7.00

- If the arterial pH is between 6.90 and 7.00, give 50 mEq of sodium bicarbonate plus 10 mEq of potassium chloride in 200 mL of sterile water over 2 hours.
- If the arterial pH is below 6.90, give 100 mEq of sodium bicarbonate plus 20 mEq of potassium chloride in 400 mL sterile water over two hours.

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PREVENTIVE MEASURES

All diabetics who are planning to observe the fasting in the month of *Ramadan* should be comprehensively educated about the possibility of developing DKA and HHNK. Their medications should be evaluated and all the necessary changes should be made before the onset of *Ramadan* mostly decrease in the dose of insulin, type of insulin-long acting versus premix, decrease in the dose of sulfonylureas. Especial emphasis should be placed on hydration status and early recognition of any signs or symptoms of DKA and HHNK.

CONCLUSION

Diabetic ketoacidosis and HHNK can be avoided in the month of *Ramadan* with proper education of the patient, their relatives, and a close communication between patient and their physicians. Sometimes, it is necessary to avoid fasting or break a fast to avoid unacceptable consequences that can result from these complications. Patients should be informed that their God is more interested in their being alive than dead.

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Chapter 20

Dyselectrolytemia in Ramadan

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Abstract

Ramadan fasting occurs at different seasons of the year because it depends upon the lunar calander. Because of heat and humid conditions, many abnormalities in fluid, blood concentration and urinary excretion of electrolytes have been reported in people with diabetes mellitus and diabetes insipidus, though these may be within the normal limits. Sodium excretion declines throughout *Ramadan* and increases in the 1st week after *Ramadan*. However, serum sodium does not change beyond normal limits. Similarly there is some decline in potassium excretion during *Ramadan* and reverts back to pre-fasting level after. Some changes in serum concentration of calcium have been reported, some have reported decrease while others have reported a minor increase. People with chronic kidney disease (CKD) are predisposed to severe hyperkalemia because of uncontrolled diabetes and consumption of high carbohydrate meal. People with diabetes insipidus are predisposed to severe dehydration and hypernatremia during the month of *Ramadan* fasting.

INTRODUCTION

During the religious festival of *Ramadan*, the majority of adult, practicing Muslims refrain from eating, drinking, smoking and sexual relationships during the hours of daylight throughout the lunar month. Since the Islamic calendar is lunar, the start of the Islamic year advances 11 days each year compared with the seasonal year; therefore, *Ramadan* occurs at different times of the seasonal year over a 33-year cycle, this can result in the *Ramadan* fast being undertaken in markedly different environmental conditions between years in the same country. In addition, the time of sunrise and sunset varies between 12 hours at the equator and about 22 hours at the 64° of latitude in summer time. For people living in the Polar regions, it is recommended, however, that they take the fasting times as those prescribed at Mecca and Medina, or from the nearest temperate zones.[1] Not only is the eating pattern greatly altered during the *Ramadan* period, but the amount and type of food eaten during the night may also be significantly different to that usually consumed during the rest of the year.

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Fasting during *Ramadan* is different from prolonged continuous fasting, during which it is done only between dawn and sunset, and people are allowed to drink and eat freely after sunset till the onset of dawn.[2]

RENAL RESPONSE TO RAMADAN FASTING

Sodium

Many changes in urinary excretion of sodium have been studied during the month of *Ramadan*. There is a decline in the 24 hours sodium (Na^+) output throughout the fasting period especially during the first 2 weeks followed by an increase thereafter and a rebound in the 1st week post-*Ramadan*. Overnight Na^+ output also declines throughout *Ramadan* and increases in the first week after *Ramadan*. In the morning, there is a small decrease in the 2nd week and the output during the afternoon being significantly lower throughout *Ramadan*. However, serum sodium does not change beyond normal limits.[3] The mechanism for the control of urinary Na^+ excretion during and after *Ramadan* is quite complex and factors like aldosterone, atrial natriuretic factor (ANF) and tubuloglomerular balance may be important, which are in turn influenced by neural hormonal and humoral factors.[4,5]

Potassium and Minerals

In general, the change in K^+ output during *Ramadan* is less dramatic compared with the Na^+. There is some decline in K^+ output in the 24 hours urine, but this is significant only in the 4th week of fasting. Except for a significant decline in the 1st week of fasting in the overnight collection, there are no significant changes in the morning, afternoon and most of the overnight output during *Ramadan*. Serum K^+ also does not show gross changes beyond accepted normal values. There is a decrease in urine inorganic phosphorus excretion.[3]

No major changes in serum concentration of calcium are observed in the month of *Ramadan*. In some studies, mean serum concentrations of calcium has been either reported to decrease 10 days after the beginning of fasting, while others have documented a slight increase as compared to pre-*Ramadan* values.[6,7] Serum phosphorus does not change in *Ramadan*.[6]

In prolonged experimental fasting, normal serum phosphorus, normal or decreased serum calcium and increased urinary excretion of calcium and phosphorus, have been reported.[8,9] Serum magnesium levels remain stable; however magnesium excretion in 24 hours urine is reported to be lower than in non-fasting individuals.[10,11] Lactating mothers who fast may lose their body water and show changes in plasma osmolality, Na^+, uric acid, lactose and potassium content of the breast milk.[12]

Electrolyte Dynamics in Special Circumstances

Although the levels of serum electrolytes remain stable in healthy individuals during *Ramadan* fasting, however same may not hold true in disease states.

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Chronic Kidney Disease and Renal Transplant Recipients

During *Ramadan*, urinary volume, osmolality, pH, nitrogen, solute and electrolyte excretion remain normal.[3] No disturbance in serum electrolytes have been noticed during *Ramadan* fasting.[13] Reduction in urinary sodium excretion during *Ramadan* and the following month compared to the month before *Ramadan* indicates that the kidneys of transplant patients respond well to the reduced fluid intake during fasting.[3] However, hyperkalemia due to consumption of huge amounts of potassium-rich food at breaking the fast, has been noticed in CKD, kidney transplant and hemodialysis patients.[14-16]

Patients with diabetes and CKD on dialysis therapy have severely impaired renal function and are at risk of lethal hyperkalemia because of hyperglycemia.[17] Patients with chronic renal failure should be advised about the potential risk of hyperkalemia and if they insist on fasting, their renal function and electrolytes should be monitored and should stop fasting if any deterioration occurs.[18]

Renal transplant recipients on immunosuppressive, therapy who have normal allograft function, experience no harmful effects from fasting and their renal concentrating ability remains unchanged.[19]

Diabetes Insipidus

Conservation of body fluid resources and balancing outer-cell liquid with inter-tissue spaces is crucial. Osmolality, which is the sign of osmosis activity of all plasma particles, is between 280 mOsm/kg and 295 mOsm/kg. Changes in the body fluid status and the amount of outer cell sodium can lead to many changes in plasma osmolality.[20] Changes in plasma osmolality of about 1–2% stimulate osmoreceptors which cause the discharge of antidiuretic hormones and stimulation of thirst.[21] Because thirst is preserved in patients with diabetes insipidus, plasma osmolality is usually maintained within the normal range, and hypernatremia usually indicates poor fluid intake than severe renal water loss.[22] During *Ramadan* fasting, Muslims abstain from food and drink for about 12–18 hours which may lead to increase in plasma osmolality, sodium and uric acid because of dehydration.[12] This effect will be more pronounced in athletes, manual laborers, in individuals who fast during summer and is more pronounced in tropical areas. With fluid restriction during the day, in *Ramadan*, coupled with continuing polyuria in patients with diabetes insipidus, severe dehydration and hypernatremia can occur which has devastating effects on central nervous system.[23]

Diabetes Mellitus

There are no major problems encountered with Type 2 diabetes (T2D) and even controlled Type 1 diabetes(T1D) patients during *Ramadan* fasting.[24,25] Some abnormalities in fluid and electrolyte balance are common biochemical findings in diabetes mellitus and have been attributed to increased losses, reduced intake/absorption or alterations in metabolism.[26,27] In diabetes mellitus, increased urinary loss due to osmotic diuresis may be a common and most important cause of reduced electrolytes, although intracellular shift also plays a role.[26] The extensive EPIDIAR

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study showed a five-fold increase in the incidence of severe hyperglycemia during *Ramadan* in patients with T2D and an approximate three-fold increase in the incidence of severe hyperglycemia with or without ketoacidosis in patients with T1D patients.[28] Patients who reported an increase in food and sugar intake had higher incidence of hyperglycemia, making them more vulnerable to hyperkalemia, despite absence of acidosis and normal serum aldosterone level.[29,30]

Insulin promotes potassium uptake by muscle cells *in vitro* even when the solution bathing the cells contains no glucose.[31] The increased urinary excretion of potassium prevents severe hyperkalemia in hyperglycemic patients with intact renal function. Usually only patients with impaired renal function have severe hyperkalemia because of hyperglycemia.[32,33]

Diabetes patients on dialysis therapy have severely impaired renal function and are reportedly at risk of lethal hyperkalemia from hyperglycemia.[17] Patients with diabetes, especially those with T1D, who fast during *Ramadan*, are at increased risk for development of diabetic ketoacidosis, particularly if their diabetes is poorly controlled before *Ramadan*. In addition, the risk for diabetic ketoacidosis may be further increased due to reduction of insulin dosages based on the assumption that food intake is reduced during the month. Hypertonicity, metabolic acidosis and insulin deficiency cause shift of potassium from intracellular compartment to extracellular compartment leading to hyperkalemia.[34,35]

Patients with T2D may suffer similar perturbations in response to a prolonged fast and the severity of hyperglycemia depends on the extent of insulin resistance and/or deficiency.

Hyperosmolar state in T2D may be precipitated by consumption of glucose rich foods overnight, resulting in extreme hyperglycemia-induced diuresis. Osmotic diuresis causes water loss in excess of sodium and produces a rise in serum Na^+ and plasma osmolality.[36]

Muslims during *Ramadan* abstain from taking food and drinks, even water, from dawn to dusk. Limitation of fluid intake during the fast is a cause of dehydration. The dehydration may become severe as a result of excessive perspiration in hot and humid climates and among individuals who perform hard physical labor. Moreover, patients with T2D have multiple co-morbidities like hypertension, may be using thiazide diuretics, which complicate the picture.[37]

Patients with uncontrolled glycemia during *Ramadan* may develop magnesium deficiency because of increased excretion of magnesium[38] and thus lead to worsening of glycemia because of suppression of glucose metabolism and insulin action.[39]

CONCLUDING REMARKS

- *Ramadan* fasting is safe in healthy individuals, with no significant electrolyte disturbances.
- Hyperkalemia has been observed in patients with CKD, patients on hemodialysis and renal transplant recipients, which may be related to consumption of fruits/juices after breaking the fast, as has been reported in normal fasting individuals.

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- Patients with T2D and controlled T1D have no major problems with fasting. However, patients with poor glycemic control are at increased risk of development of hyperkalemia, hyponatremia and hypomagnesemia.
- Patients with uncontrolled diabetes mellitus and CKD are at risk of life-threatening hyperkalemia.
- Patients of diabetes insipidus, with large volumes of polyuria, can develop profound dehydration with severe hypernatremia which can be fatal.

RECOMMENDATIONS

- Patients with diabetes mellitus should avoid the practice of consumption of large quantities of carbohydrates and fruit juices in the non-fasting hours. Calories should be distributed in two to three meals to prevent postprandial hyperglycemia and subsequent risk of electrolyte disturbances.
- Fasting should be interrupted if blood glucose exceeds more than 300 mg/dL and avoided on "sick days".
- Fluid intake (water) should be increased during non-fasting hours
- Normal levels of physical activity may be maintained, multiple prayers should be considered as a part of exercise program.
- Renal transplant recipients with normal allograft function can observe fast without additional risks
- Patients with CKD should be cautioned about the potential risk of developing hyperkalemia and their renal function and electrolytes should be monitored and should stop fasting if deterioration occurs.
- Diabetic patients on dialysis with uncontrolled glycemia should not fast because of increased risk of life threatening hyperkalemia.
- Patients with mild polyuria can fast without significant electrolyte abnormalities. Patients with large volume of polyuria should not fast and if they insist, should be monitored closely. If they lose more than 3% of body weight or if serum sodium rises above normal, should break their fast.

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Chapter 21

Management of Diabetic Patients with Co-morbid Conditions during Ramadan

Mahdi Kamoun, Ines Slim, Mouna Feki Mnif

Abstract

Patients with chronic diseases often insist on fasting even though they are permitted not to by Islamic rules. Recent studies corroborate safety of *Ramadan* fasting in diabetic patients with stable comorbidities; especially if they had a pre-*Ramadan* medical assessment and educational counseling. In such patients, medical advices regarding medications schedules, drug interactions and nonpharmacological measures should be provided. Sustained release formulations may be of particular interest during *Ramadan*. However, fasting may lead to severe alterations in patients with more serious cardiovascular and renal diseases.

The aim of this chapter is to provide a comprehensive review of the *Ramadan* management of diabetic patients with selected co-morbid conditions (hypertension, dyslipidemia, cardiovascular disease and kidney disease). The effects of fasting during *Ramadan* on this specific population are also briefly described.

INTRODUCTION

Diabetic patients often present co-morbidities; are polymedicated and are potentially more prone to adverse drug reactions. Nevertheless, most of these patients insist on fasting even though they are permitted not to by Islamic rules. Some patients arbitrarily change the intake time and dosing of drugs without getting medical advice. This behavior could affect the pharmacokinetics and pharmacodynamics of some drugs, especially those with a narrow therapeutic range, and consequently could influence the efficacy and the tolerance of such medications.[1] Others choose to ask their medical practitioner certain questions pertaining to their ability to fast safely.

Physicians may have knowledge gaps in terms of both risk assessment and management strategies in diabetic patients with comorbidities who wish to fast. Lifestyle changes during *Ramadan* affect drug intake time and dosing, and may cause deleterious effects in diabetic patients with several comorbid conditions; such as hypertension, cardiovascular diseases (CVD) and chronic kidney disease (CKD).

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However, recent studies corroborate safety of *Ramadan* fasting in diabetic patients with stable comorbidities; especially if they had a pre-*Ramadan* medical assessment and educational counseling.[2]

The aim of this chapter is to provide a comprehensive review of the *Ramadan* management of diabetic patients with selected co-morbid conditions (hypertension, dyslipidemia, cardiovascular disease and kidney disease). The effects of fasting during *Ramadan* on this specific population are also briefly described.

GENERAL CONSIDERATIONS IN MANAGEMENT OF DIABETIC PATIENTS WITH CO-MORBID CONDITIONS

The following basic considerations should be taken into account by physicians in order to assess whether or not a diabetic patients with comorbidities could fast *Ramadan* month.

Fasting Safety

Fasting that endangers health is not in accordance with Islamic jurisprudence. The *Quran* states exemption from fasting for patients with chronic diseases if fasting worsens one's illness or delays recovery. Physicians play a key role in the safety assessment of *Ramadan* fasting in diabetic patients with comorbidities. In this vulnerable population, fasting should have no deleterious impacts on both the diabetes and its associated comorbidities. It is important to know whether fasting will increase mortality risk, cause a significant morbidity (organ failure, complications…), or lead to excessive pain and difficulty. In addition, physicians need to determine whether or not it is safe to fast during periods of stability of the chronic illness of their patients.

Overall; diabetic patients with comorbidities could be divided into three categories **(Flow chart 1)**:

1. Patients who are not harmed by fasting (such as well-controlled Type 2 diabetic patients with stable comorbidities). Such patients could be advised to fast in *Ramadan*.
2. Patients who are not harmed by fasting but their treatment could be adjusted for proper control (such as antihypertensive medications).
3. Patients who are harmed by fasting or their treatment cannot be given with fasting (such as acute myocardial infarction). Such patients should avoid *Ramadan* fasting.

Pre-Ramadan Diabetic Control

Physicians should assess glycemic control of their patients before *Ramadan*. Fasting in patients with poor glycemic control could deteriorate both the diabetes and the associated diseases.

The following categories of diabetic patients are considered at very high risk; even if the comorbidities associated with diabetes are stable.[3]

- Patients with sustained poor glycemic control
- Patient with a history of recurrent hypoglycemia or with hypoglycemia unawareness

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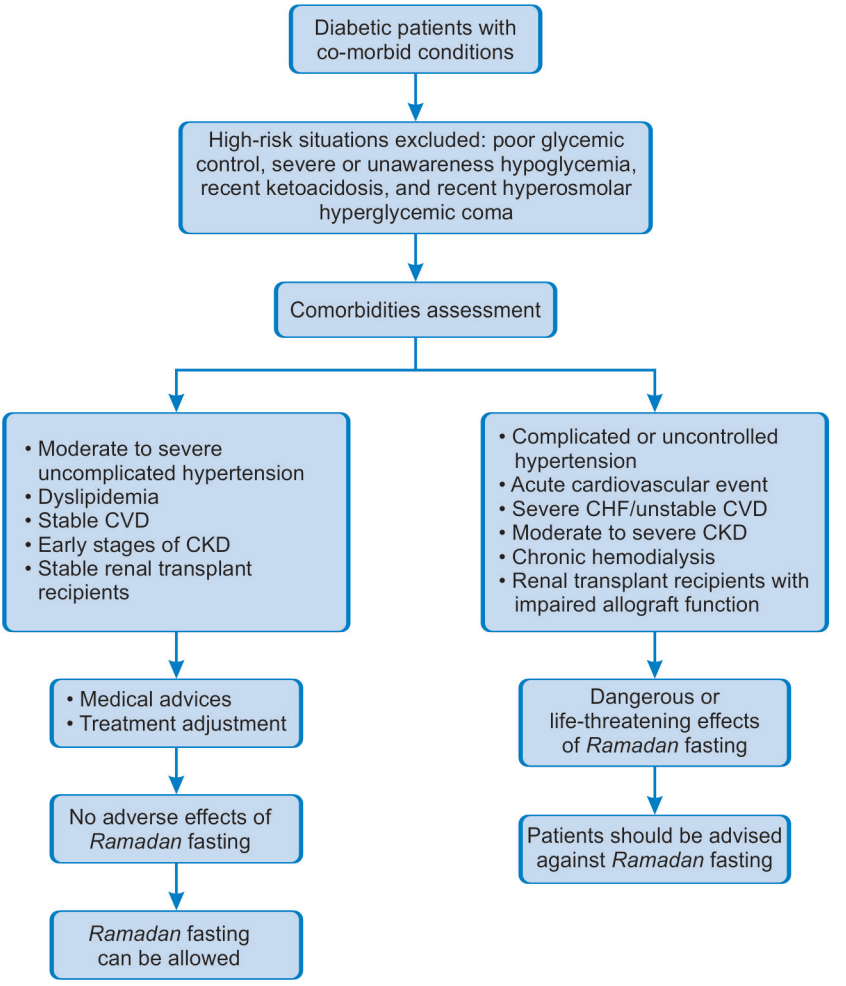
Flow chart 1: Impact of the different types of comorbidities associated to diabetes on the decision to fast *Ramadan*



Abbreviations: CVD—Cardiovascular disease; CKD—Chronic kidney disease; CHF—Congestive heart failure

- Ketoacidosis within the last 3 months prior to *Ramadan*
- Hyperosmolar hyperglycemic coma within the last 3 months prior to *Ramadan.*

Drug Pharmacokinetics and Pharmacodynamics

Pharmacokinetics examines the absorption, distribution, metabolism and excretion of drugs, and the associated toxic or therapeutic responses. Pharmacodynamics is the study of the relationship between the concentration of a drug and the response obtained in a patient. Both these two parameters could be altered by *Ramadan*

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fasting, hence their efficacy and tolerance is decreased. This is especially relevant for drugs with a narrow therapeutic index such as digoxin.[1]

Drug Interactions

Physicians should be aware of drug interactions during *Ramadan*. There is a high risk of such interactions in diabetic patients with comorbidities who often take simultaneously their daily medicines either at sunset (*Iftar*) or at sunrise (*Suhur*). As examples, amiodarone and spironolactone can increase digoxin levels and the risk of toxicity. The co-administration of digoxin and beta-blockers or calcium-channel blockers (verapamil), which also reduces heart rate, can cause serious slowing of the heart rate. Diuretic-induced reduction in blood potassium or magnesium levels may predispose patients to digoxin-induced abnormal heart rhythms.[1]

Dosing Schedule

Since drug doses can be taken only between sunset and dawn during fasting, and the time span between them is shorter than outside *Ramadan*, most medications schedules should be altered. Two different types of dosage schedule are commonly used during *Ramadan*.[1]

Single Daily Dose

Using long-acting, once-daily drugs seems to be the preferred treatment option for patients who fast *Ramadan*.

Two or More Daily Doses

Patients with two doses could take the first one at the break of fasting and the second one before the beginning of fasting.

Drug-Food Interactions

Drug-food interactions may result in reduced, delayed, or increased systemic availability of a drug. Risk of such interactions may be also increased during *Ramadan*. For example, grapefruit juice may reduce the breakdown of amiodarone in the stomach leading to increased amiodarone blood levels. Differently, the bioavailability of celiprolol diminishes when taken along with orange juice by possible mechanisms related to pH variations and changes in the function of the transporters in the intestine.[4]

The degree of interaction, and whether it positively or negatively affects drug absorption, depends on several factors, including the physical and chemical nature of the drug, the formulation, the type of meal, and the time interval between eating and dosing. Particular care should be taken in using drugs that have to be administered on an empty stomach.[1]

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MANAGEMENT OF DIABETIC PATIENTS WITH SELECTED COMORBIDITIES DURING RAMADAN

Hypertension and Ramadan Fasting

Effects of Ramadan Fasting on Hypertensive Patients

A large body of evidence suggests that there are no significant changes in blood pressure (BP) in treated hypertensive subjects during *Ramadan* with the proviso of the continuation of prescribed antihypertensive medications. This held true for average 24-hour, diurnal, and nocturnal mean of BP **(Figure 1)**.[5-7] In this regard, a study including 99 hypertensive patients was carried out by Habbal et al. in Casablanca (Morocco) during *Ramadan* in 1998. All included patients had mild to moderate hypertension. They had ambulatory BP monitoring before and during *Ramadan*. There were no significant differences in the systolic and diastolic BP values between pre-*Ramadan* and *Ramadan* periods over 24-hours, daytime and night time periods. Results from this study corroborate the finding that in patients with moderate uncomplicated hypertension, *Ramadan* fasting may be well-tolerated. The variations of BP during *Ramadan* are minimal and possibly due to some changes in sleep pattern and eating habits.[5] *Ramadan* fasting also seems to be safe for patients with moderate to severe uncomplicated hypertension. Indeed, in a study including

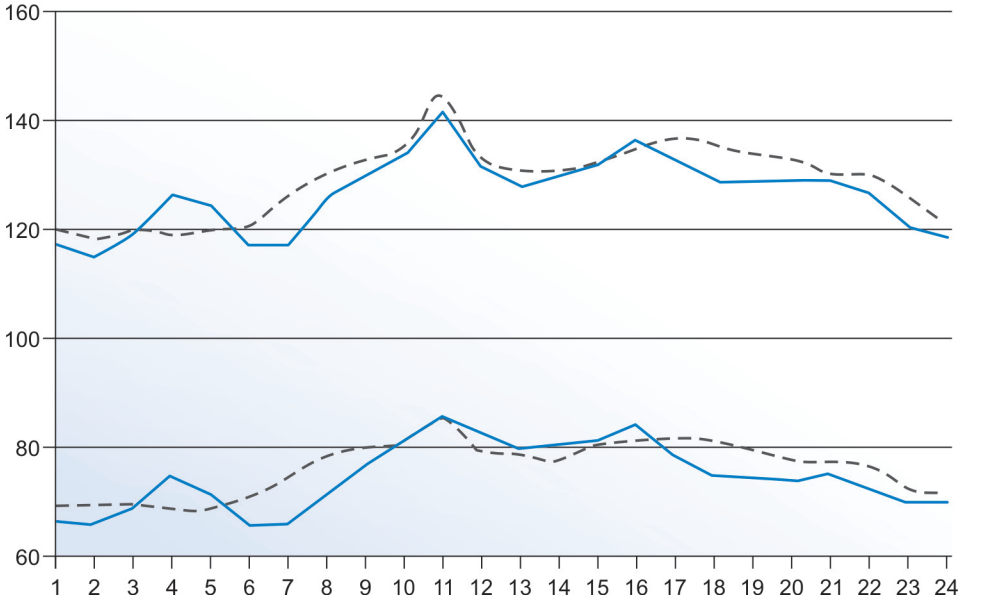

Figure 1: Twenty-four hours blood pressure monitoring in 45 patients with grade 2–3 hypertension. Measurements were taken in the month of *Ramadan* (solid lines) and in the following month (dotted line). Vertical axis: blood pressure as mm Hg, horizontal axis: time as hours. No statistically significant difference was found between 24-hour mean blood pressures in the two monitoring periods, except for a small rise before dawn while having a morning meal[6]

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45 treated patients with grade 2–3 hypertension, Ural et al. showed no significant changes in 24 hours, daytime and night time BP values of their patients, except for a small rise before dawn while having a morning meal.[6]

Management of Hypertension during Ramadan

Formal recommendations on the management of hypertension during *Ramadan* fasting have been made by two professional organizations in the Arabian Gulf region[8,9] **(Table 1)**.

- Pharmacological measures
- *Recommended antihypertensive drug classes*: Recommended antihypertensive drugs during *Ramadan* include beta blockers, calcium-channel blockers, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), vasodilators and centrally-acting antihypertensive drugs. Some are also available in patches lasting between 24–72 hours. Diuretics are better avoided, especially in hot climates or to be administered in the early evening.
- *Dosage adjustment*: Dehydration, blood volume depletion, and a tendency toward hypotension may occur during *Ramadan* fasting, especially if the fast is prolonged and is associated with excessive sweating. Hence, the dosage of antihypertensive agents may need to be adjusted to prevent hypotension.
- *Recommended schedule*: A once daily dosage schedule with long-acting preparations is recommended. In non-controlled hypertensive patients with one daily treatment basis, twice intake could be considered during *Ramadan*. In the study conducted by Ural et al. most of the patients in combination treatment group took their drugs in two separate times (before and at the break of fasting).

Table 1: Current recommendations on the management of hypertension during *Ramadan* fasting[8,9]

•	Physician's advice and management should be individualized
•	Patients should be encouraged to seek medical advice before fasting to adjust the doses of their medications
•	Patients should be advised and educated about the importance of strict compliance with nonpharmacological measures and antihypertensive therapy
•	A once daily schedule of a long-acting antihypertensive drug is recommended
•	Diuretics should be avoided, especially in hot climates
•	Where diuretic therapy is necessary, the drug should be reduced and administered after the evening meal
•	Salt intake and licorice drinks should be avoided
•	Patients with difficult to control hypertension should be advised not to fast until their blood pressure is reasonably controlled
•	Patients with hypertensive emergencies should be treated appropriately regardless of fasting

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Therefore, such regimen (drug intake twice: before fasting and after the breaking fast) seems to be a suitable alternative in patients with grade 2–3 hypertension using combination drug therapy.[6]

- Nonpharmacological measures.

Dietary salt restriction should be advised for patients with hypertension. Drinks in *Ramadan* have become part of the month's traditions. Licorice, a popular drink in many Arab countries during *Ramadan*, has been associated with an elevation in BP and or exacerbation of hypertension.[10] It inhibits the enzyme 11-ß-hydroxysteroid dehydrogenase enzyme type 2 with a resultant cortisol-induced mineralocorticoid effect and the tendency towards the elevation of sodium and reduction of potassium levels. Therefore, avoiding or at least reducing licorice consumption is recommended.[11]

Dyslipidemia and Ramadan Fasting

It is common practice that the intake of foods rich in carbohydrates and saturated fats is increased during *Ramadan*. Appropriate pre-*Ramadan* counseling should be given to avoid this practice. A practical approach for improving lipid profile and reducing cardiovascular risk would be a modified Mediterranean approach. This incorporates replacement of saturated and trans-fatty acids (FA) with mono and polyunsaturated fats, increasing ω-3 FA consumption and eating more plant sterols, viscous fiber, vegetables, low glycemic fruits, soy protein and nuts.[12] Lipid-lowering drugs that were previously prescribed should be continued during *Ramadan* month.[3]

Cardiovascular Diseases and Ramadan Fasting

Effects of Ramadan Fasting in Patients with Cardiovascular Diseases

Fasting during *Ramadan* may have negative repercussions on cardiac patients. Gumaa et al. in 1978 reported that fasting *Ramadan* increased the incidence of angina.[13] However, this finding has not been confirmed by more recent studies. Khafaji et al. in 2012 reported that fasting *Ramadan* in stable cardiac patients has no effect on their clinical status. He found that 71.4 percent had no change in their symptoms during fasting while 28.6 percent felt better.[14] In agreement with these results, Nematy et al. in 2012 found that there was significant improvement in 10 years coronary artery disease risk based on Framingham risk score.[15] Similarly, a recent systematic review of the literature showed that *Ramadan* fasting was not associated with any change in incidence of acute cardiac illness and that the majority of patients with stable cardiac illness were able to successfully undergo *Ramadan* fasting.[2] Furthermore, a recent population-based study showed that fasting has neutral overall effects on atrial fibrillation (AF) and suggested a favorable protective effect from ischemic AF.[16] Finally, only few studies assessed whether *Ramadan* fasting enhances the risk of hospitalization for congestive heart failure (CHF) in cardiac patients. In a retrospective analysis involving 2.160 cardiac patients, the number of hospitalizations for CHF was similar in the months before, during, and after *Ramadan*.[17]

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Management of Cardiovascular Diseases during Ramadan

- Pharmacological measures
- *Anti-ischemic drugs:* Anti-ischemic drugs include oral nitrates, calcium channel blockers, and β-Adrenoceptor antagonist. Both pharmacokinetics and pharmacodynamics of these medications have been shown to be influenced by the circadian time of their administration. For examples, plasma peak concentrations of nifedipine, oral nitrates and propranolol are twice as high and time to reach peak concentrations are shorter after morning dosing compared with evening dosing. Such a variation was not detected when extended release dosage forms of nifedipine and isosorbide mononitrate were used. The underlying mechanisms of their chronopharmacokinetic pattern may involve a faster gastric emptying time and higher gastrointestinal perfusion in the morning.[18]

  Shiga et al. documented that atenolol, in contrast to propranolol, is not absorbed more rapidly after morning administration compared with post-evening administration. This confirms that most lipophilic, but not hydrophilic, drugs seem to be absorbed faster in the morning as compared to evening.[19]
- *Antiarrhythmic drugs*: Amiodarone is the most widely prescribed antiarrhythmic medication. It may be administered once daily or given twice daily with meals to minimize stomach upset which is seen more frequently with higher doses. During *Ramadan*, amiodarone can be taken either at *Iftar* or at *Suhur*. There are a number of important drug interactions with amiodarone. For examples, amiodarone may interact with beta blockers or certain calcium-channel blockers, such as verapamil and diltiazem resulting in a very slow heart rate or a block in the heart's electrical conduction system. Amiodarone increases also the blood levels of digoxin when the two drugs are given together. Patients fasting *Ramadan* are at particularly high risk for the amiodarone drug interactions, as they tend to take their drugs simultaneously.
- *Heart failure drugs*: Cardiac glycosides (digoxin and digitoxin) have a narrow therapeutic range and changes in their pharmacokinetics and/or pharmacodynamics due to drug-interactions can result in toxicity (see above). There are no significant changes in the pharmacokinetics of digoxin when ingested in the morning versus evening. When digoxin tablets are taken after meals, the rate of absorption is slowed, but the total amount of digoxin absorbed is usually unchanged.[20] Consequently, during *Ramadan*, this drug can be taken either at *Suhur* or at *Iftar*. Heart failure patients should use diuretics after *Iftar* and those with severe CHF requiring high doses of diuretics should be counselled against fasting.
- *Anticoagulation drugs*: *Ramadan* fasting has been shown to have some hematological effects such as a reduction in the hematocrit and a decrease response of platelets to different aggregating agents [adenosine diphosphate (ADP), collagen and adrenaline]. These effects are associated with the prolongation of bleeding and coagulation times. However, in a study in patients with cardiovascular disease, fasting did not appear to influence the dose or the effect of warfarin anti-coagulation. Shifting from daytime to night-time administration of a long-acting anti-coagulant does not adversely affect the anticoagulant process

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and does not increase the incidence of thromboembolic events and hemorrhagic complications.[21]

- *Nonpharmacological measures*: Adequate dietary habits and weight loss should be advised for appropriately selected patients with cardio-metabolic diseases. Fluid restriction (1.500–2.000 mL) as well as the control of sodium intake (< 2 g) are relevant in patients with advanced heart failure. It should also be advised that salt substitutes must be used with caution, as they may contain potassium. In large quantities, in combination with an ACE-inhibitor, they may lead to hyperkalemia.[22,23]

Food may affect the bioavailability of some cardiovascular drugs and in some specific cases, such as dairy products and rich-inprotein diets, this should be carefully considered during *Ramadan* month. Grapefruit may enhance drug toxicity for antiarrhythmic agents such as amiodarone.[24] Therefore, patients taking oral amiodarone should avoid grapefruit juice. Regular exercise should be advocated in stable patients with CVD. The congregational night prayers of the month of *Ramadan* constitute appropriate level of physical activity equivalent to moderate physical activity.[25]

Cigarette smoking should be strongly discouraged in patients with CVD. *Ramadan* provides an excellent opportunity to give up smoking.

Kidney Disease and Ramadan Fasting

In healthy adults, urinary volume, osmolality, pH, nitrogen, solute and electrolyte excretion do not significantly change during *Ramadan* fasting. Changes in serum urea and creatinine are usually small and not statistically significant and there is only a slight increase in uric acid.[26,27]

Only a limited number of clinical studies have evaluated the effects of *Ramadan* fasting on patients with kidney disease, belonging to one of the following four clinical situations:

1. Chronic kidney diseases
2. Hemodialysis
3. Renal transplantation recipients
4. Renal stone disease.

Reduced medication compliance, fluid restriction during daylight hours, and a possible state of chronic hypohydration may lead to harmful consequences in CKD patients who fast *Ramadan*. In a small prospective study involving 15 predialysis CKD patients and six healthy volunteers as control, the urinary N-acetyl-β-D-glucosaminidase percentage change (reflecting renal tubular damage) was found to be significantly higher in the CKD patients compared to the control group. Interestingly, tubular injury correlated significantly with poor glycemic control in patients with CKD in this study. Therefore, fasting *Ramadan* may have injurious effect on the renal tubules in CKD patients with poor diabetic control.[28]

The rise in serum K^+ reported in some cases has been attributed to the traditional *Ramadan* meal, a rich source of K^+, consisting of large amounts of dates, apricot juice and coffee.[28] *Ramadan* fasting seems to be beneficial for diabetic patients with early stages of renal damage, characterized by increased levels of urine albumin excretion.

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Such beneficial effect may be explained by the favorable impact of *Ramadan* fasting on stress oxidative parameters.[29] However, these patients should be advised to reduce their protein intake, as high protein intake may promote renal damage by chronically increasing glomerular filtration rate.[30] Ramadan fasting may have unfavorable impact on patients with more advanced stage of kidney disease. A prospective observational study evaluated the effect of *Ramadan* fasting in 36 patients with moderate to severe renal insufficiency during and 2 weeks after the fasting event. There was a significant deterioration of renal function parameters which persisted for 2 weeks after the end of *Ramadan*. In nine patients, there was also a progressive fluid retention, weight gain, lower limb edema, and poor control of BP, requiring frequent adjustment of management. These findings suggest that, in patients with moderate to severe renal impairment, *Ramadan* fasting may be associated with further deterioration in renal function which may become irreversible and cause adverse serious health problems.[31]

Only one single study of 40 patients receiving hemodialysis treatment for more than 6 months examined the effect of fasting during *Ramadan*. Patients fasted on nondialysis days. An interdialytic weight gain and a significant rise in serum K^+ levels occurred, but with no change in BP. However, no hospitalization for pulmonary edema or for the adverse effects hyperkalemia was required. Based on these observations, the authors recommended that fasting on nondialysis days is probably safe and that dietary advice in fasting patients assumes increasing importance.[32] Further studies may be required to draw firm conclusions.

Ramadan fasting appears to be safe and not associated with adverse reactions in renal transplant recipients with stable normal or stable impaired renal allograft function.[33,34] Boobes et al. studied 22 kidney transplant patients with stable kidney functions, who were transplanted for more than one year, and voluntarily chose to fast during *Ramadan*. Body weight, BP, renal and metabolic parameters and cyclosporine levels remained stable after *Ramadan* fasting. The authors concluded that *Ramadan* fasting is safe for kidney transplant recipients of more than one year with stable graft function.[35] Based on these preliminary findings, there is general agreement from medical professionals that kidney transplant patients are allowed to fast in *Ramadan* when the transplanted kidney graft is functioning well for at least 1 year.[36]

There is no enough evidence in favor of increased risks of calculus formation during *Ramadan* fasting.[37] Previous studies demonstrated significant correlations between the occurrence of urinary renal colic and the hot seasons but not with *Ramadan*.[38,39] Thus, it is important to emphasize adequate hydration between sunset and sunrise for patients with previous history of renal calculus.

CONCLUSION

Diabetic patients with stable comorbidities may be allowed to fast in *Ramadan* under proper medical supervision. In such patients, medical advices regarding medications schedules, drug interactions and nonpharmacological measures should be provided. Sustained release formulations may be of particular interest during *Ramadan*. However, fasting may lead to severe alterations in patients with more serious cardiovascular and renal diseases. Further studies should be carried out to provide more guidelines about the management of diabetic patients with co-morbid conditions in *Ramadan*.

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