

RESEARCH

Management of adrenal insufficiency during Ramadan fasting: a survey of physicians

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Abstract

Introduction: Appropriate dose adjustments of glucocorticoids replacement therapy for adrenal insufficiency (AI) is vital.

Objective: We sought to scope physicians' perceptions, and practices regarding Ramadan fasting (RF) impact on the management of AI.

Methods: A web-based survey of a convenience sample of endocrinologists.

Results: Nearly two-thirds of 145 respondents (64.1%) were adult endocrinologists and almost half (49%) saw more than 10 hypoadrenal patients per year. Most respondents (78.6%) prescribed hydrocortisone, while the minority prescribed other preparations. The glucocorticoid doses were reportedly divided twice daily by 70.8% and thrice daily by 22.2% of respondents. Respondents recognized RF as having potential consequences in adrenal insufficiency patients included causing hypoglycaemia, undue tiredness, and fatigue, hypotension, feeling dizzy, and light-headedness. Symptoms of under-replacement were thought to happen in the late afternoon by 59.3% of respondents. Almost half (45.5%) of respondents thought that RF has some probable or definite impact on glucocorticoid therapy that certainly warrants specific concern and possible action. Three quarters (76.4%) of respondents confirmed providing specific management recommendations during RF. The most frequently reported recommendation was taking in the usual morning dose of hydrocortisone just before pre-dawn meal (*Suhoor*) (57.8%). A third switch patients from hydrocortisone to prednisolone/prednisone. Half reported providing patients with specific recommendations regarding breaking their fast and/or seeking help if hypoadrenal symptoms occur.

Conclusions: There is a remarkable variation in the physicians' perceptions and practices regarding the management of AI during Ramadan. This warrants professional effort to increase the awareness and dissemination of evidence-based guidelines.

Key Words

- ▶ management
- ▶ adrenal insufficiency
- ▶ Ramadan fasting
- ▶ survey
- ▶ physicians' perceptions

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Introduction

Fasting the holy month of Ramadan, one of the five pillars of Islam, is a religious obligation practiced by Muslims for centuries. The religious practice mandates abstinence from food, water, and all oral substances from dawn to sunset. To achieve good holistic management, harmony is needed between physicians and religious scholars (1).

Fasting entails protracted periods of fasting, often exceeding 12-h per day. Prolonged abstinence, particularly in hot climates, subjects many to dehydration, fatigue, dizziness, hypoglycaemia, and hypotension (2, 3). Given such, several at-risk groups (i.e. the elders, the pregnant, and the sick) have been exempted from fasting.

Despite the ease in restrictions, many with critical illnesses still chose to fast, subjecting themselves to unforeseen risks and challenges. Management of a number of chronic medical conditions in Ramadan has been addressed by Beshyah *et al.* (4). In endocrinology, the management of diabetes mellitus has attracted the most attention with the largest volume of literature (5). Nevertheless, significant deficiencies remain in guidance toward the management of other endocrinological disorders during Ramadan (6).

Adrenal insufficiency (AI) represents a major healthcare challenge for patients and physicians during the month of Ramadan. If inappropriately or inadequately managed, AI can lead to anorexia, fatigue, dizziness, nausea, vomiting, hypoglycaemia, hypotension, shock, and potentially death (7, 8). In the real world, significant barriers to diagnosis and management of adrenal insufficiency have been identified in developing regions of the world mostly on basis of resource limitation (9).

The dynamics of everyday life change significantly during Ramadan, impacting to a great extent the management of AI. Fasting involves abstinence from food, drinks and medications between dawn and sunset, constituting periods longer than the usual time frame between conventional doses. There is also a major change in the sleep/wake cycles when people may stay up till the late hours of the night, and occasionally wake up during the late hours of the afternoons or evenings. A degree of dehydration is also inevitable particularly in hot zones. Furthermore, from a professional view point, the challenge of AI management during Ramadan stems primarily from the lack of strong and uniform evidence on the topic. Without clear guidance from the field, many physicians are led astray while managing this vulnerable cohort. Also, without a clear scientific voice, religious guidance suffers; rendering patients who wish to fulfil their religious obligations vulnerable to complications (10, 11, 12, 13). A couple of review articles attempted to offer guidance on the management of AI during Ramadan. Mostly based on physiological principles and pharmacological knowledge and on extrapolation from other clinical situations (6, 14, 15).

The first and most crucial step in addressing such deficiencies starts with an up-to-date assessment of physicians' practices and perceptions of AI management during the month of Ramadan. This current cross-sectional assessment, aimed at assessing the latter, will highlight areas of deficiencies in the care of AI patients in Ramadan, thereby helping direct further education and research.

Materials and methods

Study design

This cross-sectional electronic questionnaire-based study was conducted between 10 February 2020 and 10 May 2020. For the creation, dissemination, and analysis of the questionnaire, Survey Monkey® (SVMK Inc., San Mateo, CA, USA) was used. The questionnaire was electronically sent to a convenience sample of healthcare professionals primarily residing and practicing in the Middle East and Africa and who are likely to be involved in the management of adrenal insufficiency. The practicing physicians and academics were identified on academic databases of health-related bodies, professional groups, and recent continuous professional development events (e.g. American Association of Clinical Endocrinologists Gulf Chapter annual meetings) and/or by virtue of their contribution to the medical literature. The initial invitation email explained the rationale of the study with link to the survey as was previously described (9, 16, 17) Biweekly reminders were sent for non-responders and partial responders. Repeat submissions from the same internet protocol address were automatically blocked by the survey service.

Survey questionnaire

The questions were developed de novo based on a review of the literature. The survey included questions pertaining to diagnostic evaluation and choice of therapy. Most questions required a single best response to being selected from multiple choices. A broad range of choices was given, arranged alphabetically, numerically, or in random order. A few questions were included to define the demographic and professional profiles of respondents (Table 1).

Data management and analysis

Survey responses were anonymously collected and stored electronically by the survey service, accessible in a password-protected manner. Responses from those who met the inclusion criteria only were included (adult and pediatric endocrinologists, general internal medicine specialists with interest, and practice in endocrinology). A total of 186 respondents consented to participate, with 145 providing adequate responses for inclusion in the analysis and formed the basis of this study. No data were captured on non-consenting

Table 1 The survey questionnaire's domains, questions, and potential responses.^a

- A. Demographic and professional profiles:
1. Age (<30 years; 31–50 years; 51–70 years; >70 years).
 2. Sex (male, female).
 3. Specialty (adult endocrinologist, internal physician with endocrine interest, physician in general internal medicine, pediatric endocrinologist, general pediatrician; primary care; other).
 4. Please indicate your current grade (Senior, Mid-grade, Junior).
 5. Type of practice (Academic, Public health services, Private sector).
 6. Region residence (Sub-Saharan Africa, North Africa, Arabian Gulf, Rest of the Middle East, Southeast Asia, Rest of the world) and specify the country
- B. Ramadan-adrenal questionnaire:
1. How many patients with adrenal insufficiency do you treat in a year? (0, 1–10, 11–25, 26–50, >50).
 2. What proportion of these patients are likely to observe the fasting of Ramadan 2020 (None, 25%; 50%; 75%; All).
 3. Which glucocorticoid preparation do you, most commonly, use for replacement therapy? (Hydrocortisone, Cortisone acetate, Prednisone/Prednisolone, Long-acting prednisolone, Dexamethasone).
 4. How do you usually divide the daily dose of glucocorticoids used for replacement therapy? (Once daily (full dose), Twice daily, Three times daily, Four times daily).
 5. How do you perceive the impact of Ramadan fasting (RF) on adrenal insufficiency and its management (There is no concern on glucocorticoid replacement therapy during Ramadan fasting whatsoever, Ramadan may have a possible impact on glucocorticoid replacement therapy during fasting but it does not warrant specific concern; Ramadan has some probable or definite impact on glucocorticoid replacement therapy during fasting that certainly warrants; specific concern and possible action, not sure. 'It has never happened to me to consider this question before').
 6. Features that may suggest an impact of Ramadan fasting on adrenal insufficiency and its management include: nausea and vomiting, undue tiredness and fatigue, hypoglycaemia, feeling dizzy and lightheaded, hypotension, Weight loss.
 7. If any, at what time of the day symptoms of glucocorticoid under-replacement are likely to happen? (Early morning, Mid-Day, Late afternoon, Early evening, Late evening).
 8. How I manage adrenal insufficiency and its management during Ramadan. (A. I DO provide specific recommendations. (Go to the next question); B. I DO NOT provide specific recommendations (end of the survey)).
 9. Only if you have chosen A in the previous question, please tell us how do you adjust the dose of glucocorticoids used for replacement therapy during Ramadan (choose all that may apply): (I use hydrocortisone and delay the morning dose to latest possible time before *Suhoor* and take the evening dose as usual with the first evening meal, Change all my patients on hydrocortisone and cortisone acetate to prednisolone/prednisone, I warn my patients to break the fast and take their usual dose if they feel symptoms of under replacement, I warn my patients to break the fast and seek emergency help if they experience symptoms of the impending adrenal crisis.)

^aThe initial question confirms consent with the choices; Yes, No, Never. Logic is built in to allow only consenting respondents to proceed to take the survey.

respondents nor those who did not provide reasonably complete answers. The survey management service tools were used for the examination of results and descriptive analysis. Summary statistics were prepared for responses to each question. Because not every participant answered all questions, the percentage of respondents providing a given answer was calculated individually for each question, using the number of respondents to that question as to the denominator.

Results

Profiles of respondents

The demographic and professional characteristics of the 145 respondents are detailed in [Table 2](#). The majority of respondents were from the Arabian Gulf (51.7%), followed by the Middle East (15.2%) and North Africa (14.5%). There was a slight male preponderance (53.9%). The majority (55.9%, 39.3%) were in the age groups 31–50 years and 51–70 years, respectively. Nearly two-thirds of respondents (64.1%) were adult endocrinologists and almost one-fifth (18.6%) were pediatric endocrinologists ([Table 2](#)). Senior physicians (i.e. consultants/attending physicians) represented 81.2% of respondents. Almost equal numbers of respondents reported practicing in academic centres and public health services, while one-fifth was in the independent sector ([Table 2](#)). Just over half of respondents (51.0%) reported seeing 1–10 hypoadrenal patients per year, while 22.1% see 11–25 patients per year ([Table 3](#)). Most respondents (78.6%) prescribed hydrocortisone, while the minority prescribed other preparations for replacement therapy ([Table 3](#)). The glucocorticoid doses were reportedly divided twice daily by 70.8% and thrice daily by 22.2% of respondents ([Table 3](#)).

Impact of Ramadan on adrenal replacement therapy

Of respondents, 29.4, 13.3, and 16.8% thought 25, 50, and 75% of their hypoadrenal patients are likely to observe the fasting of Ramadan, respectively ([Table 3](#)). Features recognized as potential consequences of Ramadan fasting in adrenal insufficiency patients included (in decreasing order): hypoglycaemia, undue tiredness, and fatigue, hypotension, feeling dizzy, and light-headedness ([Table 3](#)). Symptoms of glucocorticoid under-replacement were likely to happen in the late afternoon as reported by 59.3% of respondents.

Table 2 The demographic and professional profiles.^a

Variables (respondent number) ^b	Details	Results ^c
Age (years) (145)	31–50	81 (56.3%)
	51–70	57 (39.1%)
	>70	4 (2.8%)
	<30	3 (2.1%)
Sex (145)	Male	78 (53.9%)
	Female	67 (46.2%)
Specialty (145)	Adult endocrinologist	93 (64.1%)
	Pediatric endocrinologist	27 (18.6%)
	Internist with endocrine interest	17 (11.7%)
	General internist	6 (4.14%)
	General pediatrician	2 (1.4%)
Professional grade (145)	Senior	118 (81.4%)
	Mid-grade	27 (18.5%)
Type of medical practice (144)	Academic/university	57 (39.6%)
	Public health services	55 (38.2%)
	Private sector	32 (22.2%)
Region of residence and practice (145)	Arabian Gulf	75 (51.7%)
	Rest of the Middle East	22 (15.2%)
	North Africa	21 (14.5%)
	South East Asia	7 (4.8%)
	North America	7 (4.8%)
	Sub-Saharan Africa	6 (4.1%)
	Europe	4 (2.8%)

^aData on maximal of 145 eligible respondents out of a total of 186 responses received. ^bNumbers of responses to individual questions are indicated in parenthesis. ^cResults are shown as number (%).

Adrenal replacement therapy during Ramadan

Respondents' perceptions of the impact of Ramadan fasting on AI and their practices in management are detailed in Table 4. Almost half (45.5%) of respondents thought that Ramadan has some probable or definite impact on glucocorticoid replacement therapy during fasting that certainly warrants specific concern and possible action. About 37.1% reported Ramadan may have a possible impact on glucocorticoid replacement therapy during fasting but does not warrant specific concern. Three quarters (76.4%) of respondents confirmed they provide specific recommendations regarding adrenal insufficiency management during Ramadan fasting (Table 4). The most frequently reported recommendation was taking the usual morning dose of hydrocortisone at the latest possible time with the pre-dawn meal or *Suhoor* (57.8%). Over a quarter (28.5%) recommend switching patients from hydrocortisone to prednisolone or prednisone. Other management strategies, dose adjustments, and/or warnings reportedly adopted by physicians are detailed in Table 4. Only half reported providing patients with specific recommendations regarding breaking their fast and/or seeking help when hypoadrenal symptoms occur.

Discussion

AI is a relatively rare endocrine disorder, resulting from functional and/or structural defects at the level of the adrenals (primary AI or Addison's disease), pituitary (secondary AI), or hypothalamus (tertiary AI). While primary AI is primarily treated with glucocorticoid and mineralocorticoid replacement therapies, secondary and tertiary AI are managed with glucocorticoid replacement alone (8).

Oral hydrocortisone has been the preferred glucocorticoid replacement therapy in AI (7). Its relatively short half-life allows for frequent daily dosing, roughly mimicking the normal diurnal rhythm of cortisol (8, 11). According to the latest 2016 Endocrine Society guidelines, oral hydrocortisone is recommended to be administered in twice or thrice daily regimens, with the largest dose administered upon awakening, followed by a second dose in the early afternoon, and an optional smaller dose in the late afternoon (for three-dose regimen) (8).

A major challenge present in the management of AI during Ramadan has been the timing of hydrocortisone administration. With an estimated half-life of 1.5 h, the concentrations of oral hydrocortisone are significantly diminished 4–6 h after its administration (12).

Table 3 Respondents perceptions of the Impact of Ramadan fasting on adrenal insufficiency and its management.^a

Questions ^b	Response options	Results ^c
1. How many patients with adrenal insufficiency do you treat in a year? (145)	1–10	74 (51.0%)
	11–25	32 (22.1%)
	26–50	18 (12.4%)
	More than 50	14 (9.7%)
	None	7 (4.8%)
2. What proportion of patients are likely to observe the Ramadan fasting (in 2020)? (143)	25%	42 (29.4%)
	None	32 (22.4%)
	All of them	26 (18.2%)
	75%	24 (16.8%)
	50%	19 (13.3%)
3. Which glucocorticoid preparation do you, most commonly, use for replacement therapy? (145)	Hydrocortisone	114 (78.6%)
	Prednisone/prednisolone	27 (18.6%)
	Cortisone acetate	2 (1.4%)
	Long-acting prednisolone	2 (1.4%)
	Dexamethasone	0 (0.0%)
4. How do you <i>usually</i> divide the daily dose of glucocorticoids for replacement therapy? (144)	Twice daily	102 (70.8%)
	Three times daily	32 (22.2%)
	Once-daily (full dose)	10 (6.9%)
	Four times daily	0 (0.0%)
5. Features that may suggest an impact of Ramadan fasting on adrenal insufficiency and its management include: (142)	Hypoglycemia	113 (79.9%)
	Undue tiredness and fatigue	112 (78.9%)
	Hypotension	97 (68.3%)
	Feeling dizzy and lightheaded	93 (65.5%)
	Nausea and vomiting	80 (56.3%)
	Weight loss	39 (27.5%)
	Late afternoon	83 (59.3%)
6. Time of the day when symptoms of glucocorticoid under-replacement are likely to happen: (140)	Mid day	19 (13.6%)
	Early evening	15 (10.7%)
	Early morning	14 (10.0%)
	Late evening	9 (6.4%)

^aData on maximal of 145 eligible respondents out of a total of 186 responses received. ^bNumbers of responses to individual questions are indicated in parenthesis. ^cResults are shown as number (%).

Oral hydrocortisone taken at pre-dawn would leave AI patients with sub-normal cortisol levels for numerous hours from early afternoon to sunset, thereby increasing their risk for adrenal crisis.

In our analysis of 145 respondents, the majority were senior physicians from tertiary hospitals. To the best of our knowledge, most patients with AI are primarily cared for by endocrinologists and physicians with special interest in endocrinology. Many respondents (45.5%) correctly reported Ramadan fasting has an impact on the management of AI which warrants concerns and possible actions. However, the remainder of the respondent pool either reported possible impact but would not warrant concerns, no impact at all, or were not sure. The latter findings raise concerns regarding current knowledge of AI management in Ramadan, and thereby warrant a critical need for establishing uniform guidelines on the subject.

Current recommendations on adrenal replacement therapy in Ramadan are sparse and widely different. Some experts recommend taking higher doses of hydrocortisone at pre-dawn (3). Others recommend

patients be switched to longer-acting formulations of glucocorticoids, such as prednisone/prednisolone, shortly before and during Ramadan, and to be taken at pre-dawn (6, 14, 15). A few have suggested the addition of a small dose of hydrocortisone at sunset, complementing the earlier prednisone/prednisolone dose (6). In our analysis, more than half of our respondents recommended hydrocortisone to be used in Ramadan, but with an increase and delay in morning dose to the latest possible time before *Suhoor*. A third recommend switching patients to a longer-acting formulation such as prednisolone/prednisone. Although the switch to a longer-acting formulation is physiologically sound, a recent randomized double-blinded crossover clinical trial of subjects with AI showed no difference in rates of complications, mean blood glucose levels or health-related quality of life (HRQoL) between those receiving hydrocortisone or prednisolone replacement therapy during the month of Ramadan (18).

The introduction of newer formulations of modified- and dual-release hydrocortisone (Chronocort® and

Table 4 Reported physicians' attitudes and practices regarding the management of adrenal insufficiency during Ramadan fasting.

Theme/question and response options ^a	Results ^b
I. How do you perceive the impact of Ramadan fasting (RF) on adrenal insufficiency and its management? (<i>n</i> = 143)	
A. Ramadan has some probable or definite impact on glucocorticoid replacement therapy during fasting that certainly warrants specific concern and possible action.	65 (45.5%)
B. Ramadan may have a possible impact on glucocorticoid replacement therapy during fasting but it does not warrant specific concern.	53 (37.1%)
C. Not sure. It has never happened to me to consider this question before.	17 (11.9%)
D. There is no concern on glucocorticoid replacement therapy during Ramadan fasting whatsoever.	8 (5.6%)
II. How do you approach the management of adrenal insufficiency during Ramadan? (<i>n</i> = 140)	
A. I do provide specific recommendations:	107 (76.4%)
B. I do not provide specific recommendations:	33 (23.6%)
III. How do you adjust the dose of glucocorticoids used for replacement therapy during Ramadan? (<i>n</i> = 116). (More than one option is possible.)	
A. I use hydrocortisone and delay the morning dose to the latest possible time before <i>Suhoor</i> and take the evening dose with the evening meal.	67 (57.8%)
B. Change all my patients who are on hydrocortisone and cortisone acetate to prednisolone/prednisone.	33 (28.5%)
C. I warn my patients to break the fast and take their usual dose if they feel symptoms of under replacement.	57 (49.1%)
D. I warn my patients to break the fast and seek emergency help if they experience symptoms of an impending adrenal crisis.	61 (52.6%)

^aNumber of responses are shown per question. ^bResults are presented as number (%).

Plenadren®) may allow for safer fasting practices (19, 20). Chronocort®, a modified-release formulation of hydrocortisone, administered twice daily at predawn and at sunset, has been shown to resemble the physiologic cortisol rhythm (20). Plenadren®, a once-daily dual-release formulation, with an extended-release core coated by an immediate-release formulation, can be administered once daily at predawn and may aid with patient compliance (21). Additionally, the use of continuous s.c. hydrocortisone infusions (CSHI) has safely brought ACTH and cortisol toward normal circadian levels without adversely affecting glucocorticoid metabolism in the way that OHC did. Positive effects on HRQoL were noted with CSHI, indicating that physiological glucocorticoid replacement therapy may be beneficial and that CSHI might become a treatment option for patients poorly controlled on conventional therapy (22). However, their cumbersome and expensive nature renders them unfavorable, particularly in Muslim-majority populations. Furthermore, a recent study compared metabolic effects of Modified-Release Hydrocortisone MR-HC with Standard Glucocorticoid (SG) replacement in adults with AI. Randomised control trials (RCTs) were meta-analysed; non-RCT studies described narratively with critical appraisal. Nine studies were included for review (RCT, *n* = 2; non-RCT, *n* = 7). The authors suggested that in adults with AI, replacement with MR-HC associates with significant improvements in anthropometric measurements and HbA1c compared with SG replacement, particularly those with DM (23).

It is important to acknowledge that the duration of fast varies across the globe and by season. Admittedly, the questionnaires did not address this. It is noteworthy that fasting hours differ considerably, with some countries fasting for as long as 21 h, while some fast <11 h a day. These variations may reflect prescribing habits analogous to those established in the management of diabetes during Ramadan. (24). The health implications of a very long periods of fasting for AI patients includes increased risk of dehydration and hypotension due to under replacement during the fasting period. Whereas, in areas and at times of short fasting duration, no changes management may be required.

The management of AI during Ramadan should not only be limited to adjustment and/or titration of medications. Patient education is also a vital aspect of the prevention of complications associated with fasting. AI patients should be instructed to hydrate well during non-fasting periods, maintain normal salt intake, and avoid strenuous activities during fasting. The pre-dawn meal, or *Suhoor*, should be rich in complex carbohydrates, healthy proteins, and fats, and should be delayed to right before fasting starts (25). Additionally, all patients should be instructed to carry a steroid emergency card and a medical alert bracelet at all times. They should be reminded of the sick day rules (double or triple the dose of glucocorticoids in the event of fever or illness requiring bed rest). AI patients should always be supplied with i.m. glucocorticoid preparations for self-injection in the event of severe illness, trauma, or persistent vomiting, and

advised to go to the hospital after the emergency injection (25). In our study, only half reported providing patients with specific recommendations regarding breaking their fast and/or seeking help when hypoadrenal symptoms occur, the latter of which may subject AI patients to unforeseen risks and preventable dangers.

Conclusions

Hitherto, the management of AI during the fasting month of Ramadan was mostly based on translating physiological principles and pharmacological knowledge with extrapolation of experiences from other clinical situations. We provided the first assessment of physicians' practices and perceptions of AI management during the month of Ramadan. We found a remarkable degree of variation in the physicians' perceptions and practices. This warrants professional effort to increase awareness, develop evidence-based guidelines, and disseminate them widely. There are several good recommendations that can be followed up. All AI patients need to (1) be assessed in the index endocrine consultation on their intentions to observe the fast and (if any) past glucocorticoid replacement experience during the previous Ramadan. (2) adjust the doses and formulations to cover their fasting periods and (3) educated to observe the 'sick day rules' and seek with specific instructions relating to interruption of fasting and seeking of emergency care.

Disclaimer

The views expressed in this manuscript are those of the respondents and authors and do not reflect any official policy of their employers or affiliates.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Compliance with ethical principles

The study was approved by the Institutional Review Board at Sheikh Khalifa Medical City, Abu Dhabi, UAE. All participants provided informed written consent before he can proceed to the survey questions. Data were downloaded and analysed anonymously.

Author contribution statement

S A B adopted the online version of the survey, managed the electronic survey and data extraction. S A B and K F A drafted the manuscript.

All authors revised the manuscript critically for intellectual content and approved its final version.

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