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Variations in cortisol response in patients with known and suspected adrenal insufficiency

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Abstract

Adrenal insufficiency (AI) is a relatively rare disease. While the adrenocorticotropic hormone (ACTH) stimulation test remains as one of the commonly used diagnostic test for AI, to date there is no consensus on the cortisol cutoff value post-ACTH stimulation test. This study aimed to investigate and characterize the cortisol response after the standard ACTH stimulation test in a group of Saudi Arabian patients. A single center retrospective study was conducted on Saudi Arabian adult patients who underwent ACTH stimulation test at the endocrinology clinics of King Abdulaziz Medical City in Riyadh, Saudi Arabia between 2015 and 2018. Demographic, clinical and biochemical variables were collected and analyzed. A total of 154 medical records of patients (44 males, 110 females, mean age 44.4 ± 17.0 years) were included in the study. All patients underwent ACTH stimulation test. Fatigue was the most common symptom of participants. Type 1 diabetes was the most frequent comorbidity. Cortisol levels were significantly lower in patients who received corticosteroid replacement therapy, and, within the context of ACTH stimulation tests, were useful in diagnosing AI in patients with vague symptoms and signs. For basal cortisol, the cutoff of ≤258.5 has a sensitivity and specificity of 69.2% and 58.6%, respectively. For 30-minute, the cutoff of ≤386 sensitivity and specificity are 61.5% and 69.0%. For 60-minute, the cutoff of ≤491.5 has a sensitivity and specificity of 61.5% and 65.5%, respectively. Higher cortisol cutoff values have better sensitivity. Patients with AI present with mostly nonspecific symptoms, with type 1 diabetes as the most common comorbidity. The cortisol level cutoffs obtained from Arab patients who underwent ACTH stimulation tests showed wide variability for its utility in AI diagnosis. Further studies to evaluate the optimal cortisol cutoff values for AI diagnosis in this population are needed.

Abbreviations: ACTH = adrenocorticotropic hormone, AI = adrenal insufficiency, AUC = area under the curve, SA = Saudi Arabia.

Keywords: ACTH stimulation test, adrenal, cortisol, hypoadrenalism

1. Introduction

Adrenal insufficiency (AI) is a relatively rare endocrine disease characterized by a decrease in the production of adrenal hormones, primarily cortisol and aldosterone.[1] These 2 hormones have many crucial functions in the body including blood pressure regulation, electrolyte balance, metabolism and other physiologic processes. The hypothalamus–pituitary–adrenal axis is what controls the release of cortisol. The hypothalamus releases corticotrophin releasing hormone to activate anterior pituitary gland which releases adrenocorticotropic hormone (ACTH), ultimately activating the release of cortisol from the adrenal gland.[2] Thus, AI can be a primary failure of the adrenal gland to produce hormones or secondary failure of ACTH release. AI is a life-threatening disease that affects patients of all ages and both sexes. Symptoms of AI may include fatigue, weight loss, hypotension, anorexia and depression. Darkening of the skin (hyperpigmentation) due to high ACTH level occurs in patients with primary AI. These symptoms are nonspecific and usually develop very slowly which makes diagnosis difficult in early stages.[3] In a cross-sectional study of 216 patients with AI, <30% of females and 50% of males were diagnosed within the first 6 months after the onset of the symptoms.[4] The current estimated incidence of AI is 6 cases per-million population every year in European countries.[5]

A waiver of written consent was granted by the Institutional Review Board since data were only collected from medical records of patients.

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The datasets generated during and/or analyzed during the current study are not publicly available due to the data sharing policies set by the institution, but are available from the corresponding author on reasonable request.

Ethical approval was obtained from the Institutional Review Board at King Abdullah International Medical Research Center vide Letter No. RC18/370/R dated 07/01/2019.

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The ACTH stimulation test is considered as one of the most useful and widely used tests in diagnosing AI.[6] The test involves assessing the patients' baseline cortisol level, followed by administration of ACTH. The patient's cortisol response to ACTH is then measured after 30 and 60 minutes.[3] A high dose (250μg) ACTH stimulation test is the test of choice to diagnose primary AI with high sensitivity.[6] In secondary AI, both high (250μg) and low dose (1μg) ACTH stimulation tests are comparable in terms of diagnostic power, especially if the secondary AI is of subacute or chronic duration where the adrenal glands already atrophied. The Endocrine Society guidelines recommend using either tests to evaluate central AI, taking into consideration their limitations.[6,7] Unfortunately, there is no consensus on the cortisol cutoff point after ACTH stimulation. Different studies used different cortisol cutoff points ranging from 440 nmol/L up to 550 nmol/L resulting in modest outcomes.[6,8] In one meta-analysis, ACTH stimulation test was found to have significant variations between the cutoff point used and the time for the cortisol levels to peak after ACTH injection.[6] This may indicate that different populations have different normal responses to ACTH stimulation test which makes the use of a universal cortisol cutoff not practical. In fact, cortisol diurnal variations were found to be flatter in African-American and Latino patients than their White counterparts. Moreover, differences in stress exposure and lifestyle factors may affect the cortisol secretion.[9–11]

To date, there is scarcity of information about AI in the Middle East, Saudi Arabia (SA) in particular. In a single-center study conducted at the capital, Riyadh, SA, only a total of 125 patients with primary AI were recorded from 1989 till 2014.[12] To the best of our knowledge, there is a lack of studies on cortisol response to ACTH stimulation and what is considered to be normal in the Saudi population. The present study attempts to fill this gap and aims to find the optimum cortisol cutoffs of accumulated ACTH stimulation tests in Arab patients with suspected AI and determine whether such cutoffs have diagnostic value for use in the population.

2. Materials and methods

2.1. Study design and participants

This is a single-center retrospective study conducted at King Abdulaziz Medical City in Riyadh, SA. Medical records of all adult patients ≥18 who underwent standard ACTH stimulation test between January 2015 and October 2018 at the Adult Endocrinology outpatient clinics were conveniently recruited for the study. Patients with poor medical documentation in their medical files were excluded. The patient was categorized as AI if they are on corticosteroid replacement therapy at the time of the ACTH stimulation test and afterwards. Patients who were not on corticosteroid therapy at the time of the ACTH stimulation test were labeled as suspected AI. Multiple variables were collected including demographic data, ACTH stimulation test results, presenting clinical features, laboratory tests and management of the patients. The ACTH stimulation test protocol involved measurement of basal morning cortisol followed by intravenous injection of 250 μg of cosyntropin then cortisol measurement at 30 minutes and 60 minutes. All biochemical assessments were done at the central laboratory of King Abdulaziz Medical City in Riyadh. In all the patients included in the study, serum cortisol levels were measured using chemiluminescence microparticle immunoassays with a limit of detection of ≤22.07 nmol/L (Architect System, Abbott Laboratories, IL).

2.2. Sample size calculation and data analysis

Sample size calculation was done based on obtained ACTH stimulation test sensitivity of 100% and specificity of 65% with a prevalence of suspected AI at 49.0% as reported by Mongioì et al.[13] The minimum sample size required was N = 77. Data was analyzed using SPSS version 21.0 (Armonk, NY IBM Corp). Mean and standard deviations were used to present continuous variables whereas numbers and percentages (%) were used to present categorical variables. *P* values were obtained using independent sample *t* test and chi-square test for continuous and categorical variables respectively. Bivariate associations were used to determine associations between variables of interest. The receiver operating characteristic curves were used to examine the discriminatory power of ACTH stimulation test using known or partial AI as gold standard. A *P* value <.05 was considered significant.

3. Results

3.1. Baseline characteristics

A total of 154 patient records were included in the present study. Table 1 shows the differences in baseline characteristics of those who underwent steroid management (N = 64, 24 males; 40 females) and those who did not (N = 90, 20 males; 70 females). No significant differences were observed in age and body mass index, as well as medical history and comorbidities, with the exception of the prevalence of pituitary adenoma which was significantly more common among those who underwent steroid management than the non-steroid group (18.8% vs 3.3%; *P* = .001). Elevated ACTH levels consistent with primary AI was noted in 4 patients, 3 of whom received corticosteroid replacement. Furthermore, 14 patients had low ACTH levels consistent with central AI, 10 of whom received corticosteroid replacement. Among patients whose ACTH levels were within the reference range (N = 133), 50 received corticosteroid replacement, 8 were diagnosed as primary AI and the rest as central AI (Table 1).

Similarly, patients who underwent sellar surgery received corticosteroid replacement therapy more frequently (17 out of 21, 80.1%) than those who did not (26 out of 72, 36.1%; *P* < .001). Furthermore, patients with known AI were overwhelmingly found in the steroid-managed group with a ratio of 3:1 (*P* = .007). Circulating cortisol was significantly higher in the non-steroid managed patients in all time points than the steroid-managed group (*P* values <.001). Lastly, no differences in electrolytes were observed in both groups (Table 1). Fatigue was the most common symptom (13.5%), followed by hypoglycemia and dizziness, both at 10%, and headache at 7%. Worthy to note is that 11% of patients were asymptomatic. The rest of the symptoms noted are shown in Figure 1.

3.2. Cortisol levels following ACTH stimulation test

Table 2 shows the increasing mean cortisol levels over time of all participants, following ACTH stimulation test. When stratified according to AI status, between-group analysis revealed no significant difference at baseline, 30 and 60 minutes in participants with known AI versus suspected AI. However, when stratified according to steroid use, significantly higher levels across all time points were observed among those who did not take steroids as compared to the steroid-managed group (*P* values <.001).

3.3. Differences in cortisol changes according to AI status

In Table 3, differences according to mean percent change in cortisol was shown and revealed significant changes within time points in all groups. However, no significant changes were observed when compared between groups. Unadjusted differences in cortisol levels according to different comorbidities are shown in Table S1, Supplemental Digital Content, http://links.lww.com/MD/I262 and correlations with select cardiometabolic parameters and electrolytes in different time points are shown in

Table 1

Baseline characteristics of participants according to steroid management.

Parameters	All participants	Steroid management		*P* value
		Yes	No	
N	154	64	90	
Anthropometrics and patient history				
Age (yr)	44.4 ± 17.0	47.2 ± 16.1	43.4 ± 17.6	.186
BMI (kg/m^2)	29.8 ± 6.7	29.6 ± 5.7	29.9 ± 7.3	.799
Male/Female	44/110	24/40	20/70	.429
Smoke	4 (2.8)	1 (1.7)	3 (3.7)	.488
Family history of endocrinopathy	2 (1.3)	–	2 (2.2)	.271
Specific diet	7 (4.5)	–	7 (7.8)	.086
Comorbidities				
HTN	23 (14.9)	12 (18.8)	11 (12.2)	.263
Hypothyroidism	15 (9.7)	5 (7.8)	10 (11.1)	.496
Polycystic ovarian syndrome	4 (2.6)	–	4 (4.4)	.149
Pituitary adenoma	15 (9.7)	12 (18.8)	3 (3.3)	.001
T2DM	6 (3.9)	3 (4.7)	3 (3.3)	.669
T1DM	28 (18.2)	11 (17.2)	17 (18.9)	.787
Clinical presentation				
Known AI	13 (8.4)	10 (15.6)	3* (3.3)	.007
Suspected AI	141 (91.6)	54 (84.4)	87 (96.7)	
Biochemical parameters				
Sodium (Na)	137.0 ± 4.1	136.2 ± 5.5	137.3 ± 3.2	.359
Potassium (K)	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	.661
Bicarbonate (HCO3)	23.9 ± 2.8	23.3 ± 3.4	24.3 ± 2.5	.219
Basal cortisol (nmol/L)	217.8 ± 16.1	137.8 ± 114.9	267.3 ± 136.9	<.001
30-min cortisol (nmol/L)	372.7 ± 21.3	257.8 ± 174.1	484.4 ± 126.0	<.001
60-min cortisol (nmol/L)	437.2 ± 23.5	304.4 ± 195.8	564.1 ± 127.9	<.001
ACTH classification				
<4.7 pg/mL (below normal)	14 (9.3)	10** (15.9)	4 (4.5)	.02
Between 4.7 and 48.8 pg/mL (normal)	133 (88.1)	50† (79.4)	83 (94.3)	
>48.8 pg/mL (above normal)	4 (2.6)	3‡ (4.8)	1 (1.1)	
Sellar surgery				
Yes	21 (22.6)	17 (39.5)	4 (8.0)	<.001
No	72 (77.4)	26 (60.5)	46 (92.0)	
Sellar irradiation				
Yes	7 (7.4)	4 (8.9)	3 (6.0)	.590
No	88 (92.6)	41 (91.1)	47 (94.0)	

Data presented as mean ± standard deviation for continuous variables and N (%) for categorical variables.

ACTH = adrenocorticotropic hormone, AI = adrenal insufficiency, BMI = body mass index, HTN =, T1DM = type 1 diabetes mellitus.

* Received steroid during stress only.

** Central AI.

† Eight patients with primary AI and 41 with central AI.

‡ Primary AI.

Table S2, Supplemental Digital Content, http://links.lww.com/MD/I263.

3.4. Sensitivity and specificity of ACTH stimulation test

Table 4 shows the discriminating power of ACTH stimulation test. Using known AI as gold standard, the area under the curves (AUCs) for the group of patients with suspected AI due to comorbidities and or low random cortisol levels were 0.57 ± 0.08 (*P* = .42), 0.63 ± 0.08 (*P* = .14) and 0.62 ± 0.17 (*P* = .17) for basal, 30-minute and 60-minute cortisol levels respectively. The AUCs for the group showing other signs and symptoms were 0.73 ± 0.08 (*P* = .02), 0.69 ± 0.09 (*P* = .06) and 0.70 ± 0.09 (*P* = .04) for basal, 30-minute and 60-minute cortisol levels respectively. AUC coordinates for the group showing other signs and symptoms are presented as Table S3, Supplemental Digital Content, http://links.lww.com/MD/I264. For basal cortisol, the cutoff of ≤258.5 has a sensitivity and specificity of 69.2% and 58.6%, respectively. For 30-minute, the cutoff of ≤386 sensitivity and specificity are 61.5% and 69.0%. For 60-minute, the cutoff of ≤491.5 has a sensitivity and specificity of 61.5% and 65.5%, respectively. Higher cortisol cutoff values have better sensitivity, for example the cutoff of ≤325.5 for basal cortisol, ≤515.5 for the 30 minutes and ≤595 for the 60 minutes have a sensitivity of 92%. Furthermore, AUCs were also obtained after combining suspected AI due to comorbidities and/or low random cortisol level plus other signs and symptoms. The AUCs were 0.60 ± 0.08 (*P* = .22), 0.64 ± 0.10 (*P* = .10) and 0.63 ± 0.08 (*P* = .11) for basal, 30-minute and 60-minute cortisol levels, respectively (Table 4). Figure 2 shows the curves of basal, 30-minute and 60-minute cortisol levels. Around 51 patients had basal cortisol of ≤83 nmol/L and ≥415 nmol/L. Analysis on the reaming 103 patients showed similar findings to the analysis of the whole study sample in term of diagnostic ability measures of ACTH stimulation test (Tables, S4, S5 and S6, Supplemental Digital Content, http://links.lww.com/MD/I265).

4. Discussion

The present study explored the diagnostic value of ACTH stimulation test in a group of Saudi patients with known and suspected AI. While the cortisol levels at all-time points were lower in patients with known AI than suspected AI, the differences were not statistically significant. Nonetheless, patients with prescribed corticosteroid replacement had significantly lower

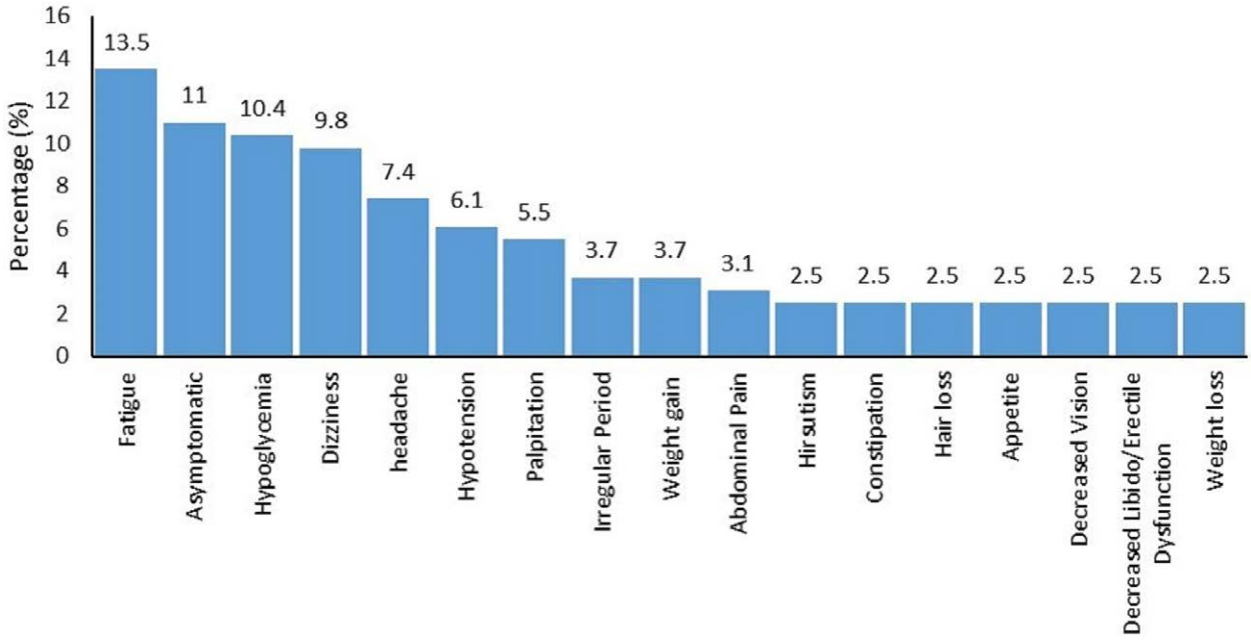

Figure 1. Percentage of patients presenting with sign and symptoms.

Table 2

Mean cortisol level according to clinical presentation.

	Basal mean+/−SD (range)	30 min mean+/−SD (range)	60 min mean+/−SD (range)	*P* value
Overall	217.8 ± 16.1(27.0–706.0)	372.7 ± 21.3 (27.0–1018.0)*	437.2 ± 23.5 (27.0–1114.0)*†	<.001
Clinical presentation				
Known AI (N = 13)	168.3 ± 38.6 (27.0–351.0)	307.5 ± 51.1 (27.0–516.0)*	361.1 ± 56.4 (27.0–605.0)*†	.005
Suspected AI (N = 141)	217.6 ± 12.0 (27.0–706.0)	397.8 ± 15.5 (27.0–1018.0)*	464.9 ± 17.1 (27.0–1114.0)*†	<.001
P value	.24	.09	.08	
Steroid use				
Yes (N = 64)	137.8 ± 16.0 (27.0–460.0)	257.8 ± 18.5 (27.0–728.0)*	304.4 ± 19.9 (27.0–850.0)*†	<.001
No (N = 90)	267.3 ± 13.5 (28.0–706.0)	484.4 ± 15.6 (175.0–1018.0)*	564.1 ± 16.8 (261.0–114.0)*†	<.001
P value	<.001	<.001	<.001	

Data presented as mean ± SE.

AI = adrenal insufficiency, SD = standard deviation.

* and

† indicate significant difference from basal and 30 minutes. $P < .05$ considered significant.

Table 3

Mean % change in cortisol level according to clinical presentation.

	Mean % change in cortisol level			
Clinical presentation	**30 min & basal**	**60 min & basal**	**60 min & 30 min**	***P* value**
Overall	130.6 ± 21.7	174.2 ± 26.9*	20.7 ± 3.5*†	<.001
Clinical presentation				
Known AI (N = 13)	146.4 ± 52.0	191.5 ± 64.5*	16.7 ± 8.3*†	<.05
Suspected AI (N = 141)	145.6 ± 15.9	193.6 ± 19.8*	20.4 ± 2.5*†	<.001
P value	.99	.98	.67	
Steroid use				
Yes (N = 64)	145.2 ± 23.7	198.2 ± 29.3*	20.4 ± 3.7*†	<.001
No (N = 90)	146.0 ± 20.0	190.0 ± 24.7*	19.8 ± 3.2*†	<.001
P value	.98	.83	.89	

% change is calculated by dividing the change (from basal) in cortisol by basal value & × 100. Data presented as mean ± SE.

AI = adrenal insufficiency.

* and

† indicate significant difference from basal and 30 minutes. $P < .05$ considered significant.

Table 4

Area under the curve using known or suspected AI as standard.

Clinical presentation	Basal cortisol	Cortisol at 30 min	Cortisol at 60 min
Rule out AI due to comorbidities/low random cortisol (N = 112)			
AUC	0.57 ± 0.08	0.63 ± 0.08	0.62 ± 0.17
P value	.42	.14	.17
Other signs and symptoms (N = 29)			
AUC	0.73 ± 0.08	0.69 ± 0.09	0.70 ± 0.09
P value	.017	.055	.040
Sensitivity	69.2	61.5	61.5
Specificity	58.6	69.0	65.5
Cutoff	258.5	386.0	491.5
Suspected AI (Rule out AI due to comorbidities/low random cortisol + signs/symptoms) (N = 141)			
AUC	0.60 ± 0.08	0.64 ± 0.10	0.63 ± 0.08
P value	.22	.10	.11

Data presented as area under the curve.

AI = adrenal insufficiency, AUC = area under the curve.

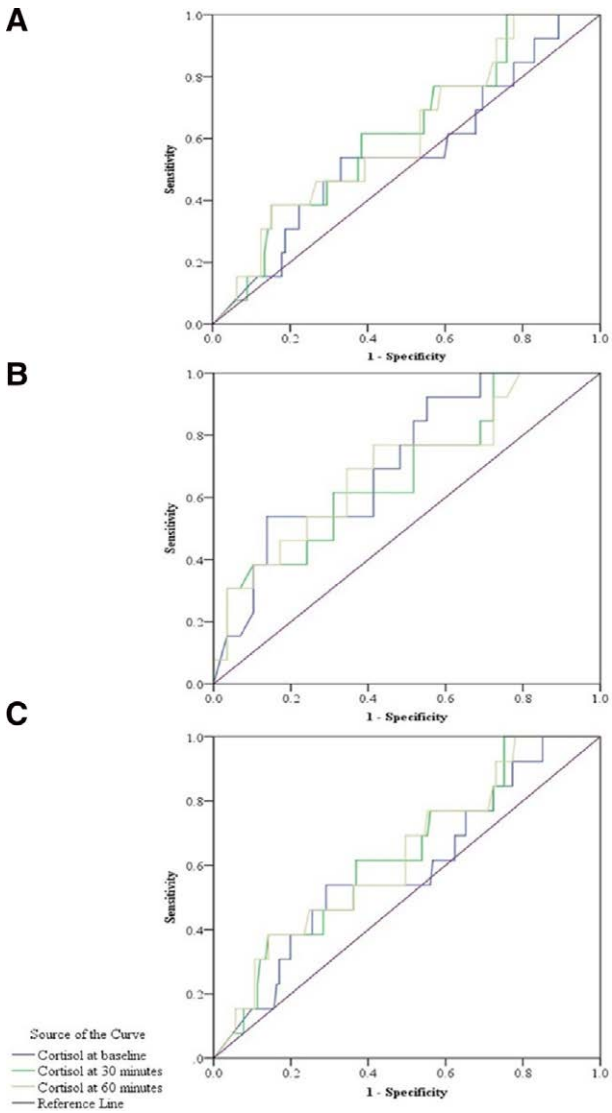

Figure 2. AUC curve (A) to rule out AI due to comorbidities/low random cortisol, (B) other symptoms and signs, and (C) suspected AI (to rule out AI due to comorbidities/low random cortisol + other signs and symptoms) against known AI. AI = adrenal insufficiency, AUC = area under the curve.

baseline, 30 minutes and 60 minutes' cortisol levels. Patients who were treated with corticosteroids had a mean cortisol level of 257.8 mmol/L at 30 minutes and 304.4 mmol/L at 60 minutes. In contrast, patients who had sufficient cortisol response had mean cortisol of 484.4 mmol/L at 30 minutes and 564.1 mmol/L at 60 minutes.

AI diagnosis is challenging given the wide spectrum of symptoms and signs the patients could present with.[14] In the present study, fatigue was the most common symptom reported in patients who underwent ACTH stimulation test. Similarly, multiple comorbidities are likely to confound the clinical presentation of the patients suspected to have AI. In this study the most common reported comorbidity is type 1 diabetes. The causes of AI vary from primary adrenal diseases to pituitary and hypothalamic disorder with ACTH deficiency. The most common cause of AI worldwide is Addison disease due to autoimmune destruction of the adrenal glands.[15] Therefore, AI in general and primary AI in particular are investigated and diagnosed more frequently in patients with autoimmune diseases such as type 1 diabetes.[14,16] In such patients, the measurement of adrenal autoantibodies helps in early prediction of AI development over time.[17] In our study, none of the patients had adrenal antibodies tested due to its unavailability. On the contrary, central AI occurs frequently due to ACTH deficiency caused by sellar tumors, sellar surgery and radiation.[18,19] Hence, significant number of the patients with pituitary adenomas or seller mass who undergo ACTH stimulation test end up being treated with corticosteroids due to AI.

Standard 250 μg ACTH stimulation test is a dynamic test that is used widely to investigate primary and central AI, however it is has its limitations such as the lack of a clear cutoff point for AI diagnosis.[1,20] The accepted cutoff point for cortisol level after ACTH stimulation is 500 mmol/L or higher to rule out AI. Furthermore, cortisol levels <500 nmol/L after ACTH stimulation may be indicative of subnormal cortisol secretion,[14] but reference values may vary in different populations and assays used.[21,22] The difficulty of obtaining a universal cutoff is complicated further by many factors affecting cortisol such as sleep pattern and stress level which should be considered in interpreting the test results.[6,7,23,24] More importantly, validation of a population and assay specific cutoff points of normal cortisol response after ACTH stimulation test are needed.[25]

Several studies have investigated the optimal cutoff value of cortisol to diagnose AI. A lower level of cortisol after ACTH stimulation of around 496 nmol/L (14 μg/dL) using new generation cortisol assays such as Elecsys II and Access has been endorsed by Javorsky et al, and Grassi et al.[21,22] In our study, chemiluminescence microparticle immunoassays (Architect, Abbott, Architect System, Abbott Laboratories, IL) were used to measure the cortisol levels. This assay has

been shown to yield similar cortisol levels when compared to Elecsys II (Roche), Access (Beckman), and LC-MS/MS. Zha et al suggested a 30-minute cortisol level of 13.2 µg/dL (364 nmol/L) and 60-minute cortisol level of 14.6 µg/dL (402 nmol/L) to diagnose AI with a sensitivity and specificity of >90% using Abbott assays.[26] Using the same levels in our study yields a sensitivity of 45 to 50% and specificity of 70%. Many patients with a 30-minute cortisol level of 358 nmol/L and 60-minute cortisol level of 437 nmol/L had acceptable cortisol secretion and did not receive corticosteroid replacement. In clinical practice, if the pretest probability of AI is low, then a lower stimulated cortisol level could be sufficient to exclude AI. On the contrary, if the pretest probability of AI is high, then a higher stimulated cortisol cutoff value is necessary to exclude AI confidently. Therefore, it seems that the clinical presentation of patients in terms of comorbidities, symptoms and risk factors for AI indirectly affects the ACTH stimulation test result interpretation. This assumption needs further investigation to consider correlating the pretest probability, the ACTH test results and its interpretation. Of note, despite that the measurement of cortisol after ACTH stimulation is widely used, there has been suggestions that the measurement of stimulated salivary cortisol may have better diagnostic utility.[18,27] Moreover, basal cortisol is as well useful test in many patients. Basal cortisol <80 to 100 nmol/L is diagnostic of AI while basal cortisol >400 nmol/L rules out AI.[28] In our study, around 33% of the patients with suspected AI had basal cortisol of <83 or >415 nmol/L which would have been enough to diagnose or rule out AI.

Steroid replacement is the ultimate treatment for patients with confirmed AI. Due to its long-term complications, it is usually reserved to be used in patients with confirmed AI.[14] As shown in the present study, majority of the patients were not treated with steroids. This finding reinforces the complexity of deciding who is eligible for long-term steroid replacement. Results of ACTH stimulation test are usually combined with other clinical variables to determine appropriateness of steroid replacement.

The authors acknowledge some limitations. The study has a small sample size focused on adults and there were no health subjects in the study; therefore, findings cannot be generalized. Moreover, sub-analysis according to sex was not performed, this is important since hypothalamus–pituitary–adrenal axis stress-response is sexually dimorphic. Lastly, the incidence of AI covered in the present study was during pre-pandemic years (2015–2018) and it will be interesting to determine whether the incidence changed following coronavirus disease 2019 since recent observations highlight increased risk of AI as a consequence of glucocorticoid co-administration post coronavirus disease 2019 infection.[29] The study nevertheless is the first to investigate the ACTH stimulation test discriminatory power for the clinical diagnosis of AI in the Saudi population.

5. Conclusion

In summary, ACTH stimulation test results obtained from Arab patients with suspected AI diagnosis showed wide variability for its utility in AI diagnosis. In particular, the cortisol cut-off values for AI diagnosis in this population were only satisfactory in terms of diagnostic accuracy and test quality. Future investigations that involve multiple centers and healthy subjects are needed to determine cortisol cutoff points at different times of ACTH stimulation test in this population.

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Author contributions

MM designed the study. AAS and AAM worked on the methodology. SDH did the statistical analysis. AAA and KA in the data curation. MM wrote the first draft. SS revised the manuscript. MMA and YA did the study supervision.

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