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Diagnosis and Management of Cushing's Disease: A Survey of Endocrinologists from the Middle East and North Africa

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Abstract

Background Cushing's disease is the most prevalent cause of endogenous Cushing's syndrome. This study aimed to scope the current clinical practice pattern in managing Cushing's disease by endocrinologists in the Middle Eastern and North African (MENA) region.

Methods A questionnaire dealing with diagnosis, treatment, and follow-up of patients with Cushing's disease was adopted and sent electronically to a convenience sample of endocrinologists from the MENA region.

Results Out of 125 responses received, 88 were eligible for inclusion in the analysis. Most respondents selected the overnight dexamethasone suppression test (ONDST) and 24-hour urinary-free cortisol (UFC) as the best screening tests, 58 (66.7%) and 50 (57.5%) respectively, followed by midnight serum cortisol and midnight salivary cortisol. Measurement of serum adrenocorticotropic hormone (ACTH; 86.2%) and classic high-dose dexamethasone suppression test (40.2%) were selected for localization of the primary lesion. The primary choice of treatment was transsphenoidal pituitary surgery (98.8%). For the recurrence of Cushing's disease, medical therapy was the preferred modality followed by repeated pituitary surgery or bilateral adrenalectomy. In case of treatment failure following the first pituitary surgery and ketoconazole treatment, 36.9% selected pasireotide, while 32.1% chose bilateral adrenalectomy.

Keywords
- clinical practice
- Cushing's disease
- diagnosis
- management
- MENA region

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Conclusion ONDST and UFC are the two most common tests used to screen an index case with features of hypercortisolism. Pituitary surgery is the primary choice of treatment in Cushing's disease. However, medical treatment by ketoconazole is preferred for recurrent cases. Bilateral adrenalectomy is followed by pasireotide may be chosen in case of treatment failure after pituitary surgery and ketoconazole.

Introduction

Cushing's syndrome results from chronic exposure to excessive circulating levels of glucocorticoids. Cushing's disease is the most common cause of endogenous hypercortisolism.[1] Elevated ACTH secretion results in excess cortisol production from adrenal glands and following clinical and paraclinical features of hypercortisolism.[1] The primary aim of treating Cushing's disease is to reverse the manifestations of hypercortisolism and achieve long-term disease-free survival.[1]

The diagnosis and management of Cushing's disease are challenging for clinicians. The Endocrine Society and The European Society of Endocrinology published evidence-based clinical practice guidelines.[2] Measurements of serum, urinary, or salivary cortisol can all be used for diagnosis. The primary recommended investigations are urinary-free cortisol (UFC), overnight 1-mg and 2-day 2-mg/day dexamethasone suppression tests (DSTs), and late-night salivary cortisol. The optimal treatment for ACTH-producing tumors is surgical resection. However, second-line options include medical therapy, repeated pituitary surgery, radiotherapy, and bilateral adrenalectomy[3,4] in surgical failure or relapse.

Due to the rarity of Cushing's disease, it has not been ascertained how closely endocrinologists adhere to the guidelines on its diagnosis and management in various parts of the world.[5] Therefore, we aimed to document the clinical practice pattern in diagnosing and managing Cushing's disease by endocrinologists in the Middle East and North Africa (MENA) region and comparing the current practice with the international recommendations. It is noteworthy that there are no MENA guidelines for the diagnosis and management of Cushing's syndrome.

Materials and Methods

Study Design

This cross-sectional study is based on an electronic survey of clinically active endocrinologists in diagnosing and managing patients with Cushing's disease. The study was conducted between February 1 and March 31, 2020.

Target Population

In the absence of a single MENA regional endocrine society with a membership list that can define a study population, the target population was identified from a list of electronic mails (e-mails) pooled from continuous professional development (CPD) delegates, speakers, authors, or members of various scientific groups or forums in various parts of the MENA region.

Survey Management

A web-based commercial survey management service (SurveyMonkey, Palo Alto, California, United States) was used. All participants received an initial e-mail that explained the rationale of the survey and what is required from the consented respondents, followed by five subsequent reminder e-mails during the study period. Each message included explaining the rationale and method of participation, full credentials, and contact details of the principal investigator, together with a unique e-mail-specific electronic link to the questionnaire. The survey service automatically blocked repeated submissions from the same IP address.

The Survey Questionnaire

The survey consisted of multiple-choice questions on diagnosis, treatment, and follow-up of an index case with features of Cushing's disease (►**Table 1**). Some questions required a single best response while others allowed multiple items to be selected independently (►**Table 1**). All potential answers were included for each question to decrease the bias. The questions were derived from a previous study with the same objectives.[5] It is noteworthy that the original questions were appraised by nine endocrinologists, experts in diagnosing, and managing Cushing's disease.[5] The survey was served in both English and French. Besides, several questions were added to define the respondents' demographic and professional profiles and identify the available resources in their practices similar to our previously published study.[6–10]

Statistical Analysis

Survey responses were anonymously collected. The survey management service tools were used for the initial examination of results. Summary statistics were calculated for responses to each question separately. Since not every respondent answered all the questions, percentage adjustment was made for individual questions by using the number of respondents to that question as the denominator.

STROBE Statement

The manuscript was prepared and checked against the items that should be included in reports of cross-sectional studies

Results

Profiles of Respondents

Out of the total of 125 responses, 88 responses fulfilled the inclusion criteria. Of these, 38 (43.2%) were from the Arabian Gulf, 32 (36.4%) from North Africa, and 18 (20.5%) from the rest of the Middle East. The majority ($n = 80$) were adult

Table 1 The MENA Cushing's survey questions and possible responses

I.	Profile of respondents and their practices:
Q1–7	Respondents professional profile: 1. consent, 2. region of residence and practice: (included: Gulf, North Africa, and Rest of the Mid East), 3. specialty: [included: adult endocrinology, pediatric endocrinology], 4. sex, 5. age group (options: <30, 31–40, 41–50, 51–60, 61–70, and >70), 6. career grade (accepted senior [consultant/attending physician], midgrade [subconsultant specialist grade]), 7. how many patients with "Confirmed or Highly Suspected" to have Cushing' syndrome you have encountered in the last 6 months: (none, 1–5, 6–10, 11–15, and >15)
Q8–9	8. Type of clinical practice (options: university or teaching hospital/district or community [nonteaching] hospital/private practice/other services). 9. please rank the availability of your patients with Cushing's syndrome (as readily [in the same city], elsewhere [national], not available). (all relevant laboratory measurements, imaging [MRI], imaging [CT], imaging [nuclear medicine], selective adrenal sampling, inferior petrosal sinus cannulation, ketoconazole, octreotide, pasireotide, cabergoline, metyrapone, mitotane, mifepristone, competent pituitary surgeon, competent adrenal surgeon, conventional radiotherapy, and stereotactic radiotherapy)
II.	**Cushing's disease survey:**
IIA. Index Case	Diagnostic evaluation: which of the following studies would you order as a screening test in the majority of patients, such as the index case: (a 32-year-old woman presents with fatigue and weight gain since 6 months ago. She also complains of oligomenorrhea and slowly progressive hirsutism. She is otherwise healthy and takes no medication except for captopril for hypertension. Her BP is 135/87 mm Hg and has an Ferriman and Gallwey score of 12 and purple striae over the flanks and lower abdomen. Fasting blood glucose level is 130 mg/dL
Q10	a. Screening: (options: 24-hour urinary-free cortisol, overnight dexamethasone suppression test, late-night salivary cortisol, midnight serum cortisol, low-dose dexamethasone suppression test, morning serum cortisol, and serum ACTH)
Q11	b. Localization of the primary gland responsible (i.e., pituitary versus adrenal)? Check all that apply (options: high-dose dexamethasone suppression test, serum ACTH, modified dose dexamethasone suppression test, CRH-stimulation test).
Q12	What would be your diagnostic approach if the preliminary evaluations were indicative of an ectopic Cushing's? Check all that apply (Options: high-resolution CT scan of the thorax, spiral CT scan of the abdomen, MRI scan of the abdomen, octreotide scan, inferior petrosal sinus sampling.)
IIB.	Initial treatment of the index case: (the index case was confirmed to have ACTH dependent Cushing's disease with a 6 mm pituitary adenoma reported in dynamic brain MRI)
Q13	Please specify your choice of primary treatment. Only one choice is possible. (options: transsphenoidal pituitary surgery, bilateral adrenalectomy, cabergoline, long-acting somatostatin analogs, mitotane, ketoconazole, and metyrapone)
IIC.	Recurrence of Cushing's disease I: (the index case was operated through a transsphenoidal sinus approach, and no evidence of hypo- or hypercortisolism was found for the following 2 years after the operation when recurrence happened that proved to be ACTH dependent. However, there was No evidence of pituitary adenoma and ectopic source for the elevated ACTH in the diagnostic evaluations).
Q14	Please specify your choice of primary treatment of the recurrent Cushing's disease (clinically and biochemically) in this setting. Only one choice is possible. (options: observation, transsphenoidal pituitary surgery, bilateral adrenalectomy, cabergoline, long-acting somatostatin analogs, mitotane, ketoconazole, and metyrapone).
	Recurrence of Cushing's disease II: (the index case was treated by ketoconazole. However, three months after the initiation of ketoconazole, liver enzymes rose to five times the upper limit of the normal range.) only one answer is possible
Q15	Please indicate your preferred choice of action at this stage. (Options: bilateral adrenalectomy, pasireotide, combination therapy with cabergoline and pasireotide, another pituitary surgery, and other).
IID. Q16	Priorities of medical therapy for Cushing's disease: please rank the following drugs according to your wish to see them available for all your patients with Cushing's syndrome. (only three choices can be made). (Options: ketoconazole, octreotide LAR, pasireotide, cabergoline, metyrapone, mitotane, mifepristone, and radiotherapy).
III.	Cushing's disease management outcome: considering the available treatment options in your country, what do you think the index case exemplifies the likely rate of success in treating ACTH-dependent Cushing's disease. Only one choice is possible
Q17	Please make a choice nearest to your perception (Options: < 30%, 31–50%, 51–70%, and >70%).

Abbreviations: ACTH, adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; CT, computed tomography; MENA, Middle Eastern and North African; MRI, magnetic resonance imaging.

endocrinologists, and eight were pediatric endocrinologists. They were split equally between sexes (45 males and 43 females). The majority were in the age groups of 41 to 50 years (36; 40.9%) and 31 to 40 years (30; 34.1%). The others were aged 51 to 60 years (11; 12.5%), <30 years (6; 6.8%), and 61 to 70 years (5; 5.7%). Regarding the career stages, most of the respondents (63 [71.6%]) were senior (i.e., consultant; attending physician), and 25 (28.4%) were of midgrade (i.e.,

Table 2 Reported availability of resources for diagnosis and management of Cushing's disease

Resources (responses)	Readily (same city; %)	Elsewhere (national; %)	Not available (%)
Imaging			
MRI ($n = 86$)	95.3	4.7	0.0
CT ($n = 86$)	91.9	5.8	2.3
Nuclear medicine ($n = 85$)	75.3	23.5	1.2
All relevant laboratory measurements (86)	83.7	15.1	1.2
Localization procedures:			
Selective adrenal sampling (83)	54.2	34.9	10.8
Inferior petrosal sinus sampling (84)	47.6	29.8	22.6
Competent surgeons			
Pituitary (85)	76.5	21.2	2.4
Adrenal (84)	76.2	22.6	1.2
Radiotherapy			
Conventional (85)	76.5	21.2	2.4
Stereotactic (85)	50.6	24.7	24.7
Medical treatment			
Cabergoline (82)	91.5	6.1	2.4
Octreotide (83)	75.9	9.6	14.5
Ketoconazole (85)	55.3	10.6	34.1
Mitotane (79)	30.4	26.6	43.0
Pasireotide (80)	27.5	16.3	56.3
Metyrapone (81)	17.3	18.5	64.2
Mifepristone (82)	14.6	22.0	63.4

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

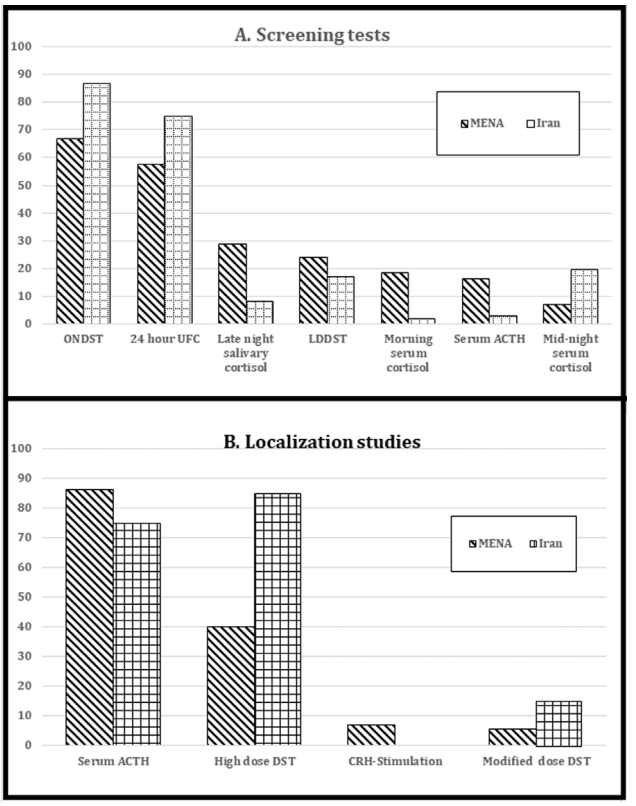

Fig. 1 Percentage of respondents who would select the listed laboratory tests for screening (**A**) or localization (**B**) in a patient with clinical evidence of hypercortisolism in the present study and the results of the study from Iran (2016) extracted from reference [5]. ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression tests; LDDST: low-dose dexamethsone suppression test; MENA, Middle Eastern and North African; ONDST, overnight DST; UFC, urinary-free cortisol.

subconsultant specialist). The respondents reported the number of patients with "confirmed or highly suspected" to have Cushing's disease that has been encountered in the previous 6 months as none by 23.0% of respondents, 1 to 5 patients by 72.4% of respondents, and 6 to 10 patients by 4.6% of respondents. Majority of the respondents (50.9%) practice in university or teaching hospitals (tertiary care), 25.3% in private practice, 12.% in district or community (nonteaching) hospitals, and 1.1% in other facilities. The majority of the respondents saw less than 10 newly diagnosed patients with Cushing's disease annually. The availability of diagnostic facilities and treatment resources for patients with Cushing's syndrome are ranked as readily available (same city), nationally available, or not available as detailed in ►**Table 2**.

Diagnostic Evaluation

The respondents' choices of screening tests are shown in ►**Fig. 1A**. Assessment of fasting serum cortisol after an overnight dexamethasone suppression test (ONDST) and 24-hour UFC as a screening test has been obtained by 58 (66.7%) and 50 (57.5%) of the respondents, respectively. Thirty-two (36.4%) respondents selected both of the above screening tests simultaneously. In response to the question on the localization of the primary gland responsible for Cushing's syndrome (i.e., pituitary vs. Adrenal; ►**Fig. 1B**), the majority would order serum adrenocorticotrophic hormone (ACTH; 86.2%) or high-dose dexamethasone suppression test (40.2%), the respondents were also asked to provide their diagnostic approach if the preliminary evaluations were indicative of an ectopic Cushing's disease. Of the 86 respondents, 63 (73.3%) selected a high-resolution computed tomography (CT) scan of thorax, and 33 (38.4%) selected a spiral CT scan of the abdomen; 58 (76.3%) would use both tests to assess an ectopic source; 26 (30.2%) of the respondents selected an octreotide scan, while 24 (27.9%) chose to use inferior petrosal sinus sampling, and 15 (17.4%) chose to order a magnetic resonance imaging (MRI) scan of the abdomen.

Primary Treatment

The participants stated that their primary treatment choice in an index case of ACTH-dependent Cushing's disease with a 6-mm pituitary adenoma reported in dynamic brain MRI.

Transsphenoidal pituitary surgery (TSS) was selected by 85 (98.8%) of the respondents; a single respondent (1.2%) preferred cabergoline. None of the respondents chose any other modality of treatment.

Recurrence of Cushing's Disease

The index case had pituitary surgery through a TSS approach, and no evidence of hypo- or hypercortisolism was detected for the following 2 years after the operation when recurrence happened that proved to be ACTH dependent. However, there was no evidence of pituitary adenoma and ectopic source for the elevated ACTH in the diagnostic evaluations. The respondents were further asked to specify their options in treating the index case at this stage. Of the respondents, 65 (74.7%) chose medical treatment as the preferred treatment modality for the recurrence of Cushing's disease in this clinical setting, 5 (5.7%) preferred bilateral adrenalectomy, and 9 (10.3%) favored further pituitary surgery.

Furthermore, in the given clinical scenario, the case was treated with ketoconazole. However, three months after the initiation of ketoconazole, liver enzymes rose to five times the upper limit of the normal range. The respondents were then asked to select their choice of action. Recurrent Cushing's disease after pituitary surgery and ketoconazole failure would be treated by more respondents using pasireotide (31 [36.9%]) than bilateral adrenalectomy (27 [32.1%]). Furthermore, 19 endocrinologists (22.6%) chose to use combination therapy with cabergoline and pasireotide, and 7 (8.3%) of them would recommend another pituitary surgery.

Quality of Care and Outcome

The respondents were asked about the success rate in treating ACTH-dependent Cushing's disease in their country of residence. Thirty-eight (43.7%) reported a success rate of 31 to 50%, and 30 (34.5%) believed that this rate seemed higher (51–70%). They were also asked to prioritize a list of drugs they would like to be available for treating Cushing's disease in their country; 61.9% of the respondents selected ketoconazole as their first drug of choice, while 45.85% chose pasireotide (►**Fig. 2**).

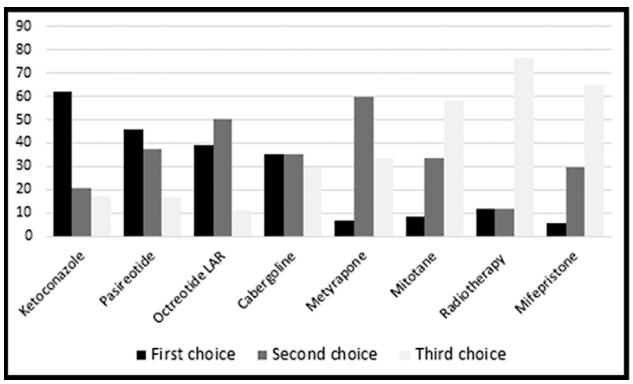

Fig. 2 Medical therapy priorities expressed by the ranking of listed therapeutic choices according to the respondent's wish to see them available for all of their patients with Cushing's disease. Only three choices were allowed. The first choice presents choices in decreasing order.

Discussion

Guidelines for the diagnosis, treatment, and follow-up of the patients for Cushing's disease have been developed by international experts under the auspices of the endocrine societies, published in high-impact journals in endocrinology, and they are being updated when required. Nevertheless, implementing these guidelines is not possible worldwide because of some limitations, including some suggested drugs, inadequate laboratory facilities, and others. Hence, each country can adjust the guidelines according to its conditions.

In the present study, we aimed to ascertain the approach of endocrinologists from the MENA region to diagnosing and treating Cushing's disease. The data were obtained from the responses of endocrinologists to a questionnaire including questions regarding the diagnosis and management of the patients with Cushing's disease. We employed an online survey method to reach all interested target populations with no delay and extra cost. Also, responses can be made by the respondents at their own time and comfort. We used a questionnaire that was validated and used in a recent national study from Iran.[5] The survey was structured in its original version on clinical scenarios to follow-up the possibilities encountered in a real-life case. The findings should find out the clinical decisions made by physicians when faced with similar cases. We only included practitioners in the consultant and subconsultant specialist grades, most of whom work in leading teaching hospitals. Predictably, the number of respondents was not very large but hopefully representative of endocrinologists dealing with Cushing's disease.

The results revealed that the majority of the MENA endocrinologists would choose UFC and ONDST as screening tests. We also found that they prefer transsphenoid pituitary surgery for patients with a pituitary-dependent source for hypercortisolism. However, when the first pituitary surgery failed, ketoconazole was the treatment of choice. More than one-third would resort to novel medical treatments such as pasireotide in the case of treatment failure with pituitary surgery and ketoconazole (due to side effects). In comparison, bilateral adrenalectomy was preferred by less than one-third. The survey also scoped the resources available to the respondents which may provide useful information to policymakers and health care planners.

The diagnostic trends identified in this study are compatible with the latest clinical practice guidelines.[2] These guidelines indicate that there is no single best screening test for Cushing's syndrome. Therefore, random serum cortisol or plasma ACTH is not recommended for screening. Moreover, 24-hour UFC, late-night salivary cortisol, 1-mg ONDST, and longer low-dose DST were offered for the initial investigation. In this survey, only a few participants selected random serum cortisol and plasma ACTH.

Furthermore, the measurement of late-night salivary cortisol was not popular as the initial investigation. Salivary cortisol represents the active form of serum cortisol which is not affected by saliva flow rate.[11,12] As the salivary glands express 11β-hydroxysteroid dehydrogenase type 2, licorice

or using tobacco may produce a false-positive result.[13,14] In the present study, a small number of participants selected late-night salivary cortisol for the initial investigation, and this may have been due to the unavailability of the test or lack of knowledge about its existence. However, more traditional tests such as ONDST and 24-hour UFC have been available for several years. Therefore, the majority of endocrinologists are familiar with their use in clinical practice.

Considering the treatment pattern, the first-line treatment for Cushing's disease is the surgical removal of the pituitary adenoma by a transsphenoidal approach.[3] The remission rate for microadenomas was reported to be 65 to 90%, with a recurrence rate of 10 to 20% at 10 years. [15,16]

The majority of the respondents in this survey selected TSS as the primary treatment choice in an index case with an ACTH-dependent Cushing's disease caused by a pituitary microadenoma. However, after a proven recurrence, medical treatment with ketoconazole was the preferred choice of action by nearly three quarters of the participants. Nonetheless, the questions did not establish the rationale for choosing ketoconazole rather metyrapone, that is, based on the efficacy of former or lack of availability in the region. The treatment of choice for a Cushing's disease patient who underwent a noncurative surgery in the latest clinical practice guideline includes pituitary reoperation as the first line, particularly in patients with incomplete resection evidenced pituitary lesion on imaging.[2] Perhaps, the respondents assumed that surgery was not feasible. Perhaps, the respondents assumed that surgery was not feasible. Medical treatment has gained a significant space in recent years in the management of Cushing's disease. It might be employed prior to surgery to diminish the risk of the procedure itself and/or control the metabolic consequences of high-circulating cortisol levels.[17] Furthermore, medical treatment could reduce hypercortisolism and should be considered before bilateral adrenalectomy.

Bilateral adrenalectomy provides control of hypercortisolism immediately. However, glucocorticoid and mineralocorticoid replacement will be needed lifelong.[18] Although the second-line treatment for a recurrence of Cushing's disease should be individualized, bilateral adrenalectomy is indicated when hypercortisolism persisted despite medical therapy.[18] Ketoconazole inhibits cortisol production by its action on 11β-hydroxylase. The reported average remission rate for patients with Cushing's disease is around 70%.[19] However, reversible elevations of liver enzymes occur in 5 to 10% of the patients, and serious hepatic injury has been reported in 1 out of 15,000 cases.[20]

In this study, pasireotide was selected by more than a third of the respondents when a patient experienced treatment failure with pituitary surgery and ketoconazole. Recent studies demonstrated that somatostatin receptor subtype 5 (SSt5) and dopamine receptor subtype 2 are frequently expressed by corticotroph adenomas.[21–25] Octreotide, a somatostatin analog (SSA) with binding affinity to somatostatin type-2 receptors, does not have suppressive action on ACTH.[26,27] Pasireotide that binds to SSt5 was reported to normalize UFC in 15 and 26% of patients with Cushing's disease following the 6 months of therapy with a dose of 600 and 900 µg, respectively.[28] Drug-induced hyperglycemia is the major adverse event reported in the majority of patients. Diarrhea, nausea, and abdominal pain are other most common events observed with pasireotide treatment.[29]

The study made some contribution to the literature, however it has some notable limitations. It is limited by its design being a survey of perception and what would be done by the respondents in response to a hypothetical index case. It is not a clinical audit of actual practice procedures and outcomes. Potential selection bias may result from the database used and by self-selection by opting in by clinical endocrinologists. The sample size is relatively small but it is probably appropriate for careful selection of physicians identified as endocrinologists, majority of whom came from tertiary centers and would be the ones involved in management of this rare condition.

Conclusion

The present survey showed that traditional ONDST and 24-hour UFC are still the most popular tests for the initial evaluation of patients with symptoms and signs suggestive of hypercortisolism. Regarding the treatment, TSS is the initial treatment of choice in Cushing's disease, while ketoconazole is the preferred medication in case of recurrence. Moreover, bilateral adrenalectomy is second to pasireotide when pituitary surgery and ketoconazole fail to cure the patient.

Box 1. The study's contribution to knowledge and clinical practice

What Is Already Known on This Topic

- Guidelines for the diagnosis, treatment, and follow-up of the patients for Cushing's disease have been developed by international experts under the auspices of the endocrine societies,
- Management of Cushing's disease is primarily by curative pituitary surgery, if cure is expected, followed by adrenal surgery or medical treatment for failures chosen on individual basis.
- Implementing guidelines is not possible worldwide because of some limitations, including some suggested drugs, inadequate laboratory facilities, and others. Hence, each country can adjust the guidelines according to its conditions.

What This Study Adds

- To the best of our knowledge, it is first in the Middle Eastern and North African (MENA) region and is second of its nature worldwide. Although it does not add to the international scene, it sends important messages for the region.

- The study provided an opportunity to evaluate the current clinical practice in diagnosing and treating Cushing's disease in the MENA region.
- The resulting information should help focus educational activities and inform any possibilities of developing national and regional clinical practice guidelines or adapting internationally accepted guidelines to best suit local circumstances

Authors' Contributions

All authors contributed to the conceptualization, design of the study, and the process of data collection; S.A.B., M.A.E., and K.M.A.D., were actively involved in interpretation of data and drafted the manuscript for all authors to critique and make relevant corrections. All the authors have read and agreed to final version of this manuscript.

Compliance with Ethical Principles

The study was conducted following the principles of the Declaration of Helsinki. The Institutional Review Board approved the study at Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates. All participants provided informed consent before they could proceed to the survey questions.

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None.

Conflict of Interest

None declared.

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