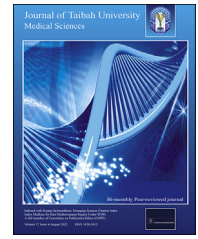




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## Journal of Taibah University Medical Sciences

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Original Article

## The short synacthen test: Variations in methodology and protocols in KSA

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Received 24 November 2021; revised 28 December 2021; accepted 29 January 2022; Available online 11 February 2022



### المخلص

**أهداف البحث:** لمقارنة الممارسة الحالية على مستوى المملكة مع دراسات المؤسسة السابقة حول هذا الموضوع. أيضا، لتحديد ما إذا كان تخصص أو درجة الطبيب ترتبط بميله نحو بروتوكول معين عند إجراء اختبار سيناكتين القصير.

**طرق البحث:** قمنا باستطلاع رأي الأطباء المسجلين لدى المجلس الصحي السعودي لتحديد مختلف البروتوكولات المتبعة عند إجراء اختبار سيناكتين القصير بالمملكة العربية السعودية.

**النتائج:** تلقينا 162 ردا. من هؤلاء، كان 66 (41%) مشاركا من أطباء الغدد الصماء، والباقي من أطباء الباطنة. كان 61 (38%) من المستجيبين من درجة استشاري، بينما كان الباقي من درجة غير استشاري. اعتبر الأطباء الخلل الأيضي مثل انخفاض ضغط الدم (78%)، نقص صوديوم الدم (65%)، نقص السكر في الدم (59%)، وفرط البوتاسيوم (54%) هي الأسباب الرئيسية لإجراء الاختبار. اعتمد أغلب الأطباء بروتوكول اختبار سيناكتين القصير، لقياس هرمون الكورتيزول الأساسي في الدم (90%)، والهرمون الموجه للغدة الكظرية (78%) في يوم الاختبار. قام 75% من الأطباء بقياس كلا من هرمون الكورتيزول في الدم بعد 30 و 60 دقيقة بعد حقن الهرمون الموجه للغدة الكظرية. من هؤلاء، أفاد 13% من الأطباء أن مستويات الكورتيزول كانت أقل من الحد الأدنى المقبول بعد 30 دقيقة ولكنها وصلت فقط بعد 60 دقيقة. جاءت نتائج 90% من اختبار سيناكتين القصير التي تم إجراؤها طبيعياً. اعتبر 93% من الأطباء أن مستوى هرمون الكورتيزول المحفز البالغ 50 نانومول/لتر هو الحد الأدنى الطبيعي لوظائف الغدة الكظرية.

**الاستنتاجات:** أكدت هذه الدراسة أن قياس هرمون الكورتيزول في الدم بعد 60 دقيقة يجب أن يكون جزءاً من بروتوكول اختبار سيناكتين القصير لتجنب وجود نتائج إيجابية كاذبة. وعلاوة على ذلك، يتعين على الأطباء مراعاة الأسباب الأخرى لهذا الخلل الأيضي قبل الترتيب لإجراء اختبار سيناكتين القصير خصوصاً مع وجود احتمال منخفض ما قبل الاختبار.

**الكلمات المفتاحية:** كوسينترابين؛ جهاز الغدة النخامية؛ قصور الغدة الكظرية؛ اختبار سيناكتين القصير؛ مرض أديسون

### Abstract

**Objectives:** This study aimed to compare the current Kingdom-wide practice with our prior institutional study on use of the short synacthen test (SST), and to determine whether physician specialty or grade is associated with a tendency toward using a particular protocol.

**Method:** We surveyed clinicians registered with the Saudi Medical Council to determine the different SST protocols used within KSA.

**Results:** We received 162 responses, 66 (41%) from endocrinologists and the remainder from internists. A total of 61 (38%) respondents were consultants, whereas the rest were non-consultant grade. The clinicians indicated metabolic derangements, such as hypotension (78%), hyponatremia (65%), hypoglycemia (59%), and hyperkalemia (54%), as the main reasons for performing the test. Most clinicians used the SST protocol, which measures baseline serum cortisol (90%) and ACTH (78%) on the test day. A total of 75% of the physicians measured both the 30- and 60-minute serum cortisol after ACTH injection. Of these clinicians, 13% reported that the cortisol levels were below the pass threshold at 30 min but reached the pass threshold only at 60 min. The SST was

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Peer review under responsibility of Taibah University.



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normal 90% of the time when performed. A total of 93% of the clinicians considered a stimulated cortisol level of 550 nmol/L to be the threshold for normal adrenal function.

**Conclusion:** The survey confirms that 60-min serum cortisol should be part of the SST protocol to avoid false-positive results. Moreover, clinicians should consider other causes of these metabolic derangements before requesting a SST, particularly in patients with a low pretest probability.

**Keywords:** Addison disease; Adrenal insufficiency; Cosyntropin; Pituitary-adrenal system; Short synacthen test

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## Introduction

The short synacthen test (SST) is a dynamic endocrine test indicating the integrity of the hypothalamic pituitary adrenal (HPA) axis. The SST has several benefits, including the ease of conducting the test in an ambulatory setting without requiring hospital admission. It can be performed within an hour, mainly under the supervision of nursing or laboratory staff, and a clinician need not be physically present at all times.

A variety of SST protocols are used. Some protocols involve the measurement of serum cortisol at 30 and 60 min after ACTH injection, whereas others involve just a 30- or 60-min cortisol measurement after the injection. Likewise, some protocols include baseline serum cortisol and ACTH measurement before the ACTH injection, whereas other protocols do not require this step.

Our earlier single center study<sup>1</sup> has indicated that clinicians use the SST excessively, even when the pretest probability of adrenal insufficiency is low. Baseline cortisol can be used to triage patients who need a formal SST. Similarly, we have reported that protocols that measure only the 30-min serum cortisol might over-diagnose adrenal insufficiency; therefore, measurement of the 60-min cortisol level is essential.

Herein, we surveyed clinicians to understand the different SST protocols used in KSA. Our objectives included the following:

1. To compare the current Kingdom-wide practice with the results of our prior study on this subject.<sup>1</sup>
2. To determine whether physician specialty or grade might be associated with an inclination toward using a particular SST protocol.
3. To assess whether the indications for performing an SST might be associated with a particular physician grade or specialty.

## Materials and Methods

We conducted a multicenter study with a web-based questionnaire. We used the password-protected research electronic data capture (REDCap) software hosted at our institution and accessible only to the investigators. The data were safe and are available for reference if needed. Through this software, we sent email invitations to the clinicians registered with the Saudi Commission for Health Specialties. The participating clinicians were able to share their SST protocols. Participation was voluntary, and the data collection was anonymized. The survey required 5 min for completion.

We conducted the study from mid-January 2021 to the end of February 2021. After the initial invitation, we sent three further reminders, each 1 week apart. We concluded the survey 6 weeks after the initial invitation, then proceeded with data analysis. We collaborated with the institutional biostatistics department in the design of the questionnaire survey and the data analysis.

We invited endocrinologists and internists, including those in other associated sub-specialties registered with the Saudi Medical Council. We extended the invitation to consultants, associate consultants, assistant consultants, registrars, and endocrinology training fellows.

We reminded the clinicians of their responses to the standard dose SST (250 mcg cosyntropin injection) to enable comparison with our previous study.<sup>1</sup> We excluded pediatric clinicians from the survey.

We used frequency measures and percentages to describe physicians' common practices and attitudes toward the test protocols. We used chi-square tests to analyze the associations between the indications of SST with physicians' specialties and grades.

We conducted the survey according to the ethical principles and policies of the Clinical Research Department at the King Faisal Specialist Hospital & Research Centre, which, together with the Saudi Medical Council, approved the study.

Abbreviations: Adrenocorticotropic hormone (ACTH), Hypothalamic-pituitary-adrenal (HPA), Short Synacthen test (SST), Intramuscular (IM), Intravenous (IV).

## Results

A total of 464 physicians accepted the survey invitation, of whom 162 met the inclusion criteria and whose responses were included in the analysis.

Table 1 shows the descriptive information for the various test protocols performed by the physicians. The respondents were equally distributed between endocrinology and internal medicine. Clinicians across all grades participated in the survey. A total of 38% of the responses came from consultants. Approximately one-third of the study respondents were endocrinology training fellows.

Table 1 lists frequent indications for performing an SST. The clinicians were able to select more than one reason for

**Table 1: Descriptive data for SST protocols and participants' responses n = 162.**

<b>Specialty, n (%)</b>	
- Endocrinology and diabetes	66 (41%)
- Internal/general/acute medicine	66 (41%)
- Others*	27 (16%)
- No response	3 (2%)
<b>Grade of physician, n (%)</b>	
- Consultant	61 (38%)
- Associate consultant	13 (8%)
- Assistant consultant	13 (8%)
- Registrar	23 (14%)
- Endocrinology fellow	48 (30%)
- No response	4 (2%)
<b>Indications for performing SST, n (%)**</b>	
- Hypotension	130 (78%)
- Hyponatremia	109 (65%)
- Hypoglycemia	99 (59%)
- Hyperkalemia	91 (54%)
- History of pituitary tumor	54 (32%)
- Hyperpigmentation	52 (31%)
- Weight loss	48 (28%)
- Gastrointestinal symptoms	42 (25%)
- Visual field deficit	20 (11%)
<b>Basal morning cortisol threshold precluding the need for SST, n (%)</b>	
- >200 nmol/L	23 (14%)
- >250 nmol/L	20 (12%)
- >300 nmol/L	23 (14%)
- >350 nmol/L	23 (14%)
- >400 nmol/L	70 (44%)
- No response	3 (2%)
<b>Baseline serum ACTH tested as part of the SST protocol</b>	
- Yes	100 (62%)
- No	32 (20%)
- Tested only if clinician suspects central pituitary disease	27 (16%)
- No response	3 (2%)
<b>Baseline serum cortisol tested as part of the SST protocol, n (%)</b>	
- Yes	145 (90%)
- No	14 (8%)
- No response	3 (2%)
<b>Preferred route of ACTH injection</b>	
- IM	52 (32%)
- IV	45 (28%)
- Both	62 (38%)
- No response	3 (2%)
<b>Protocol after ACTH injection</b>	
- Both 30- and 60-min serum cortisol	121 (75%)
- 30-min serum cortisol only	18 (11%)
- 60-min serum cortisol only	16 (10%)
- Any other combination	4 (2%)
- No response	3 (2%)
<b>Stimulated cortisol threshold for normal SST</b>	
- $\geq 400$ nmol/L	20 (12%)
- $\geq 450$ nmol/L	16 (10%)
- $\geq 500$ nmol/L	81 (50%)

**Table 1 (continued)**

- $\geq 550$ nmol/L	33 (21%)
- $\geq 600$ nmol/L	8 (5%)
- No response	4 (2%)

SST = short synacthen test, ACTH = adrenocorticotrophic hormone, IM = intramuscular, IV = intravenous.

\*Others = related medical subspecialties: gastroenterology, allergy and immunology, pulmonology, nephrology, rheumatology.

\*\*More than one indication for performing SST.

**Table 2: SST protocol including testing both 30- and 60-min serum cortisol, n = 99\*.**

	Group A	Group B	Group C	Group D
SST result	70 (71%)	10 (10%)	13 (13%)	6 (6%)

Group A = Stimulated cortisol threshold reached at both 30 and 60 min.

Group B=Stimulated cortisol threshold not reached at either 30 or 60 min.

Group C=Stimulated cortisol threshold not reached at 30 min but reached at 60 min.

Group D = Stimulated cortisol threshold reached at 30 min but did not remain above the threshold at 60 min.

SST = short synacthen test.

\*Of 121 clinicians (75%) who tested both 30- and 60-min serum cortisol after ACTH injection as in Table 1, 99 responded to this question.

performing an SST. Clinicians ranked metabolic derangements including hypotension (78%), hyponatremia (65%), hypoglycemia (59%), and hyperkalemia (54%) as the typical reasons for performing an SST. Most physicians measured baseline serum cortisol as a part of their SST protocol.

Table 2 collates responses from clinicians who measured 30- and 60-min serum cortisol after ACTH injection. The results indicated that 13% of patients did not reach the peak cortisol at 30 min and attained a pass threshold only at 60 min.

Table 3 shows the correlation between the indications for performing the SST and physician specialty. Compared with other physicians, endocrinologists indicated hypoglycemia, a prior history of pituitary tumors, and hyperpigmentation as the primary reasons for conducting the test, and this result was statistically significant.

Table 4 shows the correlation between the SST protocol and physician specialty. A total of 83% of the endocrinologists performed 30- and 60-min serum cortisol after ACTH injection, whereas 62% of the internists followed this protocol. This contrast in practice was statistically significant.

Table 5 demonstrates the correlation between the SST protocol and the physician grade. The sample size was too small to draw any firm conclusions.

**Table 3: Correlation between the indications for SST\*\* and physician specialty.**

	Endocrinology (n = 66)	Internal medicine (n = 66)	Others* (n = 27)	P-value***
Hypoglycemia	53 (80%)	32 (48%)	14 (52%)	0.0004
History of pituitary tumor	42 (64%)	9 (14%)	3 (11%)	<0.0001
Visual field deficit	15 (23%)	3 (5%)	2 (7%)	0.0047
Hyperpigmentation	31 (47%)	16 (24%)	5 (19%)	0.0047

\*Others = related medical subspecialties: gastroenterology, allergy and immunology, pulmonology, nephrology, rheumatology.

\*\*More than one indication for performing SST.

\*\*\* Significant P-value <0.005.

SST = short synacthen test.

**Table 4: Correlation between the SST protocol and physician specialty.**

	Endocrinology (n = 66)	Internal medicine (n = 66)	Others* (n = 27)	P-Value
<b>Baseline serum cortisol tested as part of the SST protocol, n (%)</b>				
- Yes	62 (94%)	57 (87%)	26 (96%)	0.1156
- No	4 (6%)	9 (13%)	1 (4%)	
<b>Protocol after ACTH</b>				
- Both 30- and 60-min serum cortisol	55 (83%)	41 (62%)	25 (93%)	0.0039**
- 30-min serum cortisol only	3 (5%)	13 (20%)	2 (7%)	
- 60-min serum cortisol only	8 (12%)	8 (12%)	0	
- Any other combination	0	4 (6%)	0	

\*Others = related medical subspecialties: gastroenterology, allergy and immunology, pulmonology, nephrology, rheumatology.

\*\* Significant P-value <0.005.

ACTH = adrenocorticotrophic hormone, SST = short synacthen test.

**Table 5: Correlation between the SST protocol and physician grade (n = 158).**

	Consultant (n = 61)	Non-consultant (n = 97)	P-value*
<b>Baseline serum cortisol tested as part of the SST protocol, n (%)</b>			
- Yes	54 (88%)	90 (93%)	0.3925
- No	6 (10%)	6 (6%)	
- No response	1 (2%)	1 (1%)	
<b>Protocol after ACTH</b>			
- Both 30- and 60-min serum cortisol	48 (79%)	73 (75%)	0.0031
- 30-min serum cortisol only	2 (3%)	15 (16%)	
- 60-min serum cortisol only	11 (18%)	5 (5%)	
- Any other combination	0	4 (4%)	

ACTH = Adrenocorticotrophic hormone, SST = short synacthen test.

\* Significant P-value <0.005.

## Discussion

Our survey results showed similarities and differences between our single center<sup>1</sup> and the multicenter national practice.

Our survey did not indicate any baseline morning cortisol levels that most clinicians considered adequate for the integrity of the HPA axis and will refrain from conducting SST. In contrast to this observation, we have previously shown<sup>1</sup> that a baseline morning cortisol threshold of 226 nmol/L has a 93% positive predictive value for a normal SST. Yip et al.<sup>2</sup> and Watts et al.<sup>3</sup> have reported

identical results. The SST involves extensive planning and time for clinicians, patients, and nursing staff. Furthermore, the pharmacy and the laboratory costs are high. Therefore, clinicians should use targeted testing of SST in patients with a high pretest probability of HPA axis abnormality or with low baseline serum cortisol results.

Most clinicians (90%) performed the baseline serum cortisol testing as part of the SST protocol. This practice mirrors our institutional approach.<sup>1</sup> However, the utility of this baseline cortisol level on the test day is questionable, because the results are reviewed only after completion of the entire examination. Additionally, the assessment of an

intact HPA axis is based on the peak cortisol threshold reached instead of the baseline cortisol level. Given the limited clinical utility and pressure to conserve resources, clinicians should review this practice of determining baseline serum cortisol as part of the SST.

A total of 11% of the clinicians performed only the 30-min serum cortisol after the ACTH injection and did not check the 60-min serum cortisol. In this situation, basal cortisol results have some value if the cortisol change from baseline to 30 min is robust but remains below the pass threshold.<sup>1</sup> In this setting, clinicians should consider repeating the SST with the inclusion of a 60-min cortisol value.

A total of 7% of the respondents observed that cortisol peaked at 30 min but decreased below the pass threshold at 60 min. We, along with other researchers, have not observed such results.<sup>1,4–6</sup> Additionally, these results are higher than reported in similar studies.<sup>7,8</sup> Our current study is survey based and therefore is subject to recall bias. Additionally, the lack of proper understanding of the question, particularly among colleagues from different specialties, might have influenced these divergent results.

A total of 13% of the clinicians reported encountering cortisol levels below the pass threshold and peak cortisol levels being reached only 60 min after the ACTH injection. Other studies have reported similar results and have suggested that 60-min cortisol measurement is integral to the SST protocol.<sup>4–8</sup>

In sharp contrast to the findings of our institutional study,<sup>1</sup> we observed a significantly higher proportion of clinicians measuring the baseline ACTH nationally as a part of the SST. Elevated ACTH in patients who do not attain the peak cortisol threshold during the SST indicates primary adrenal insufficiency. We assume that many clinicians working at ambulatory care centers, or primary or secondary care institutions, had a pretest suspicion of primary adrenal insufficiency, thus supporting the measurement of baseline ACTH as part of the SST. Our hospital is a tertiary care referral center for neurosurgery with a substantial number of patients with pituitary disorders and prior pituitary surgery. In this scenario, we presume that the clinicians chose to omit ACTH and relied on the peak cortisol level reached with the SST to determine adrenal gland integrity.

Our study has several strengths. The participation of clinicians from a wide range of specialties and grades increased the power of our survey data. This survey, the first from our region, provides insight into the different SST protocols used in our area and the variations in practice among different grades and specialties. Therefore, this survey adds invaluable information to the literature.

Our survey also has some limitations. Because of its retrospective nature, it is subject to recall bias. A lack of clear understanding of the questions might have led to inaccurate answers, thus influencing our results.

## Conclusion

We conclude that clinicians should evaluate patients for other causes of metabolic derangements before performing an SST. They might consider checking the morning baseline

cortisol to triage patients who will need an SST. The 60-min serum cortisol should be part of the SST protocol to avoid any false positive findings. The results of this study support adoption of a nationally standardized protocol for SST.

## Source of funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The authors have no conflicts of interest to declare.

## Ethical approval

We conducted the study according to the guidelines outlined in the Declaration of Helsinki. The research committee of King Faisal Specialist Hospital & Research Centre approved the project, Ethics approval number 2211010, Ethics approval date 10 Jan 2021.

## Authors contributions

The authors declare the following contributions. Concepts and design: MIB, MR, and AB; data analysis: MB, NA, AB, and MR; table and figure preparation: MIB and NA; manuscript writing: MB and NA. All authors critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

## Acknowledgment

We thank the Saudi Commission for Health Specialties for facilitating the distribution of the survey to the physicians.

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**How to cite this article:** Butt MI, Alzuhayri N, Riazuddin M, Bakhsh AMK. The short synacthen test: Variations in methodology and protocols in KSA. *J Taibah Univ Med Sc* 2022;17(4):596–601.