

Preferred screening test for Cushing's syndrome screening

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Received date: August 10, 2020; **Accepted date:** August 20, 2020; **Published date:** August 31, 2020

Citation: Ahmed I. Siddiqi (Siddiqi AI), (2020) Preferred screening test for Cushing's syndrome screening J. Endocrinology and Disorders 4(1); DOI:10.31579/2640-1045/053

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Abstract

Background: In our practice 24 hours urine collection for free cortisol (24Hr UFC) and overnight dexamethasone suppression test (ONDST) are initial investigations to screen patients for hyper-cortisolism. I audited our practice to find our clinicians' and patients' choice of first screening investigation for hyper-cortisolism.

Method & material: Electronic and paper medical records of patients who underwent 24Hr UFC and/or ONDST at our hospital over previous consecutive twenty four months were examined. 62 such patients were identified but 12 patients were excluded from analysis. We tried to contact 30 patients over consecutive 48 hours over the phone who underwent both 24Hr UFC and ONDST. We managed to contact 18 patients and asked them two study questions.

Data & results: 33 (66%) patients were female and 17 (33%) were male. 20 (40%) had 24Hr UFC alone and 30 (60%) patients had both. In total 80 such investigations completed 30 being ONDST and 50 24hr UFC. 53 (66%) of the investigations were requested by Endocrinologists, 21 (26%) by Hospital General Physicians and 6 (8%) by General practitioners (GP). For UFC 10 (20%) were true positive, 31 (62%) were false positive, 6 (12%) were true negative and 0% false negative. 3 (6%) 24Hr UFC samples were not collected properly and were not processed for results. Out of the total false positives (31 patients), 6 (19.3%) cases were of alcohol excess, 4 (13%) of depression, 3 (9.7%) of inhaled steroids and 1 (3.2%) of sleep apnea. For the ONDST 7 (23.3%) true positive, 4 (13.3%) false positive 19 (63.4%) true negative and 0% false negative. All 18 patients contacted over the phone answered both questions. 16 preferred ONDST over 24Hr UFC, 1 patient had no preference and 1 patient preferred 24Hr UFC over ONDST.

Conclusion: Patients overwhelmingly preferred ONDST as first screening test in contrast to physician's choice of 24Hr UFC.

Key words: cushing's syndrome; cushing's disease; pseudo-cushing's; cushing's screening; overnight dexamethasone suppression test; 24 hours urinary free cortisol; patient preference

Introduction

Cortisol is produced and secreted by adrenal glands under stimulatory effect of adrenocorticotropin hormone (ACTH) of pituitary gland. ACTH in turn is regulated by Corticotropin releasing hormone (CRH) of hypothalamus. The stimulatory effect of ACTH is balanced by negative feedback of cortisol circulating in peripheral blood (1). This state of dynamic equilibrium is often called adreno-cortical axis. Cortisol remains the main hormone with widespread systemic effects in this axis and remaining hormones of this axis have either minimal or no known systemic effects.

This dynamic equilibrium is pathologically disturbed either by uncontrolled production of ACTH which then leads to excessive cortisol production (Cushing's disease) or ACTH independent uncontrolled production of cortisol due adrenal gland pathology (Cushing's syndrome). At times, CRH/ACTH can be produced from sources other than pituitary gland (ectopic ACTH/CRH production) and can still stimulate adrenal glands to produce excessive uncontrolled amounts of cortisol resulting in hyper-cortisolism (2). For the sake of this manuscript I'll use term

Cushing's syndrome to cover all of these (Cushing's disease, ectopic CRH/ACTH production and Cushing's syndrome).

During these pathological states usual stimulatory and inhibitory effects are no longer functional and cortisol production is increased by several folds exposing tissues to these excessively high levels of cortisol.

Clinical presentation in these patients can be variable. Pseudo-Cushing's is the term used for patient with excessive cortisol production and clinical features of Cushing's syndrome with potentially reversible precipitating factors. Excessive alcohol consumption, depression and sleep apnea are common precipitating factors. The excessive cortisol production is usually continuous but can be cyclical termed as cyclical Cushing's. These episodes of excessive cortisol production are variable in duration and severity. As expected the diagnosis of this type of Cushing's disease is even more challenging. Excessive cortisol production in these patients can lead to metabolic changes including hyperglycemia and puts patients at risk of complications of hyperglycemia like diabetic ketoacidosis and hyperosmolar hyperglycemic state (3). Patients with Cushing's disease of pituitary origin can present with effects of pituitary adenoma affecting

other hormones of pituitary gland or its mass effect on surrounding structures especially on optic chiasm affecting visual fields (4) (5).

Biochemical investigations sit at the heart of diagnostic work up for Cushing's syndrome. Imaging studies are required to localize the abnormality to help plan the management strategy. In our center twenty-four hours urine free cortisol (24Hr UFC) and overnight dexamethasone suppression test (ONDST) were the two most commonly employed tests for screening patients for hyper-cortisolism. Most patients would have only one screening test and only if it is abnormal or the results are not decisive further investigations would be carried out. Localization investigations are generally carried out if these screening tests confirm biochemical evidence of hyper-cortisolism. I audited our practice of screening such patients and also collected data on patients' preference of a screening test. We wanted to see if clinicians' choice matches with patients' choice of investigation.

Method and material

I retrospectively collected data from paper and electronic medical records of adult patients (over 18 years old) who underwent screening for hyper-cortisolism over previous consecutive twenty-four months at our hospital. Patients were identified by screening laboratory investigation data of all adult patients of our hospital who had any of the screening tests for hyper-cortisolism - 24Hr UFC, ONDST, MCL (midnight cortisol level) and/or SCL (Salivary cortisol level). Requesting physicians' details were recorded from investigation request form and paper medical records. All patients above 18 years of age who had investigations sent to our Trust's laboratory (both from hospital and community) for hyper-cortisolism screening were included. Once the patients were identified their paper medical records were used to collect remaining data. Some patients underwent 24Hr UFC more than once. I included their first 24Hr UFC requests and result for this audit. Since I was auditing our Trust practice I did not include those patients who had their screening investigations completed elsewhere and then presented to our Trust for further management of their condition.

I looked at clinical notes of 62 patients who underwent the Cushing's screening tests. I primarily looked at the laboratory investigations

performed for screening these patients for hyper-cortisolism. 12 patients were excluded from this study as they underwent these investigations not for hyper-cortisolism screening.

I tried to contact those 30 patients over the phone who had both 24Hr UFC and ONDST. I managed to contact 18 patients. I completed collecting this data over phone over two days. All these patients agreed to participate in the study. 4 patients required interpreter and one of their family members helped with this. The questions were clearly read out to them and I confirmed that they understood those questions well. I did not ask the reason for them to prefer one of the tests over the other but all the patients voluntarily explained the reason while answering these two questions. Their answers were recorded on electronic pro forma straight away. I could not manage to contact the remaining 12 patients who had both 24Hr UFC and ONDST within these two days. We asked them two questions: 1) which of the two tests they found was easier for them? 2) Which of the two they would like to have done if they were to take one of these tests again?

Data Analysis and results

50 patients fulfilled the criteria for this audit. 33 (66%) patients were female and 17 (33%) were male. 20 (40%) had 24Hr UFC alone and 30 (60%) patients had both. None of the patients had any other screening tests. There were total 80 such investigations completed 30 being ONDST and 50 24hr UFC. 56 (70%) of the investigations were requested by Endocrinologists (consultants, specialist registrars, specialist nurses), 21 (26%) by Hospital General Physicians (clinicians of all grades other than Endocrinologists) and 3 (4%) by General practitioners (GP). The 1 ONDST completed by GP was advised over the phone by specialist registrar. Most of the investigations requested by clinicians other than Endocrinologists were requested in acute medical unit or Emergency department when these patients presented with other medical conditions and Cushing's screening investigations were requested. Almost all the investigations requested by Endocrinologists were requested in clinic setting when patients were attending clinic for another Endocrinology disorder or GP had referred these patients for screening. (Table 1)

	Endocrinologist	Hospital Doctors	GP	Total for each investigation
24hr UFC	54% (27)	42% (21)	4% (2)	50 (100%)
ODST	96% (29)	0% (0)	4% (1)	30 (100%)
Total requests	70% (56)	26% (21)	4% (3)	80 (100%)

Table 1: Investigations requested by each specialist

For UFC 10 (20%) were true positive, 31 (62%) were false positive, 6 (12%) were true negative and 0% false negative. 3 (6%) 24Hr UFC samples were not collected properly. In our audit there were 10 patients who were eventually diagnosed with Cushing's syndrome. All of those patients had their 24Hr UFC levels assessed and all of those showed hyper-cortisolism on their results. Since all these 10 patients of Cushing's syndrome were picked up by 24Hr UFC the sensitivity of the test in this study is 100%. All these 10 patients had more than one 24Hr urine collection but I included only their first collection details for this audit. 100% sensitivity is ideal for a screening test and 24Hr UFC fulfilled this criteria in our study. The true negative rate of 24Hr UFC in my study is a bit less than what is reported in literature. The lower the cut off value is set for a screening test the higher is its sensitivity but it can compromise

its specificity. In our laboratory the normal range for 24Hr UFC is set at <150 nmol/day. Patients with values three times the upper normal limit are likely to be suffering from Cushing's syndrome and patients with a value less than three times the upper normal limit but higher than 150 nmol/day are investigated further. This value of 150 nmol/day is perhaps lower than many studies and thus reduces true negative results. Approximately two third of the patients had false positive results. This is due to lower cut off value of laboratory results and to some extent incomplete pre-test screening. It is interesting to note that samples could not be processed for 3 patients. In all these cases the samples submitted were not collected properly. The urine volume was too less and patients confirmed that collection had been less than accurate when contacted over

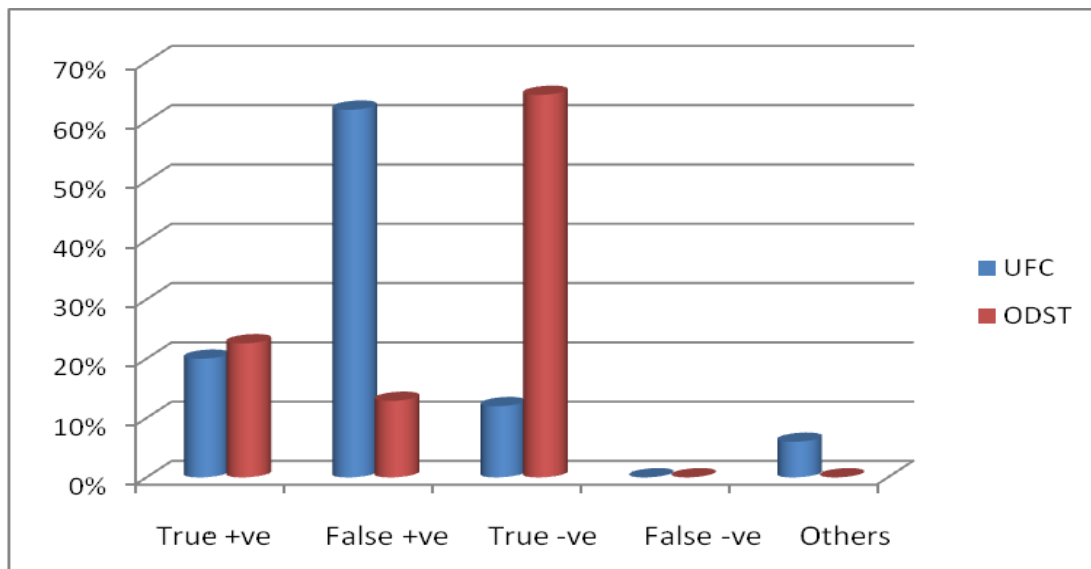
the phone. This points to challenges some of the patients face while completing this particular investigation.

For the ONDST 7 (23.3%) true positive, 4 (13.3%) false positive 19 (63.4%) true negative and 0% false negative. Sensitivity was 100% also for ONDST. 7 of those 10 patients who were later diagnosed to have Cushing’s syndrome underwent ONDST. All these 7 patients failed to suppress cortisol to less than 50 nmol/l. The cut off value for ONDST is <50 nmol/l in our laboratory and anyone who fails to suppress cortisol to <50 nmol/l undergoes further investigations for hypercortisolism. The false positive rate for ONDST is far less than 24Hr UFC in this study. One of the reasons may have been that all the ONDST were requested by specialists who completed the pre-test screening properly and only suitable patients underwent the test. Also, all the patients included in this audit managed to complete the test properly in the first go. It could have been that Endocrinologists would have got more time to explain the procedure in detail to patients in their clinics who then managed to complete the test properly. Compared to 24Hr UFC where a significant

number of these investigations were requested by General Physicians it is very likely that they would not have got time to explain things in detail to patients who may have seen patients in a general medical ward even in A&E. Since all the ONDST were requested in clinics by specialists these patients are likely to be otherwise healthy and would not have stress related excessive cortisol production. Many of the 24Hr UFC requested by clinicians other than Endocrinologists were requested while patients were attending hospital for another illness and were likely to have illness related stress induced high cortisol levels. This must have contributed to high false positive results in patients undergoing 24 Hr UFC. Two thirds of the patients had true negative results with ONDST. This figure is a lot higher than 24Hr UFC results (table 2). Once again the pre-screening assessment completed by Endocrinology specialists would have helped with this result to ensure only suitable patients undergo this test. Interestingly none of the patients had false negative results. This is encouraging to know that both screening tests fulfilled the essential criteria of a screening test that neither of the two missed any of the patients of Cushing’s syndrome.

	24Hr Urine Free Cortisol	Overnight Dexamethasone Suppression Test
True positive	20% (10)	23.3% (7)
False positive	62% (31)	13.3% (4)
True negative	12% (6)	63.4% (19)
False negative	0% (0)	0% (0)
Others	6% (3)	0% (0)

Table 2: Breakdown of results on each investigation



17 of the 50 24Hr UFC investigations were falsely high with no obvious factors to cause cortisol hypersecretion. Most of these investigations were requested by Endocrinologists and they documented in the notes that there were no obvious cause for high cortisol levels in urine. 14 of the 50 24Hr UFC investigations were carried out on patients who had obvious factors to have hyper-cortisolism. These factors are known to directly cause

cortisol hypersecretion other than Cushing’s syndrome and many of these cause pseudo-Cushing. Patients with obvious pseudo-Cushing’s factors ideally should not have these screening tests performed and these factors such be controlled prior to running these screening tests. All these patients who had these known factors of cortisol hyper secretion were requested by clinicians other than Endocrinologists. There is always a possibility that patients with these pseudo-Cushing’s factors may develop Cushing’s

syndrome and in presence of appropriate clinical signs and symptoms these screening tests may have to be run. Such a decision should be made by a specialist Endocrinologist who can then interpret these investigations accordingly. This information was not clearly mentioned in patients' records and the screening tests were requested in view of presence of "clinical features of Cushing's syndrome" in these patients. For the sake of this audit we considered these results as false positive results when factors known to cause cortisol hyper secretion were present in such patients. Out of these false positives 6 (19.3%) cases were due to alcohol excess, 4 (13%) due to depression, 3 (9.7%) were using inhaled steroids, 1 (3.2%) with sleep apnea and 17 (54.8%) had no obvious cause for high UFC. I recommend clinicians other than Endocrinologists should consider screening patients for Cushing's syndrome but should make sure that the investigations are run in suitable patients. Abnormal results in unsuitable

patients not only increases cost of running these investigations but also cause unnecessary anxiety among patients.

For ONDST false positive rate was much less. Out of the false positive 1 (25%) case was due to alcohol excess and 1 (25%) was due to depression (table 3). One of the reasons could be that all ONDST were requested by specialist Endocrinologists who screened patients appropriately. The patient with depression had recently been diagnosed with depression and this information was not available to endocrinologist at the time of requesting this test. The patient with excessive alcohol consumption denied consuming alcohol at the time of requesting the test. This information was later shared by patient's relative once the patient had to be admitted to hospital for another reason. At that time patient informed clinical staff about his excessive alcohol drinking.

	UFC False +ve	ODST False +ve	Comments
Alcohol consumption	19.3% (6)	25%	Half the patients with false +ve results in both the groups had factors known to cause false +ve results.
Steroids (inhaled/oral/topical)	9.7% (3)	0	
Sleep apnea	3.2% (1)	0	
Depression	13.0% (4)	25%	
None of the above/Remaining	54.8% (17)	50%	

Table 3: Factors which can cause false +ve results.

30 patients underwent both 24Hr UFC and ONDST. 18 patients could be contacted and response rate to participate in the survey was 100%. 11 of these patients were females and 7 were male. The survey was designed to be short, simple and focused with only two questions. The results show that almost 90% of the patients clearly preferred ONDST over 24Hr UFC. All female patients in this survey preferred ONDST over 24Hr UFC. Almost all the patients associated the word "difficult" with 24Hr UFC. 1 patient had no specific preference as long as the results are reliable and the medical condition is properly diagnosed he would go ahead with any of the investigations his clinicians chooses for him. The only patient in this survey who preferred 24Hr UFC over ONDST was needle phobic and wanted to avoid the needle prick. Since the survey did not ask the reason for preference of a particular investigation their comments were recorded as free text on the pro forma. Collection of urine during the day and night in big bottles and dropping off to surgery or hospital was all too complex for patients compared to a simple pill at night and a blood test the following morning.

Discussion

A screening test is expected to pick up all the cases with a particular condition. A good screening test should have a high sensitivity. The test should be simple and easy to be performed, ideally on outpatient basis and results should be easy to interpret (6). There is no single test which fulfils all these criteria (7) however, high sensitivity is probably the most important criteria so that none of the patients with that particular condition are missed by a screening test. Both these investigations fulfil these criteria for a good screening test.

My data suggests that there was clinical bias among clinicians in choosing the first screening test for patients suspected to have hyper-cortisolism. It was encouraging to see that a significant number of screening tests were requested by clinicians who were not Endocrinologists. With an increase in number of patients with obesity and metabolic syndrome presenting to

medical services it is important that such patients are screened by clinicians other than Endocrinologists so that such patients could be diagnosed as soon as possible and appropriately treated. Having said that, it is important to see that 24 Hr UFC was their investigation of choice as first line screening investigation for such patients. Only Endocrinologists selected any of the other screening tests although, they also requested 24 Hr UFC in a significant number of patients. Since all the screening tests have very high sensitivity and there is not much difference among these tests there is nothing wrong in choosing anyone of these but the patient choice survey shows an overwhelming preference for ONDST compared to 24Hr UFC. ~ 90% patients chose ONDST over 24Hr UFC. The only patient who chose 24Hr UFC was needle phobic and wanted to avoid a needle prick.

In conclusion the ONDST can be used reliably as first line screening test. It is easier to do for both patient and laboratory. Furthermore, it is more cost effective. However if Cushing's syndrome is highly suspected clinically and ONDST is not suitable for that patient we may proceed to 24 Hr UFC test. I am not omitting the 24Hr UFC test but I am making it as second line. Patients found ONDST much easier to perform and chose that as their preferred first line investigation for screening.

I recommend that patients should have the option of selecting the screening test of their choice. Clinicians should have a discussion with patients about the available screening tests and arrange the one which patient prefers to undertake. Our survey suggests that majority of patients preferred ONDST over all other available screening tests. There should be continuous education and discussion on the subject with colleagues of other specialties and general practitioners who are actively involved in investigating patients to screen for hyper-cortisolism.

Conflict of interest: I declare I have no conflict of interest to declare in publication of this study.

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DOI:10.31579/2640-1045/053

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