Thieme

Comparison of 1 mg versus 2 mg Dexamethasone Suppression Test in Patients with Obesity

Authors
Sandrine Andrea Urwyler[1, 2*], Nina Cupa[1, 2*], Mirjam Christ-Crain[1, 2]

Affiliations
1 Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Switzerland
2 Department of Clinical Research, University Hospital Basel, Switzerland

Key words
metabolic syndrome, obesity, dexamethasone suppression test, Cushing's syndrome

received 11.04.2017
accepted 29.08.2017

Bibliography
DOI https://doi.org/10.1055/s-0043-119128
Published online: 29.9.2017
Horm Metab Res 2017; 49: 854–859

ISSN 0018-5043

Correspondence
Sandrine Urwyler, MD
University Hospital
Petersgraben 4
4031 Basel
Switzerland
Tel.: +41/61/265 25 25, Fax: +41/61/265 51 00
sandrine.urwyler@usb.ch

ABSTRACT

In this study, we compared the 2 mg dexamethasone suppression test (DST) with the gold-standard 1 mg DST in obese patients in order to reduce the false-positive rate for Cushing's syndrome (CS). The primary endpoint was the comparison of serum cortisol levels after 1 mg versus 2 mg DST in patients with a BMI >30 kg/m^2 and at least one additional feature of the metabolic syndrome. Secondary endpoints were comparison of salivary cortisol and ACTH levels, respectively. Fifty-four obese patients were included. Median serum cortisol levels after 1 mg DST and 2 mg DST were similar [28 nmol/l (20; 36) vs. 28 nmol/l (20; 38), p = 0.53]. Salivary cortisol was 8.2 nmol/l (4.7; 11.7) after the 1 mg DST vs. 6.7 nmol/l (4.2; 9.5) after the 2 mg test, p = 0.09. ACTH levels were higher after the 1 mg DST compared to the 2 mg DST [10.0 pg/ml (7.6; 10.7) vs. 5.0 pg/ml (5.0; 5.1), p < 0.0001]. The false positive rate after the 1 mg DST was 14.8 % (n = 8) and was reduced to 11.1 % (n = 6) after the 2 mg DST. All non-suppressors (n = 8) had type 2 diabetes and most of them took a medication interacting with cytochrome P450 3A4 (CYP3A4). In individuals with obesity, the 2 mg DST was not superior to the 1 mg DST in regard to serum cortisol levels. However, in some patients, particularly with poorly controlled diabetes or medication interacting with CYP3A4 and without adequate suppression after the 1 mg DST, the 2 mg DST might prove helpful to reduce the false-positive rate for CS.

ClinicalTrials.gov Number: NCT02227420

Introduction

Obesity is a pandemic with increasing prevalence worldwide. Prevalence has more than doubled from 1980 until 2014. In 2014, over 600 million people worldwide were obese [1]. Visceral obesity is also the most common clinical manifestation of Cushing's syndrome (CS) and other components of the metabolic syndrome such as type 2 diabetes mellitus (DM), dyslipidemia and hypertension also occur with CS [2]. However, only in a minority of obese patients the underlying cause of obesity is CS [3]. In clinical practice a differentiation of patients with obesity (with metabolic syndrome) due to CS from patients without CS is crucial.

The 1 mg overnight dexamethasone suppression test (DST) is a well-known, widely used, simple and established screening test to rule out CS [4, 5]. However, in obese subjects an increased number of false positive test results has been reported, previously even up to 50 % [6]. Using a cut-off level of 50 nmol/l revealed a false-positive rate of up to 16 % in obese individuals, in contrast to only 1 % false positive test results in normal weight people [5, 7]. This might be due to an elevated cortisol production and secretion in obesity [8, 9]. The lack of adequate cortisol suppression in obesity is also described [9] as a marker of hypothalamic-pituitary-adrenocortical axis (HPA) hyperactivity [10]. Furthermore the increased distribution volume of dexamethasone in obese individuals might be another reason for the lack of cortisol suppression. Therefore, in obese individuals the use of a higher dose of dexamethasone has been recommended to reduce false positive test results [11].

The overnight 2 mg DST would be an easy and feasible way for a better suppression of cortisol levels in obese individuals. Howev-

* Equally contributing first authors

er, so far, only one study [12] investigated the value of the 2 mg DST. The comparison of the 2 mg DST with the 1 mg DST was done only in only eight patients showing a reduction of the false-positive rate from 8 % to 2 % after the 2 mg DST. We herein aimed to compare the 1 mg and the 2 mg DST in a larger group of patients with obesity.

Subjects, Materials, and Methods

Subjects

We recruited 54 patients from our obesity clinic at the department of endocrinology, diabetology, and metabolism at the University Hospital of Basel. Inclusion criteria were age 18–80 years, body mass index (BMI) > 30 kg/m^2, and at least one additional feature of the metabolic syndrome (hypertension, dyslipidemia, DM, prediabetes). Exclusion criteria were medication with glucocorticoids, known CS, pregnancy, breastfeeding or other factors influencing cortisol levels such as evidence of an acute disease or chronic consumption of alcohol. The exclusion of CS was confirmed by lack of progression of "specific" clinical signs and symptoms in the follow-up visits (e. g., striae rubrae, proximal muscle weekness, easy bruising, arterial hypertension, DM, osteoporosis) and a normal 24-h urinary free cortisol. The study protocol was approved by the ethics committee of Northwestern Switzerland (EKNZ) and Swissmedic. The study was conducted in accordance with ICH-GCP. All patients gave their informed and written consent to the study.

Design and procedure

Patients were seen four times for study visits, that is, for a screening visit, a baseline visit, a visit after intake of 1 mg dexamethasone orally at midnight (taking place the day after the baseline visit), and a visit after intake of 2 mg dexamethasone orally at midnight (with a time delay of at least two weeks as wash-out period for dexamethasone), respectively. According to the Endocrine Society Guidelines 2008 the cut-off level of serum cortisol < 50 nmol/l (1.8 µg/dl) was used to determine normal cortisol suppression and exclude CS [13]. At the screening visit eligibility criteria were checked, informed consent obtained, and medical history collected. A study doctor performed a clinical examination and instructed patients about the study schedule. At the baseline visit, blood and saliva samples were taken after an overnight fast to determine serum cortisol, ACTH, and salivary cortisol and to assess clinical parameters. At visit one, the patients followed the same procedure after the intake of 1 mg dexamethasone orally at midnight, at visit two, after the intake of 2 mg dexamethasone orally at midnight, respectively.

Blood sampling and salivary cortisol

At the baseline visit, visit one (after 1 mg DST) and visit two (after 2 mg DST) blood samples were collected. The sample to assess ACTH was collected on ice and was immediately brought to the laboratory. Cortisol was measured with an electrochemiluminescense immunoassay (Elecsys Cortisol Test; Roche Diagnostics GmbH, Mannheim, Germany) with an intra-assay coefficient of variation of 1.0–1.7 %, and inter- assay coefficient of variation of 1.4–2.8 %. ACTH was determined with chemiluminescence immunoassay (ACTH Immulite, Siemens Healthcare Diagnostics Products Ltd., Gwynedd, UK), with a reference range of < 46 pg/ml.

Salivary cortisol was collected at each visit by chewing for at least 5 min on cylindrical cotton swab [Salivette® Cortisol (Art.-Nr.

▶ **Table 1** Baseline characteristics and parameters of all patients.

Characteristics	Patients (n = 54)
Age (years)	54 (46; 64)
Ethnicity, Caucasian	50 (92.6 %)
Weight (kg)	106.5 (96.8; 123.3)
Height (cm)	172 (164; 175)
BMI (kg/m^2)	35.5 (33.3; 41.0)
Waist circumference (cm)	119 (112; 129)
Waist to hip ratio of males	1.06 (1.01; 1.08)
Waist to hip ratio of females	0.92 (0.87; 0.96)
Sex, female	28 (51.9 %)
Hypertension	41 (75.9 %)
Dyslipidemia	43 (79.6 %)
Diabetes mellitus type 2	34 (63.0 %)
Impaired glucose tolerance	11 (20.4 %)
Blood pressure systolic (mmHg)	143 (129; 152)
Blood pressure diastolic (mmHg)	86 (77; 92)
Heart rate (bpm)	79 (72; 87)
Body temperature (°C)	36.4 (36; 36.8)
Hemoglobin (g/l)	144 (134; 152)
Leucocytes (x 10^9/l)	7.07 (6.31; 8.96)
Platelets (x 10^9/l)	244 (203; 274)
HbA1c (mmol/mol)	46 (40; 65)
Cholesterol (mmol/l)	4.59 (3.55; 5.20)
LDL-Cholesterol (mmol/l)	2.38 (1.82; 3.10)
HDL-Cholesterol (mmol/l)	1.12 (0.95; 1.41)
Triglyceride (mmol/l)	1.77 (1.30; 2.43)
C-Reactive protein (mg/l)	3.5 (2.1; 7.0)
Basal cortisol (nmol/l)	454 (373; 549)
Basal salivary cortisol (nmol/l)	19.0 (14.9; 26.0)
Basal ACTH (pg/ml)	26.5 (18.5; 33.0)
Oral antidiabetic drugs	28 (51.9 %)
Insulin	19 (35.2 %)
GLP-1 analogue	11 (20.4 %)
Antihypertensive medication	38 (70.4 %)
Statin	26 (48.1 %)
NSAID	3 (5.6 %)
Antidepressant drugs	9 (16.7 %)
Antipsychotic drugs	0 (0 %)
Anticonvulsive drugs	4 (16.7 %)
Oral contraceptive pill	1 (1.9 %)

Data are expressed as median (IQR) or number (%).

▶ **Table 2** Baseline characteristics and parameters of suppressors and non-suppressors after the 1 mg DST.

Characteristics	Suppressors (n = 46)	Non-suppressors (n = 8)	p-Value
Age (years)	53 (46; 63)	62 (56; 68)	0.07[1]
BMI (kg/m^2)	36.0 (33.3; 41.0)	35.1 (32.5; 41.3)	0.68[1]
Sex, female	26 (56.5 %)	2 (25 %)	0.14[2]
Hypertension	33 (71.7 %)	8 (100 %)	0.18[2]
Dyslipidemia	36 (78.3 %)	7 (87.5 %)	1.00[2]
Type 2 diabetes mellitus	26 (56.5 %)	8 (100 %)	< 0.05[2]
HbA1c (mmol/mol)	44 (39; 62)	58 (51; 72)	< 0.05[1]
Cholesterol (mmol/l)	4.65 (3.66; 5.33)	3.97 (3.50; 4.80)	0.12[1]
LDL-Cholesterol (mmol/l)	2.39 (1.84; 3.14)	2.37 (1.43; 2.65)	0.54[1]
HDL-Cholesterol (mmol/l)	1.16 (1.02; 1.45)	0.87 (0.63; 1.28)	0.05[1]
Triglyceride (mmol/l)	1.75 (1.32; 2.43)	1.92 (1.00; 2.64)	0.95[1]
C-Reactive protein (mg/l)	3.9 (1.8; 7.0)	2.8 (2.2; 7.5)	0.90[1]
Basal Cortisol (nmol/l)	444.0 (368.0; 524.0)	568.5 (418.8; 644.5)	0.06[1]
Basal salivary cortisol (nmol/l)	18.8 (15.1; 25.5)	24.3 (12.7; 27.5)	0.86[1]
Basal ACTH (pg/ml)	26.7 (18.0; 33.2)	23.5 (19.2; 29.4)	0.60[1]
Statin	19 (41.3 %)	7 (87.5 %)	< 0.05[2]
Insulin	14 (30.4 %)	7 (87.5 %)	< 0.01[2]
GLP-1 analogue	7 (15.2 %)	4 (50 %)	0.01[2]

Data are expressed as median (IQR) or number (%). p-Value was calculated with Mann–Whitney U-test[1] or Fisher's exact-test.[2]

51.1534.500) from Sarstedt AG & Co, Nümbrecht]. The patients were instructed to appear fasted, without teeth brushing at baseline visit and after the intake of dexamethasone to not influence the result of the salivary cortisol levels. All parameters were measured in the central laboratory of our hospital.

Study hypothesis

The hypothesis of this study was that in obese individuals serum cortisol levels after the 2 mg DST are lower compared to the 1 mg DST.

Endpoints

The primary endpoint of this study was the comparison of morning serum cortisol levels after the 1 mg DST and the 2 mg DST. Secondary endpoints were comparisons of morning salivary cortisol and ACTH after the 1 mg DST and the 2 mg DST.

Statistics

Discrete variables were expressed as counts (percentage) and continuous variables as medians (interquartile range) if not stated otherwise. For two group comparisons with paired data we used the Wilcoxon–Mann–Whitney U-test. Unpaired two-group comparisons were performed by Mann–Whitney U-test in continuous variables and Fisher's exact test in categorical variables. Testing was two-tailed, and p-values < 0.05 were considered statistically significant. All data were calculated with GraphPad Prism®, Version 6 for Windows (GraphPad Software, San Diego California, USA).

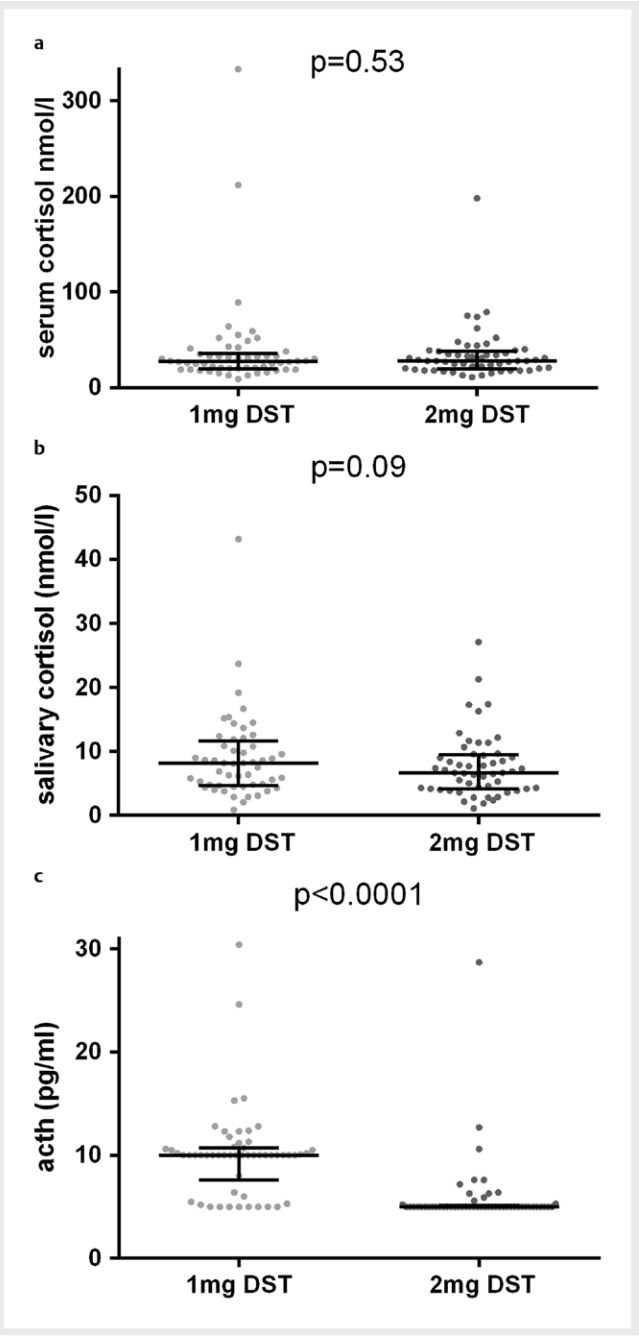
Results

The median age of all patients was 54 years (46; 64) with a median BMI of 35.5 kg/m^2 (33.3; 41.0). Twenty-eight were females (51.9 %). Forty-one (75.9 %) suffered from hypertension, 43 (79.6 %) from dyslipidemia, 34 (63.0 %) from DM, and 11 (20.4 %) had an impaired glucose tolerance. A detailed description of all baseline characteristics is reported in ▶ **Table 1.**

Serum cortisol levels after 1 mg DST and 2 mg DST in all 54 patients were similar [median (IQR) 28 nmol/l (20; 36) vs. 28 nmol/l (20; 38), p = 0.53]. Salivary cortisol levels after the 1 mg DST were 8.2 nmol/l (4.7; 11.7) as compared to 6.7 nmol/l (4.2; 9.5) after the 2 mg DST, p = 0.09. ACTH levels were higher after the 1 mg DST compared to the 2 mg DST [median (IQR) 10.0 pg/ml (7.6; 10.7) vs. 5.0 pg/ml (5.0; 5.1), p < 0.0001] (▶ **Table 2**, ▶ **Fig. 1a–c**).

Eight of the 54 patients (14.8 %) did not suppress adequately [median serum cortisol 62 nmol/l (53; 181)] after the 1 mg DST. In 6 of these non-suppressors, the 2 mg DST also did not lead to adequate suppression of cortisol [median (IQR) 62 nmol/l (52; 242)]. In 2 of these non-suppressors (3.7 %), the 2 mg DST showed an adequate suppression (< 50 nmol/l) to 48 nmol/l and 29 nmol/l, respectively (▶ **Table 3**). Consequently, the 2 mg DST reduced the false positive rate from 14.8 % to 11.1 %, p = 0.78.

All non-suppressors after the 1 mg DST (n = 8) suffered from DM, hypertension and had higher HbA1c-levels in comparison to the suppressor group. Seven out of eight patients were treated with at least one medication interacting with cytochrome P450 3A4 (CYP3A4) (e. g., statin). For detailed description see ▶ **Table 3**.



▶ **Fig. 1** **a**: Serum cortisol levels after 1 mg and 2 mg DST: Comparison of cortisol levels after the 1 mg overnight dexamethasone suppression test (DST) and the 2 mg DST using the Wilcoxon–Mann–Whitney U-test in patients with obesity (n = 54). Error bars show median and IQR. **b**: Salivary cortisol levels after 1 mg and 2 mg DST: Comparison of salivary cortisol levels after the 1 mg DST and the 2 mg DST using the Wilcoxon–Mann–Whitney U-test. Error bars show median and IQR. **c**: ACTH levels after 1 mg and 2 mg DST: Comparison of ACTH levels after the 1 mg DST and the 2 mg DST using the Wilcoxon–Mann–Whitney U-test. Error bars show median and IQR.

Discussion

The main finding of our study is that serum cortisol levels in obese individuals are similar after the 1 mg and the 2 mg DST. Second, based on serum cortisol levels false positive test results could only be reduced from 14.8 % to 11.1 % by using the 2 mg DST. We found a trend towards a better suppression of salivary cortisol levels after the 2 mg DST compared to the 1 mg DST. However, there exist to date no validated cut-off levels for salivary cortisol after DST for Cushing's diagnostics making the use of salivary cortisol difficult with regard to this research question.

When using the DST for Cushing's diagnostic a high sensitivity is warranted in order not to miss patients with CS. Nevertheless, in obese individuals false positive test results are more frequent compared to normal weight people [14]. Several studies have reported a high false positive rate in individuals with obesity using the 1 mg DST [7, 12]. Ness-Abramof et al. [7] reported a false positive rate of 15.1 % after the 1 mg DST in patients with obesity, whereas another study group reported a false positive rate of only 1.1 % after the 1 mg DST, however using a high cut-off of < 140 nmol/l in 90 overweight patients with poorly controlled DM [15].

A test with just as a high sensitivity but a better specificity compared to the 1 mg DST would be helpful to avoid unnecessary further evaluation of patients with obesity. An increase of the dexamethasone dose in individuals with obesity has been thought to improve the specificity of the test [11]. Therefore, the 2 mg DST was suggested [12] as an easy, feasible test leading to more accurate test results in patients with obesity. Indeed, preliminary data in 8 patients with obesity show a reduction of the false positive rate from 8 % after the 1 mg DST to 2 % after the 2 mg DST.

We could not entirely confirm this former results, as we only found a reduction of the false positive rate from 14.8 % to 11.1 %, p = 0.78 (only two individuals showed a better suppression after the 2 mg DST) by using the 2 mg DST in a larger cohort of obese individuals.

Although serum cortisol levels were nearly identical after either test, the 2 mg DST tended for a better suppression of salivary cortisol levels, even though missing statistical significance. One reason for the slightly different comportment of serum and salivary cortisol might be that salivary cortisol measures only the free cortisol fraction independent from corticosteroid binding globulin and therefore is the more sensitive parameter than serum cortisol [16]. Consequently, salivary cortisol levels after the 1 mg DST has been described as a sensitive marker to exclude CS with similar sensitivity and specificity as the midnight salivary cortisol [16]. However, so far there is still no validated cut-off level for normal suppression of salivary cortisol after the DST and we therefore do not recommend the measurement of salivary cortisol levels after the DST, as we do not see any benefit yet.

In addition, ACTH levels after the 2 mg DST were significantly lower compared to after the 1 mg DST ($p < 0.0001$). This likely reflects a stronger negative feedback of the 2 mg DST compared to the 1 mg DST. A dose-response suppression of ACTH level has already been shown by Pasquali et al. [10] and implied a normal central feedback regulation on patients with obesity. However, similarly to salivary cortisol we also see no benefit in routinely measuring ACTH levels after DST.

Importantly, two of the 8 patients who had a cortisol level > 50 nmol/l after the 1 mg DST (defined as non-suppressors), had a suppressed serum cortisol below the threshold of 50 nmol/l after the 2 mg DST. Thus, the false-positive test results were reduced

▶ **Table 3** Clinical and biochemical profile of non-suppressors (n = 8) after the 1 mg DST.

Entry	Sex	Age	BMI (kg/m²)	Diagnosis	Basal cortisol (nmol/l)	Cortisol after 1 mg DST (nmol/l)	Cortisol after 2 mg DST
1	M	64	43.9	DM, Hyp, Lip	592	59	75
2	F	60	35.3	DM, Hyp, Lip	668	333	79
3	F	66	42	DM, Hyp	662	52	52
4	M	68	34.8	DM, Hyp, Lip	499	212	198
5	**M**	**59**	**33.5**	**DM, Hyp, Lip**	**553**	**89**	**48**
6	**M**	**55**	**31.8**	**DM, Hyp, Lip**	**392**	**55**	**29**
7	M	37	32.1	DM, Hyp, Lip	308	64	74
8	M	73	39.2	DM, Hyp, Lip	584	52	62

The two patients, who suppressed after the 2 mg dexamethasone suppression test are marked in bold (Entries 5 and 6); F: Female, M: Male; DM: Type 2 diabetes mellitus; Hyp: Hypertension; Lip: Dyslipidemia.

from 14.8 % to 11.1 %. Notably, all non-suppressors had DM, a higher HbA1c and a greater part (7 out of 8 patients) was on at least one medication interacting with CYP3A4. It is known that the 1 mg DST should be interpreted cautiously in patients taking medication interacting with CYP3A4 due to their significant interaction leading to more false-positive test results [17]. Therefore, a helpful strategy to reduce false-positive test results could be repeating the 1 mg DST after stopping the interacting medication. If stopping the medication is not possible due to medical reasons, the 2 mg DST might prove helpful.

Our study has limitations. First and foremost, we did not include a control group of CS. Therefore, our data cannot exclude that the 2 mg DST would have resulted in false negative results in patients with CS. However, reassuringly, Sahin et al. included patients with CS in their study and found no false-negative results after the 2 mg DST [12]. Second, the patients in our study did undergo the two tests in a non-randomised order. However, the wash out period of at least 2 weeks is arguably long enough to avoid remaining effects of dexamethasone.

Conclusion

In conclusion, we do not recommend the use of the 2 mg DST in obese individuals in general, especially as it has never been investigated in patients with CS. However, we consider that further studies should focus on obese patients with poorly controlled type 2 diabetes and taking a medication interacting with CYP3A4, who do not suppress with cortisol levels after the 1 mg DST. In this special group of patients, the use of a 2 mg DST might prove helpful to avoid further investigations.

Acknowledgements

We thank all patients for their participation. We thank the staff of the laboratory, the staff of the Department of Endocrinology, Diabetology and Metabolism, and especially, our study nurses Cemile Bathelt and Nina Hutter for their most helpful support during the study.

Funding Information

Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung Nr. PP00P3-12346 and Universität Basel Nachwuchsförderung 2015.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] [Anonymous]. World Health Organization. Obesity and Overweight. www.who.int

[2] Chanson P, Salenave S. Metabolic syndrome in Cushing's syndrome. Neuroendocrinology 2010; 92 (Suppl 1): 96–101

[3] Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet 2015; 386: 913–927

[4] Cronin C, Igoe D, Duffy MJ, Cunningham SK, McKenna TJ. The overnight dexamethasone test is a worthwhile screening procedure. Clin Endocrinol 1990; 33: 27–33

[5] Montwill J, Igoe D, McKenna TJ. The overnight dexamethasone test is the procedure of choice in screening for Cushing's syndrome. Steroids 1994; 59: 296–298

[6] Eddy RL, Jones AL, Gilliland PF, Ibarra JD Jr., Thompson JQ, MacMurry JF Jr. Cushing's syndrome: A prospective study of diagnostic methods. Am J Med 1973; 55: 621–630

[7] Ness-Abramof R, Nabriski D, Apovian CM, Niven M, Weiss E, Shapiro MS, Shenkman L. Overnight dexamethasone suppression test: A reliable screen for Cushing's syndrome in the obese. Obes Res 2002; 10: 1217–1221

[8] Mussig K, Remer T, Maser-Gluth C. Brief review: Glucocorticoid excretion in obesity. J Steroid Biochem Mol Biol 2010; 121: 589–593

[9] Marin P, Darin N, Amemiya T, Andersson B, Jern S, Bjorntorp P. Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism 1992; 41: 882–886

[10] Pasquali R, Ambrosi B, Armanini D, Cavagnini F, Uberti ED, Del Rio G, de Pergola G, Maccario M, Mantero F, Marugo M, Rotella CM, Vettor R.Study Group on Obesity of the Italian Society of E. Cortisol and ACTH response to oral dexamethasone in obesity and effects of sex, body fat distribution, and dexamethasone concentrations: A dose-response study. J Clin Endocrinol Metab 2002; 87: 166–175

[11] Reincke M. Subclinical Cushing's syndrome. Endocrinol Metab Clinics North Am 2000; 29: 43–56

[12] Sahin M, Kebapcilar L, Taslipinar A, Azal O, Ozgurtas T, Corakci A, Akgul EO, Taslipinar MY, Yazici M, Kutlu M. Comparison of 1 mg and 2 mg overnight dexamethasone suppression tests for the screening of Cushing's syndrome in obese patients. Intern Med 2009; 48: 33–39

[13] Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008; 93: 1526–1540

[14] Abraham SB, Rubino D, Sinaii N, Ramsey S, Nieman LK. Cortisol, obesity, and the metabolic syndrome: A cross-sectional study of obese subjects and review of the literature. Obesity 2013; 21: E105–E117

[15] Leibowitz G, Tsur A, Chayen SD, Salameh M, Raz I, Cerasi E, Gross DJ. Pre-clinical Cushing's syndrome: An unexpected frequent cause of poor glycaemic control in obese diabetic patients. Clin Endocrinol 1996; 44: 717–722

[16] Castro M, Elias PC, Quidute AR, Halah FP, Moreira AC. Out-patient screening for Cushing's syndrome: The sensitivity of the combination of circadian rhythm and overnight dexamethasone suppression salivary cortisol tests. J Clin Endocrinol Metab 1999; 84: 878–882

[17] Lammert A, Nittka S, Otto M, Schneider-Lindner V, Kemmer A, Kramer BK, Birck R, Hammes HP, Benck U. Performance of the 1 mg dexamethasone suppression test in patients with severe obesity. Obesity 2016; 24: 850–855