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Assessment of the diagnostic performance of the 1 mg dexamethasone suppression test in class 3 obese patients

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Objective. This study was aimed to evaluate the prevalence of Cushing's syndrome and the diagnostic performance of the 1 mg dexamethasone suppression test in class 3 obese patients.

Methods. Anthropometric measurements and other laboratory data, including 1 mg dexamethasone suppression test of 753 class 3 obese patients, who applied to the Endocrinology and Metabolism Outpatient Clinic for the pre-bariatric surgery evaluation between 2011 and 2020, were evaluated retrospectively.

Results. An abnormal response to the 1 mg dexamethasone suppression test (cortisol ≥1.8 mcg/dl) was observed in 24 patients and the presence of Cushing's syndrome was confirmed by additional tests in 6 patients. The prevalence of abnormal dexamethasone suppression test was 3.18% and the prevalence of Cushing's syndrome 0.79%. The specificity value was determined as 97.5% for 1 mg dexamethasone suppression test with cortisol threshold value ≥1.8 mcg/dl.

Conclusions. The prevalence of Cushing's syndrome was found to be low in class 3 obese patients and 1 mg of dexamethasone suppression test had a very sufficient performance for Cushing's syndrome screening in this patient group.

Key words: obesity, Cushing's syndrome, screening, dexamethasone suppression test

Cushing's syndrome (CS) is a disease caused by a chronic exposure to excessive glucocorticoids (Lacroix et al. 2015). CS is not a common disease since it is associated with prevalent comorbidities in society such as obesity, hypertension, hyperlipidemia, and depression. Due to the many features of CS overlapping with the obesity rapidly increasing in society, the hypercortisolism distinguishing in the obese patients has become even more crucial.

The term Pseudo-Cushing's syndrome (PCS) is used for people, who do not have CS, but they present mild clinical and/or biochemical features of CS. Conditions such as obesity, polycystic ovary syndrome, poorly controlled diabetes, and chronic alcoholism can be listed as the most common causes of PCS (Nieman 2002).

Since the obese bariatric surgery candidates may present signs and symptoms of hypercortisolism, distinguishing between PCS and CS before bariatric surgery is crucial for the appropriate treatment of obesity in this patient group.

This study is aimed to evaluate the prevalence of CS and the diagnostic performance of the 1 mg dexamethasone suppression test (DST) in class 3 obese patients evaluated before bariatric surgery together with a long-term follow-up of the patients.

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Materials and Methods

Study protocol. The study included 753 class 3 obese [body mass index (BMI) ≥40 kg/m^2] adult patients, who applied for the pre-bariatric surgery evaluation in the Endocrinology and Metabolism Outpatient Clinic of our hospital between 2011 and 2020. The study protocol was approved by the local ethical committee. Pregnant women, patients with alcohol abuse, exogenous glucocorticoid use, kidney or liver diseases or patients previously suspected with CS or adrenal mass were excluded from the study.

Clinical and demographic parameters, detailed medication, and additional disease history were obtained from the medical records. Laboratory data collected between 08:00 and 09:00 a.m. after an overnight fast according to the standard procedure [thyroid stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine, calcium, albumin, complete blood count (CBC), fasting plasma glucose and insulin, HbA1c, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and total cholesterol], and 1 mg dexamethasone suppression test (DST) result were obtained from the medical records for each patient.

Fasting glucose level was measured using an enzymatic UV test (hexokinase method); AST and ALT were measured using a kinetic UV method; uric acid, total cholesterol, HDL, and triglycerides were analyzed using an enzymatic colorimetric method with AU5800 Clinical Chemistry Analyzer (Beckman Coulter, USA). HBA1c was analyzed using a boronate affinity chemistry with high-performance liquid chromatography on a Premier Hb9210 (Trinity Biotech, USA). CBC was evaluated with electrical impedance on Beckman DXH800 hematology analyzer. The insulin level was analyzed using the immunoassay method with Unicel DXI 800 automated analyzer (Beckman Coulter, USA).

Height (cm), weight (kg), BMI (kg/m^2), waist circumference (cm), and systolic and diastolic blood pressure (mmHg), which are routinely measured in the pre-surgical evaluation, were obtained from the records. All patients' heights and body weights were measured with calibrated devices with an error margin of 0.5 cm and 0.1 kg, respectively. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. Waist circumference was taken from the midpoint between the iliac crest and the lower costal margin, with the patient standing and feet touching.

Hypothalamic–pituitary–adrenal (HPA) axis evaluation. 1 mg DST was performed by oral administration of 1 mg dexamethasone tablet at 23:00 and measurement of serum cortisol level at 08:00 the next morning. The cutoff value for cortisol after 1 mg DST was 1.8 mcg/dl (Nieman et al. 2008).

In patients without sufficient suppression with 1 mg DST, the presence of drug use that could affect the test result was questioned again in detail first, then and all the drugs that the patient used were examined in detail for CYP34A interaction. In the case of suspected drug use, the 1 mg DST test was repeated at least 4 weeks after the last drug use. The 24-hour urinary free cortisol level (UFC) and midnight serum cortisol level (MSC) were performed as additional tests on patients that still did not show sufficient cortisol suppression for 1 mg DST after drug manipulation or on the ones that did not use suspected drugs. The 24-hour urine creatinine measurement was also performed to find out the adequate urine collection throughout the UFC test.

Endogenous hypercortisolemia was excluded in patients with normal UFC and MSC values, and it was thought that insufficient suppression after the 1 mg DST test might be due to application and measurement errors. Pathologically measured UFC and MSC values were confirmed by at least two measurements on different days. Values exceeding the assay upper limit for UFC were considered pathological. MSC value was obtained at 23:00 while the patient was awake and the cutoff value was accepted as 7.5 mcg/dl.

The presence of endogenous hypercortisolism was accepted in patients with pathological results in at least one of the UFC and/or MSC tests along with 1 mg DST. All of these patients were further investigated by pituitary or adrenal imaging based on their basal adrenocorticotropic hormone (ACTH) levels.

Serum cortisol was determined by chemiluminescence immunoassay (ADVIA Centaur XP, Siemens Healthcare, Germany). MSC was analyzed by a radioimmunoassay method after ethanol extraction (Steroid-Laboratory, Institute of Pharmacology, Heidelberg, Germany). UFC was determined by liquid chromatography tandem mass spectrometry.

Statistical analysis. SPSS software version 20.0 was used for statistical analysis of the data. The Kolmogorov-Smirnov normality test was used to determine the distribution pattern of the variables. Continuous variables were presented as mean and standard deviation (SD) using descriptive statistics.

Categorical variables were presented as numbers and percentages. Categorical data were analyzed using the Chi-square (χ^2) test or Fisher's exact test, whichever appropriate. Student's t-test and analysis of variance were used for parametric variables. A p-value <0.05 was considered significant.

Specificity was calculated by the division of false-positive DST results by all test results without confirmed Cushing's syndrome.

Multiple linear regression analysis was performed to define the predictors of DST. We analyzed anthropometrical data and cortisol after DST by regression analysis.

Results

The clinical and laboratory findings in the patients included in the study are shown in Table 1. In the study cohort, the female/male sex ratio was 72/28%, mean age was 40±12 years, mean BMI was 46±7.2 kg/m^2 (Table 1). The study cohort included type 2 diabetes, hypertension, depression, and hyperlipidemia in 24.7%, 20.4%, 11.1%, and 8.4%, respectively (Table 1).

In the entire study cohort of 753 patients, 24 patients (3.18%) showed insufficient suppression (cortisol ≥1.8 mcg/dl) after 1 mg DST. Of the patients with insufficient suppression after 1 mg of DST, antidepressant use was decided in 4 patients and oral contraceptive use in 2 patients. The cortisol level of these patients was found to be suppressed after repeated 1 mg DST following 4 weeks of drug discontinuation. For the remaining 18 patients, 1 mg DST was repeated considering possible problems with testing and measurement. After repeating 1 mg DST, cortisol level was suppressed in only 1 patient. For 17 patients whose cortisol levels were not suppressed after repeated 1 mg DST, UFC, and MSC tests were repeated twice as a confirmatory test. Hypercortisolemia was excluded in patients with normal results for both UFC and MSC measurements and the presence of hypercortisolemia was considered confirmed in patients with at least one abnormal result. Both UFC and MSC measurements in 11 patients were normal. In conclusion, the presence of CS was confirmed in 6 of 24 patients with abnormal 1 mg DST test results. The test results of patients with a confirmed diagnosis of CS are shown in Table 2.

Table 1
Demographic characteristics of the study cohort.

Parameter	n (%)	Parameter	Mean±SD
Gender (F/M)	545/208 (72/28)	Age (years)	40±12
Hypertension	154 (20.4)	Weight (kg)	127±21
Type 2 diabetes	186 (24.7)	BMI (kg/m2)	46±7.2
Hyperlipidemia	64 (8.4)	Waist circumference	132±11
CVD	18 (2.3)	Systolic blood pressure (mmHg)	134±18
Primary hypothyroidism	48 (6.3)	Diastolic blood pressure (mmHg)	82±12
Depression	84 (11.1)		

Abbreviations: CVD – cardiovascular disease; F – female; M – male; SD – standard deviation.

Table 2
Test results of patients with confirmed Cushing's syndrome.

Patient number	Gender	Age (years)	Co-morbidity	1 mg DST (mcg/dl)[a]	Basal ACTH (pg/ml)	UFC (mcg/day)[b]	MSC (mcg/dl)[c]
1	Female	50	HT, DM, Hypothyroidism	13.7	5.1	330	9.2
2	Male	53	HT	2.38	24.9	182	5.2
3	Male	39	-	4.63	26.1	282	8.7
4	Female	58	DM, HT, Hyperlipidemia	11.3	68.5	154	7.8
5	Female	61	DM, HT, Hyperlipidemia	2.04	124	265	6.5
6	Female	48	HT	1.98	34.2	242	8.1

Abbreviations: ACTH – adrenocorticotropic hormone; DM – diabetes mellitus; DST – dexamethasone suppression test; HT – hypertension; MSC – midnight serum cortisol; UFC – 24-hour urinary free cortisol. [a]normal range: <1.8 mcg/dl; [b]normal range: 36–137 mcg/day, [c]normal range: <7.5 mcg/dl.

Table 3
Specificity values according to 1 mg dexamethasone suppression test cutoff values in the entire study cohort,

Parameter	Cortisol (mcg/dl)			
	<1.8	≥1.8	≥2.89	≥5
n	729	24	4	6
Confirmed hypercortisolism (n)	0	6	1	2
Pathological DST (n)	–	18	3	4
Specificity (%)	–	97.5	99.0	99.4

Abbreviations: DST – dexamethasone suppression test; n – number of patients.

An etiological evaluation was performed depending on basal ACTH levels in patients with a confirmed diagnosis of CS. ACTH values of 5 patients were measured above 20 pg/ml, suggesting pituitary etiology. In 4 patients suspected with pituitary etiology, adenoma ≥6 mm was detected in pituitary MRI and transsphenoidal adenomectomy operation was performed. A patient with suspected pituitary etiology had an adenoma <6 mm on pituitary MRI and was referred to a center experienced in the inferior petrosal sinus sampling (IPSS) procedure. IPSS results indicated a pituitary adenoma and this patient underwent transsphenoidal adenomectomy. ACTH value was measured as 5.1 pg/ml in only 1 patient, ACTH-dependent CS was detected in these patients, and adrenalectomy was performed. The pathology results of the operated patients were reported as ACTH-secreting pituitary adenoma and cortisol-secreting adrenal adenoma, in accordance with the suspected etiological cause.

The prevalence of abnormal 1 mg DST within the entire patient group was 3.18%. The prevalence of confirmed CS patients was 0.79%, and the specificity of 1 mg DST was determined as 97.5% with a cutoff value of 1.8 mcg/dl (Table 3).

Analysis of the relationship between DST and demographic and laboratory findings with the regression analysis of 729 patients whose suppressed cortisol level was measured after 1 mg DST revealed age as the only independent factor for 1 mg DST.

No CS signs and/or symptoms developed in the follow-up in any of the patients whose 1 mg DST result showed suppression and whose UFC and MSC tests were normal after an abnormal 1 mg DST result.

Discussion

In this study, examining the preoperative evaluation data of class 3 obese patients admitted to a tertiary hospital for bariatric surgery, the prevalence of CS to be 0.79% in this patient group was found. The performance of 1 mg DST was found to be quite successful (specificity 97.5% for cortisol <1.8 mcg/dl). In addition, regression analysis found no association between patients' anthropometric measurements, including BMI and laboratory results, and 1 mg DST, except for age.

Tiryakioglu et al. (2010) have reported the prevalence of CS as 9.3% in morbidly obese patients evaluated before bariatric surgery and this high rate attracted considerable attention CS is a rare disease with an estimated annual incidence of 0.5–2 per million and an estimated prevalence of 39–79 cases per million (Lacroix et al. 2015). It is known that the prevalence of CS increases up to 1–5% in patients with poorly controlled diabetes, osteoporosis and suspected secondary hypertension (Catargi et al. 2003; Omura et al. 2004; Newell-Price et al. 2006; Reimondo et al. 2007).

The data reported by Tiryakioglu et al. (2010) have brought forward the question of whether the prevalence of CS in morbidly obese patients has increased similar to the conditions mentioned above. However, the studies published after Tiryakioglu et al. (2010) and in a systematic review, the prevalence of CS in obese patients has been reported in the range of 0.6–0.9% (Fierabracci et al. 2011; Jankovic et al. 2012; Tamada et al. 2013; van Hulsteijn et al. 2020).

Two recent studies have reported the prevalence of CS as respectively 0.7% and 0.77% in class 3 obese patients, the same patient group analyzed in our study (Lammert et al. 2016; Yavuz et al. 2020). In both studies, 24-hour urinary cortisol, midnight saliva or serum cortisol, low dose dexamethasone suppression test (LDDST), baseline ACTH level, and radiological imaging were used for confirmation and differential diagnosis of endogenous hypercortisolemia after 1 mg DST. Consistent with the general literature, our study found the prevalence of CS in obese patients to be 0.79%. 1 mg DST remains as the recommended test for CS screening at the first step. Besides, it is known that DST outperforms UFC and MSC in the comparison of screening tests in cohorts with a low prevalence of CS (Elamin et al. 2008).

Considering that CS is a rare disease, it is crucial to use a screening test with a high specificity value to avoid unnecessary additional testing and procedures. The specificity value of 1 mg DST, determined as 97.5% for class 3 obese patients in our study, can be considered a very good value. In the two recent studies mentioned above, the specificity values for 1 mg DST (threshold value for cortisol <1.8 mcg/dl) for the same patient group as our study were found to

be 92% and 96.8%, respectively (Lammert et al. 2016; Yavuz et al. 2020).

As a result of the regression analysis of the group including patients with suppression after 1 mg DST, no correlation was observed between anthropometric and laboratory measurements and 1 mg DST, except for age. Age was found to be the only parameter associated with 1 mg DST. The results of the regression analysis were found to be compatible with other related recent studies (Lammert et al. 2016; Yavuz et al. 2020). In addition, the existence of a significant relationship between age and 1 mg DST has been shown in different studies before (Knoops et al. 2010; Gungunes et al. 2014; Lammert et al. 2016; Yavuz et al. 2020). The results of the regression analysis suggest that 1 mg dexamethasone dose is sufficient even in class 3 obese patients, and there is no correlation between BMI and cortisol level after 1 mg DST.

The major limiting factor in our study is the absence of a gold standard test for evaluation. Due to the lack of the gold standard test, it is not possible to determine the true prevalence and sensitivity. Furthermore, the fact that the patients in our cohort evaluated in our Outpatient Clinic prior to bariatric surgery were relatively younger and severely obese and most of these patients had early manifestations of metabolic diseases, may possibly cause that the prevalence of hypercortisolism was slightly higher compared to epidemiological data.

Conclusion

From the results of our study and the literature data, it can be concluded that the prevalence of Cushing's syndrome in the class 3 obese patients is close to the non-obese population of peoples. Moreover, 1 mg dexamethasone suppression test showed up as an adequate test with a very good performance in Cushing's syndrome screening in this patient group.

Conflict of interest: *The authors declare no conflicts of interest.*

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