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ORIGINAL ARTICLE

Cushing's syndrome in obese patients with type 2 diabetes: A single center screening study

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Abstract The frequency of Cushing's syndrome (CS) in obese patients was not properly determined and the studies focused on the frequency of occult CS and the possible improvement of diabetes and obesity with treatment of CS are needed. In this study, we aimed to investigate the frequency of CS in obese patients with type 2 diabetes. The study enrolled with 200 obese (body mass index (BMI) >30 kg/m^2), type 2 diabetes patients between 2009 and 2011 in Sisli Etfal Training and Research Hospital, Turkey. Twenty-eight males and 172 females were recruited to the study. Mean age of the study group was 51.7 ± 8.5. Nineteen patients (9.5 %) failed to suppress cortisol levels less than 1.8 μg/dL after a 1-mg overnight dexamethasone suppression test (ODST) and these patients proceeded to have a 2-day 2-mg low-dose dexamethasone suppression test. After further screening, three (%1.5) patients were diagnosed with CS in our study. Among the three patients diagnosed with CS, the tumor was located in the pituitary gland in two patients. The present study revealed that the frequency of Cushing's syndrome in obese and diabetic patients were 1.5 %, which was much higher than the general population. Occult CS should take into account as an exacerbating factor for diabetes and screening for CS should be considered in poorly controlled diabetic patients.

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Introduction

Cushing's syndrome (CS) is a rare disease with an estimated incidence of 1:50,000 to 1:100,000 inhabitants in the general population [1, 2]. Mortality rate of the patients with CS are four times higher than healthy subjects [3, 4]. Diagnosis of CS is more straightforward, when the specific signs of the disease are present. However, none of these signs or symptoms is pathognomonic and secretory activities of the tumors are variable over time [5, 6]. Subclinical hypercortisolism (SH) is a recently described entity characterized by impaired cortisol homeostasis without specific signs or symptoms of CS [7].

Type 2 diabetes and obesity are common disorders that can develop secondary to CS and approximately 80 % of patients with CS display glucose intolerance or type 2 diabetes due to insulin resistance [1, 8]. Although its epidemiological impact on diabetes and obesity development is trivial because of the low prevalence, SH which is definitely more frequent than overt CS, can play an important role in the development of these diseases in the general population [7, 9]. Moreover, it has been suggested that the patients with diabetes experienced clinical improvement after SH removal [10]. However, systematic screening for CS in patients without specific signs of hypercortisolism is not established. While a screening strategy is reasonable, if its efficacy is evident and if the pros surpass the cons, the previous studies focused on the frequency of occult CS in obese patients with diabetes, have conflicting results. Leibowitz et al. demonstrated CS in 3 % of 90 overweight patients with diabetes [11]. Chiodini et al. found that the prevalence of CS was 9.4 % in 294 diabetic patients [12]. On the other hand, any case of CS was not detected in a study with 154 diabetic patients [13]. Thereby, the frequency of CS

in obese patients was not properly determined and the studies focused on the frequency of occult CS and the possible improvement of diabetes and obesity with the treatment of CS are needed. In this study, we aimed to investigate the frequency of CS in obese patients with type 2 diabetes.

Materials and methods

Two hundred obese patients (body mass index (BMI) >30 kg/m^2) with type 2 diabetes were consecutively included to the study between 2009 and 2011 in Sisli Etfal Training and Research Hospital, Istanbul, Turkey. Twenty-eight males and 172 females were recruited to the study. The mean age of the study group was 51.7 ± 8.5. From admission to our outpatient clinic, 112 (56 %) patients were treated with at least one oral antidiabetic drug (OAD), 12 (6 %) patients were treated with insulin, and 76 (38 %) patients were treated with the combination of OAD and insulin treatment. The mean diabetes duration was 7.4 ± 5.5 years. Additionally, 136 (68 %) and 72 (36 %) patients were treated with antihypertensive drugs and statins, respectively.

All patients were subjected to a careful clinical examination and none of them displayed specific signs of hypercortisolism such as purple striae, ecchymoses, skin atrophy, or proximal muscle wasting. The patients using systemic or inhaled steroids, antidepressants, antipsychotics, or other drugs, which might interfere with dexamethasone metabolism, having a malignancy or other clinically significant disease, known or suspected abuse of alcohol were excluded from the study.

A one-milligram overnight dexamethasone suppression test (ODST) was performed as the first screen test in all patients. The patients were administered to take 1 mg of dexamethasone at 2300 and blood samples were collected on the next morning at 0800 for measurement of serum cortisol level. The patients with serum cortisol levels above 1.8 μg/dL (50 nmol/L) were considered abnormal and underwent a 2-day 2-mg low-dose DST (LDDST). The patients were advised to take 0.5 mg of dexamethasone at 0600, 1200, 1800 and 2400 for two consecutive days. The sample for serum cortisol was collected at 0800 on the third day. Patients with serum cortisol level below 1.8 μg/dL after LDDST were considered as normal. The patients with serum cortisol level above 1.8 m μg/dL were evaluated for CS. Plasma ACTH and serum cortisol concentrations were measured to evaluate diurnal rhythm. A 24-h urinary free cortisol level was assessed and high-dose DST (2 mg of dexamethasone at 0600, 1200, 1800, and 2400 for two consecutive days and blood samples were collected on the next morning at 0800) was performed.

Abdominal computed tomography (CT), pituitary magnetic resonance imagining (MRI), or inferior petrosal sinus sampling (IPSS) were performed to clarify the diagnosis if necessary.

This study was approved by the local ethics committee of Sisli Etfal Training and Research Hospital and informed consent was obtained from all individual participants included in the study.

Statistical analysis

The quantitative variables are presented as mean ± standard deviation. Mann Whitney-*U* test was used for comparison of the means of two groups. Pearson's correlation was used to evaluate the relationship between the two variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SPSS software, version 13.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

The clinical features of the patients were shown in Table 1. Dexamethasone suppression test was performed in all patients and 19 (9.5 %) patients failed to suppress cortisol levels less than 1.8 μg/dL after ODST (Table 2). There was no significant difference in age, sex, or metabolic parameters such as BMI, glucose, HbA1c, and cholesterol levels between DST suppressors and non-suppressors. Also, cortisol level after the dexamethasone suppression test was not correlated with any of these parameters. Nineteen patients with DST non-suppression were further evaluated by LDDST. Serum cortisol levels of 16 patients were below 1.8 μg/dL and Cushing's syndrome was excluded in these patients. Physical examination considering Cushing's syndrome was carefully performed in the remaining three patients and none of them displayed specific signs of hypercortisolism such as purple striae, ecchymoses, skin atrophy, or proximal muscle wasting. Further biochemical and imaging studies were obtained in these patients (1.5 % of the whole series). Clinical features of these patients with Cushing's syndrome are shown in Table 3.

The 24-h urinary cortisol and midnight cortisol were 63 μg/24 h and 11 μg/dL in patient 1, respectively. ACTH level of this patient was under 5 pg/mL and cortisol level after high-dose DST was 12 μg/dL. These findings were compatible with ACTH-independent Cushing's syndrome and MRI revealed a 2.5-cm adenoma in the right adrenal. The patient underwent right adrenalectomy and histological investigation revealed an adrenal adenoma. Adrenocortical insufficiency developed in the postoperative period and this patient was treated with oral replacement therapy for 9 months. After cessation of replacement therapy, 7 % reduction in body weight and 1.4 % reduction in HbA1c were observed at the end of first year of surgery, while only metformin therapy was resumed.

Table 1 Clinical features of study group

	Mean ± S.D.
Age (y)	51.7 ± 8.5
BMI (kg/m^2)	37.6 ± 5.6
Waist circumference (cm)	113.4 ± 7.4
DM duration (y)	7.4 ± 5.5
Triglyceride (mg/dL)	185.1 ± 144.5
Total cholesterol (mg/dL)	196.7 ± 43.0
LDL (mg/dL)	113.6 ± 36.8
HDL (mg/dL)	49.2 ± 10.9
Fasting Blood Glucose (mg/dL)	188.1 ± 75.4
HBA1c (%)	8.4 ± 2.1
Systolic blood pressure (mmHg)	133.5 ± 7.1
Diastolic blood pressure (mmHg)	83.4 ± 4.6
ODST (μg/dL)	1.25 ± 1.6

BMI body mass index, *DM* diabetes mellitus, *LDL* low density lipoprotein

HDL high density lipoprotein, *ODST* 1 mg overnight dexamethasone suppression test

The other two patients had ACTH level above 10 pg/mL and high-dose DST suppression was observed in these patients. Although pituitary MRI of patient 2 displayed a 5-mm microadenoma in the right side of the pituitary, no adenoma was detected in patient 3 and inferior petrosal sinus sampling (IPSS) was performed to confirm Cushing's disease. The center-to-periphery ACTH ratio after CRH stimulation was 290:1 and left to right petrosal sinus ratio was 8:1. Thus, IPSS supported the diagnosis of Cushing's disease and showed left lateralization. Transsphenoidal surgery was performed and the histopathological diagnosis was ACTH-secreting adenoma in both patients. Six months after surgery, cortisol response was normal with ACTH stimulation and glucocorticoid replacement therapy was stopped in patient 2. Serum cortisol was suppressed by ODST in this patient. A better metabolic profile was attained, with 2.5 % reduction of HbA1c, 4.5 % of weight loss, and a 32-U reduction in insulin dosage, while the diabetes medications were switched from basal bolus insulin to metformin plus basal insulin therapy. However, glucocorticoid replacement therapy was not needed after surgery and no other anterior pituitary hormone deficiency was observed in patient 3. Serum cortisol was suppressed by ODST and at the sixth month of surgery, 3.3 % reduction in HbA1c and 6 % weight loss were achieved in this patient, while diabetes medications were switched from basal bolus insulin to metformin and gliclazide therapy.

Discussion

In the present study, we investigated 200 obese patients with type 2 diabetes for CS. Nineteen patients failed to suppress cortisol level after ODST and these patients proceeded to have LDDST. After further screening, three (%1.5) patients were diagnosed Cushing's syndrome in our study. Among the three patients diagnosed with CS, the tumor was located in the

Table 2 Comparison of characteristics of patients according to ODST

	Cortisol >1.8 (n = 19)	Cortisol ≤1.8 (n = 181)	P
Male (n)	2	26	0.3
Female (n)	17	155	0.4
Age (year)	54 ± 8.1	51.4 ± 8.5	0.1
BMI (kg/m^2)	35.0 ± 3.4	37.8 ± 5.8	0.056
Waist circumference (cm)	110 ± 6.6	113 ± 7.5	0.1
DM duration (year)	7.1 ± 4.4	7.4 ± 5.6	0.9
Triglyceride (mg/dL)	166 ± 66	187 ± 150	0.8
Total cholesterol (mg/dL)	200 ± 34	196 ± 43	0.4
LDL (mg/dL)	120 ± 33	113 ± 37	0.3
HDL (mg/dL)	47 ± 10	49 ± 10	0.5
Fasting blood glucose (mg/dL)	210 ± 81	185 ± 74	0.1
HBA1c (%)	9.2 ± 2.8	8.4 ± 2.0	0.3
Systolic BP (mmHg)	134 ± 5	133 ± 7	0.4
Diastolic BP (mmHg)	84 ± 4.5	83 ± 4.6	0.1
TSH (uIU/mL)	1.6 ± 0.7	1.6 ± 1.4	0.1
ODST (μg/dL)	4.9 ± 3.4	0.86 ± 0.27	0.000

BMI body mass index, *DM* diabetes mellitus, *LDL* low-density lipoprotein

HDL high density lipoprotein, *TSH* thyroid stimulating hormone, *ODST* 1-mg overnight dexamethasone suppression test

Table 3 Clinical features of the patients with Cushing's syndrome

Patient no.	1	2	3
Etiology	Adrenal	Hypophysis	Hypophysis
Sex	Female	Female	Male
Age (year)	50	55	52
BMI (kg/m^2)	39.1	34.1	32.3
Waist circumference (cm)	110	104	102
ODST (μg/dL)	7.8	8.0	14.4
LDDST (μg/dL)	4.8	2.8	5.6
Urinary cortisol (μg/24 h)	63	61	256
Basal cortisol (μg/dL)	18	23.5	29
Midnight cortisol (μg/dL)	11	17.6	16.6
High-dose DST (μg/dL)	12	3.9	1.92
IPSS	Not performed	Not performed	Left lateralization
Localization	2.5 cm adenoma, right adrenal	5 mm microadenoma. right side of pituitary	Normal
ACTH (pg/mL)	<5	26	21
Fasting blood glucose (mg/dL)	214	263	303
HbA1c (%)	8.4	10.9	9.6
Triglyceride (mg/dL)	89	123	145
Total cholesterol (mg/dL)	207	203	192
LDL (mg/dL)	128	130	124
HDL (mg/dL)	61	48	39
TSH (uIU/mL)	2.1	2.7	1.4

BMI body mass index, *ODST* 1-mg overnight dexamethasone suppression test, *LDDST* 2-day 2-mg overnight dexamethasone suppression, *IPSS* inferior petrosal sinus sampling, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TSH* thyroid stimulating hormone

pituitary gland in two patients. In the literature, there are conflicting results in the prevalence of occult CS between obese and diabetic populations. The prevalence of CS in patients with diabetes ranges from 0 to 9.3 % in different studies [14]. Leibowitz et al. demonstrated CS in 3 % of 90 overweight patients with diabetes [11]. Catergi et al. found that four of 200 overweight patients with diabetes had CS [15]. Additionally, the frequency of CS had been found 0.72 and 9.3 % in 277 and 150 obese patients in the Turkish population, respectively [16, 17]. In another Turkish study, Sahin et al. demonstrated CS in 3 % of 100 obese patients [18]. On the other hand, no CS was detected in a study of 154 diabetic patients [13]. Our center is the endocrinology clinic of a tertiary hospital in which generally, dysregulated diabetic patients are referred and the frequency of occult CS could be more likely to increase. The differences in the prevalence of CS in patients with T2DM can be explained by the selection of the patients, methodological discrepancy (preferred test, cortisol assays, etc.), and also cut-points.

ODST is the mainstay of the biochemical screening for CS [19]. However, the appropriate cut-point of ODST is still a matter of debate in the screening of CS. While cortisol suppression to ODST achieves superior diagnostic performance with the 5-μg/dL threshold at 97 % specificity, the lower 1.8-μg/dL level provides less optimal 80 % specificity in the general population [20]. On the other hand, it has been demonstrated that cortisol levels by ODST were established <2 μg/dl (<55 nmol/L) in all healthy persons using the newer immunoassays and a cut-point of 1.8 μg/dL (50 nmol/L) has been recommended [21, 22]. In a previous study, an 8 % false positive rate of a 1-mg ODST had been found in obese Turkish patients and it has been suggested that a 2-mg ODST could have more specifity compared to a 1-mg ODST [18]. In agreement with that study, the present study showed that cortisol suppression to ODST with the cut-point of 1.8 μg/dL was false positive in 16 (8 %) patients. Potential confounders including stress, simple obesity, dysregulated diabetes, and the activators of cytochrome P-450 3A4 system such as statins should be considered. However, in agreement with the previous study, no correlation was found between DST results, BMI, and glycated hemoglobin levels in our study [23]. Additionally, use of statins was not significantly different in the patients with false positive DST results. These results emphasized that high false positivity of ODST should be considered in the clinical practice and additional tools such as the 24-h urinary free cortisol or the late-night salivary cortisol test must be employed to confirm the diagnosis of CS.

Cortisol excess leads to metabolic abnormalities, such as impaired glucose tolerance and insulin resistance [24, 25]. It has been suggested that glucose metabolism and also cardiovascular risk could be improved by the removal of adrenal incidentaloma in subclinical CS [26, 27]. Leibowitz et al. in all five patients and Taniguchi et al. in all two patients had observed the improvement of diabetes after the cure of CS [11, 28]. Although assessment of the metabolic impact of the cure in occult CS is out of scope in the present study, diabetes improved and a significant weight loss was achieved after surgery. Further long-term studies are warranted to determine the improvement of diabetes and obesity in occult CS.

In conclusion, the present study revealed that the frequency of Cushing's syndrome in obese and diabetic patients were 1.5 %, which was much higher than the general population. Occult CS should be taken into account as an exacerbating factor for diabetes and screening for CS should be considered in poorly controlled diabetic patients. The results of ODST above the cut-point of 1.8 μg/dL must be carefully evaluated and additional tools should be employed to confirm the diagnosis of CS. Further prospective studies which also represent the impact of the cure of CS are warranted to determine the clinical approach for occult CS in obese patients with diabetes.

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Compliance with ethical standards

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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