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RESEARCH

Long-term outcomes of the patients with Cushing syndrome after endocrine remission

Endokrin remisyon sonrası Cushing sendromlu hastaların uzun dönem izlem sonuçları

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Abstract

Purpose: The study aimed to evaluate metabolic parameters and bone density measurements during the active phase and after long-term remission, as well as to present long-term follow-up results of patients with Cushing Syndrome.

Materials and Methods: In 20 patients with Cushing Syndrome, weight, waist circumference, fasting plasma glucose, lipid parameters, blood pressure and bone mineral density were evaluated during the active disease and after endocrine remission.

Results: All patients were female, premenopausal with mean age of 35±9.5 (range 27-45). During the long-term follow-up (median 60 months), weight (87.6±21.2 vs 71.1±18.8) and waist circumference (98.02±11.5,) were decreased significantly compared to baseline measurements. While total cholesterol and triglyceride values were similar between before and after remission, LDL cholesterol (143.6±35.8 vs 127.7±37.06) was decreased significantly in all patients. During the hormonal remission, 63.6% of patients' antihypertensive medication was discontinued. Bone mineral density in lumbar spine was increased compared to the baseline values of all patients.

Conclusion: Metabolic parameters and bone status were improved during the long-term follow-up time in patients with Cushing syndrome. Age, gender and duration of hypercortisolism or following time can influence the recovery of these comorbidities.

Keywords: Cushing syndrome, hypertension, osteoporosis, hypercortisolemia, 24 hour urine cortisol

Öz

Amaç: Bu çalışma, Cushing Sendromlu hastaların aktif dönem ve uzun süreli remisyon sonrası metabolik parametrelerini ve kemik yoğunluğu ölçümlerini değerlendirmeyi ve uzun süreli takip sonuçlarını sunmayı amaçlamıştır.

Gereç ve Yöntem: Cushing Sendromu tanısı almış ve takipte endokrin remisyona ulaşan 20 hastanın plazma glukoz, lipid değerleri, kan basıncı ölçümü, ve kemik mineral dansitesi değerlendirilip kayıt edildi.

Bulgular: Çalışmaya dahil edilen tüm hastalar kadın hasta olup ortalama yaşları 35±9.5 (aralık 25-45) olarak değerlendirildi. 60 aylık ortalama takip süresi boyunca kilo değişimi (87.6±21.2 vs 71.1±18.8) ve bel çevresi değişimi (98.02±11.5) anlamlı olarak saptandı. Endokrin remisyon öncesi ve sonrası total kolesterol ve trigliserid değerleri benzer iken, LDL kolesterol (143.6±35.8 vs 127.7±37.06) anlamlı olarak azalmıştı. Takip süresi boyunca hastaların %63.6'sı antihipertansif tedavi kesildi. Kemik mineral yoğunluğu ölçümü ise bazal ölçümlere göre anlamlı olarak artmıştı.

Sonuç: Bu çalışmada Cushing Sendromu nedeni ile takip edilen hastaların takipte metabolic parametrelerinin ve kemik yoğunluğunun iyileştiğini saptadık. Ancak bu parametrelerin değişmesinde yaş, cinsiyet ve hiperkortizolizm süresinin etkili olduğu ve komorbiditelerin iyileşmesinde major rolü olduğu kanatindeyiz.

Anahtar kelimeler: Cushing sendromu, hipertansiyon, osteoporoz, hiperkortizolemi, 24 saatlik idrar kortizolü

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INTRODUCTION

Cushing Syndrome (CS) is characterized by excess glucocorticoid and leads to various complications. Cushing syndrome is a condition that summarizes the consequences of exposure of excess hypercortisolism related to exogenous or endogenous glucocorticoids. Exogenous hypercortisolism is more common compared to endogenous hypercortisolism due to wide use of systemic or topical glucocorticoids[1]. Endogenous cushing syndrome is generally caused by excessive secretion of adrenocorticotropic hormone (ACTH) from pituitary tumors or less frequently adrenocortical tumours. The incidence of endogenous Cushing syndrome is very low (0.7-2.4 per million population per year) but the prevalence can be seen in special populations including patients with difficulty control type 2 diabetes or hypertension[2].

Untreated Cushing Syndrome is related to significant morbidity and mortality including hypertension, osteoporosis, insulin resistance, type 2 diabetes, dyslipidemia and abdominal obesity which contribute to the adverse outcomes such as cardiovascular diseases[3,4]. Many of of the patients (80-90%) with CS have hypertension at diagnosis and some of them have been admitted to hospital due to resistant hypertension. Long-term exposure of hypercortisolism causes left ventricular hypertrophy, increased carotid intima-media thickness and smaller systolic lumen diameter[5]. Studies have shown that cardiovascular disease confers 4-fold increase in mortality of patients with persistent disease during the short-term follow- up[6-8]. Although there have been limited studies related to the outcomes of hypercortisolism; following the treatment for cushing syndrome; the prevalence of hypertension, dyslipidemia or type 2 diabetes improves even decreasing carotid intima-media thickness. Glucocorticoid excess also affects bone status through bone turnover and indirectly through the alteration of calcium homeostasis[9,10] due to imbalance between bone formation and resorption. It has been reported that an impairment of bone status has been described in 64-100% of patients with CS; in particular, osteopenia occurs in 40-78%, osteoporosis in 20-57% and skeletal fractures in 1-76% of patients[11,12].

We know that all these metabolic changes and bone deformities are closely related to hypercortisolism. Metabolic abnormalities are clearly related to the duration of hypercortisolism or to the demographic characteristics of patients (age or gender). And after treatment of hypercortisolism, long-term following time is required improvement all above mentioned comorbidities. And more clinical observations are needed to learn more literal knowledge for these patients. Overall, we also observed that the data on the duration of hypercortisolism were lacking or there was no long-term following studies[13]. Otherwise, it has been unclear whether these comorbidity rates can be completely regulated by the resolution of hypercortisolism.

Although few data are available on the comparison of metabolic profile and osteoporosis risk before and after treatment it is still not known whether disease remission entirely reverses these morbidities or mortalities normalizes survival rate. Based on this background, we aimed at evaluating metabolic parameters and bone density measurement during the active phase and after long term remission. We also aimed to present our long-term follow-up results of patients with Cushing Syndrome with literature.

MATERIALS AND METHODS

Sample

Between 2014-2018 years, we included 20 patients diagnosed with Cushing Syndrome in our University Hospital, retrospectively. Retrospectively, the electronic medical files of all patients were reviewed manually. All specialist outpatient visits and hospital admissions have been coded with ICD-10 codes by the national database where they have been stored. After the detailed evaluation for hypercortisolism, 20 patients with adrenal adenoma were treated surgically in our University Hospital. All patients were evaluated CS between 2014 and 2018, and mean age of the patients was 35±9.5 and all patients were female and premenopausal.

Patients with aged 18-70 and diagnosed as Cushing Syndrome after careful examination were included in our study. We retrospectively searched and recorded patients with Cushing Syndrome in our database (ENLIL healthcare system). We obtained 60 patients but some data of 20 patient's were missing.

We excluded the patients

a) who were found co-secrete aldosterone

b) with adrenocortical carcinoma

c) who were taking steroid drugs for any indications and

d) who did not achieve endocrine remission for CS

e) hypercortisolemia related to pituitary adenoma,

f) patients with alcohol abuse,

g) patients working on shifts,

h) patients with missing data

Procedure

The retrospective nature of this study was approved by the ethical review board of the Cukurova University Hospital, Turkey (Ocotber 7th, 2022, No. 126).

The diagnosis of Cushing syndrome was made in accordance with international criteria as follows: 1) increased daily urinary free cortisol (UFC), 2) failure to suppress cortisol after 1 mg dexamethasone suppression test (DST) 3) elevated midnight cortisol. Cut-off values of these tests have been previously reported[14]. After the biochemical tests, non-contrast adrenal CT was performed to all patients based on available hormonal test. Differential diagnosis of CS among Cushing Disease, Ectopic ACTH Syndrome and autonomous cortisol secretion was made based on ACTH levels, overnight 8 mg DST, corticotropin releasing hormone stimulation test and appropriate imaging depending on the results' hormonal work-up. After the detailed evaluation, patients underwent surgery. Duration of hypercortisolism was considered as a time between the date of diagnosis and that of surgery.

Endocrine remission criteria

Biochemical cure was defined to have occurred if at last follow-up visit patient had adrenal insufficiency or glucocorticoid replacement therapy and initial morning plasma cortisol less than <50 nmol/L after 4 weeks of surgery, normal UFC or suppression of plasma cortisol less than <50 nmol/L after DST.

Patients were following the endocrine remission at 0-6-12 months. After the endocrine remission urine free cortisol, plasma cortisol and ACTH values, biochemical parameters and bone densitometer were performed and recorded to our SPSS system.

Definition of comorbidities

Patients were described as hypertensive if they were currently taking antihypertensive agents and/or had a systolic blood pressure of > 130 mm/Hg and diastolic blood pressure of > 80 mm/Hg. Impaired glucose tolerance was defined as glucose levels after 2-hours oral glucose tolerance test (OGTT) 140-200 mg/dl (7.8-11.1 mmol/l) and Diabetes Mellitus as fasting glucose levels 126 mg/dl (> 7 mmol/l) in two consecutive measurements. Osteoporosis was defined as either the presence of fragility fractures or low bone density as measured available technology.

Data collection

Preoperative and postoperative metabolic parameters including weight (kg), body mass index (BMI, kg/m^2), blood pressure (mm/Hg), weight circumference (cm), fasting plasma glucose (mg/dL), HbA1c (%), lipid parameters, serum baseline cortisol (μg/dL), ACTH (pg/mL), post DST cortisol values, urinary free cortisol (μg/24 h), bone density measurements were collected and recorded to the SPSS system.

Fasting plasma glucose or lipid parameters were evaluated after the 8-hour fasting status. Basal plasma cortisol and ACTH were taken at 08.00 a.m and mid-night cortisol was taken at 11.00 p.m. Preoperative and postoperative adrenal imaging techniques (abdominal MRI) and bone mineral densitometry (BMD, lumber spine, L2-L4) were performed.

Fasting plasma glucose, triglyceride, low-density lipoproteins (LDL), high-density lipoproteins (HDL) were measured by standard protocols. ACTH and cortisol values were analyzed by using the enzymatic-labeled chemiluminescent immunometric assay method, and chemiluminescence (Beckman DXI 800 auto analyzer; Beckman Coulter Diagnostics, Fullerton, CA, USA), respectively. The high-performance liquid chromatography (HPLC) method was used to analyze urine cortisol and metanephrine values.

Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and IQR: Inter Quartile Range where appropriate. The normality of distribution for continuous variables was confirmed with the Shapiro Wilk test. For comparison of two related (paired) continuous variables, paired samples t-test or Wilcoxon Signed Rank test were used depending on whether the statistical hypotheses were fulfilled or

not. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was to be 0.05. SPSS reference: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

RESULTS

The mean duration of all patients was 4±6 months. Preoperative mean weight of all patients was 87.6±21.2 kg (range 53-145). Mean baseline BMI of all patients (32.8 ±2.3 vs 26.7±2.6, p=0.02) was significantly decreased than the measurement of after the endocrine remission. The mean follow-up period was 72±12 months and all patients received endocrine remission. Postoperative measurement of mean waist circumference (80.6±12.2 vs 98.2±11.5, p=0.002) was significantly decreased compared to preoperative measurements. No difference in fasting blood glucose was observed between preoperative and follow-up values of patients. While impaired glucose tolerance (IGT) was diagnosed in twelve patients (n=12, 60%) as an active disease, during the follow-up period none of them had IGT (fig 1a). Total cholesterol (T-Chol) and triglyceride (TG) were similar in the preoperative and follow-up periods, while LDL cholesterol decreased in the follow-up period (p=0.031) (fig 1b). Detailed metabolic parameters are shown in Table 1. Preoperative and postoperative mean cortisol levels of all patients were 19.5±5.4 vs 4.71±6.73 μg/dL, respectively (p=0.001). As expected, preoperative 24-hour urine cortisol of all patients was 694.6±328.84 mcg/day, postoperative urine cortisol was 48.3±50.7 (p=0.005) (fig 1c). Preoperative mean adrenal mass size was 31.7±8.2 mm and all pathological results were confirmed as an adenoma. Preoperative and postoperative follow-up values of hormone parameters are shown in Table 2.

While 71.1% of all patients with CS were treated with antihypertensive therapy, 22.2% of them received antihypertensive medication in the postoperative follow-up period (p=0.002). But there was no significance in patients with preoperative and postoperative antidiabetic medicine. At baseline, BMD of the spine was -2.0±0.86 (min-max, from -3.2 to 0.2) and T score at the spine was defined as an osteopenia for all patients. Mean postoperative measurement of BMD of the spine in all patients was -1.3±1.1 (min-max, from -2.0 to 1.1) (p=0.035). Mean BMD in femoral neck was similar at baseline and after endocrine remission (p=0.056) (Fig 1d).

Table 1. Metabolic parameters in patients with CS at baseline and after the cure of hypercortisolism

N=20	Baseline	After cure of hypercortisolism*	p
Weight (kg)	87.6±21.2	71.1±18.8	0.001
Waist Circumference (cm)	98.02±11.5	80.6±12.2	0.002
FPG (mg/dL)	92.06±15.8	90.6±17.3	0.96
HbA1c (%)	5.9±1.03	5.4±0.03	0.009
T. Chol.	238.5±40.3	201.3±49.9	0.063
LDL	143.6±35.8	127.7±37.06	0.031
HDL	45.8±15.8	60.9±12.8	0.007
TG	167.6±55.06	137.2±57.1	0.132
ALT	24.6±7.7	25.8±18.7	0.585
HT (n)	11 (71.1%)	4 (22.2%)	0.003
IGT(n)	122 (60%)	NA	0.004

FPG; Fasting Plasma Glucose, T.Chol.; Total Cholesterol, LDL; Low Density Lipoproteins, HDL; High Density Lipoproteins, TG; Triglyceride, HT; Hypertension, DM; Diabetes Mellitus; *: time since cure of CS was 48 months

Table 2. Hormonal parameters and data after cure of hypercortisolism

	Baseline	After cure of hypercortisolism*	p
Cortisol	19.5±7.4	6.2±4.7	0.001
ACTH (pg/ml)	6.4±5.4	27.1±25.3	0.012
Urine cortisol (24 hour)	694.60±328.8	48.3±50.7	0.005
BMD at lumbar spine (T score/Z score)	-2.0±0.86	-1.3±1.1	0.035
BMD at proximal femur (T score/Z score)	-1.8±1.03	-1.0±0.6	0.056

BMD: Bone Mineral Density

*: time since cure of CS was 48 months

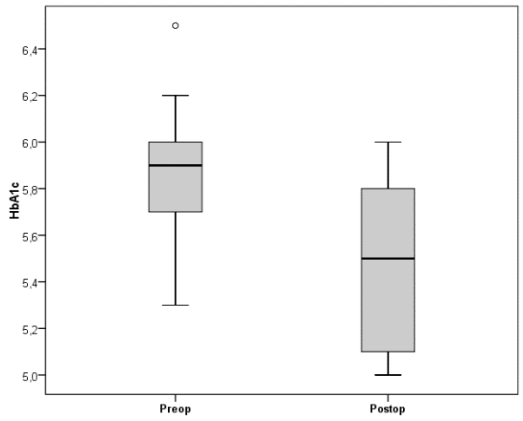

Figure 1a. Before and after treatment of HbA1c levels in patients' with Cushing Syndrome.

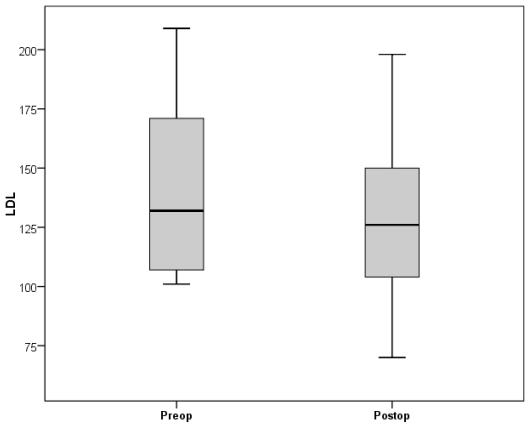

Figure 1b. Before and after treatment of LDL levels in patients' with Cushing Syndrome.

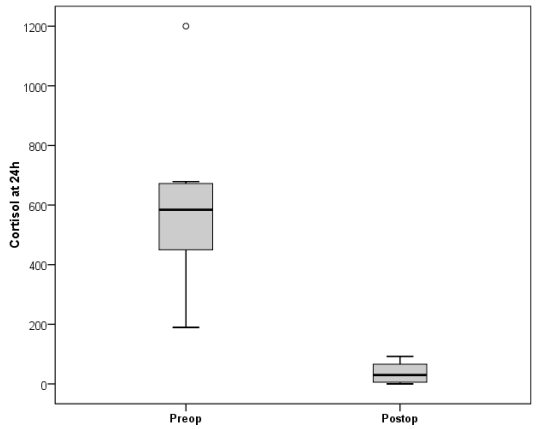

Figure 1c. Before and after treatment of 24 hour urine cortisol levels in patients' with Cushing Syndrome.

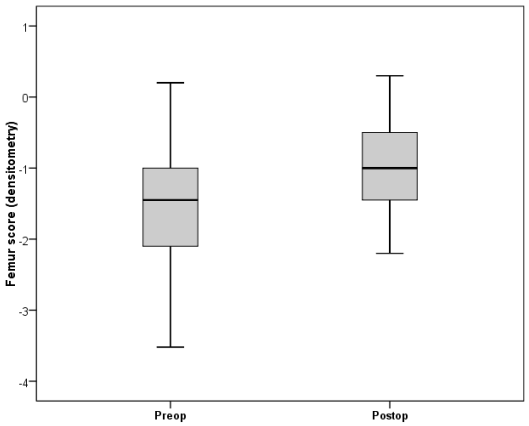

Figure 1d. Before and after treatment of densitometry of femur levels in patients' with Cushing Syndrome

DISCUSSION

In our study, metabolic parameters such as fasting plasma glucose or lipid values and bone health might be improved after the endocrine remission of patients with Cushing Syndrome. The results of our study may confirm improvement of metabolic parameters including weight, waist circumference, HDL and LDL cholesterol after the cure of CS. In addition, most of the patients had successful remission of hypertension with a recovery of hypercortisolism. Even though it has limited sample size; a significant improvement in mean spine BMD was showed in all patients with CS.

In patients with CS there are multiple comorbidities related to overt cortisol secretion. These comorbidities include a specific form of metabolic syndrome characterized by hypertension, visceral obesity, impairment of glucose metabolism and dyslipidemia. And these clinics are strictly correlated with cardiovascular disease [15-17]. Overt glucocorticoids in the human body may lead to insulin resistance by direct or indirect mechanisms. Pre-adipocyte differentiation, occurring lipogenesis and inhibiting pancreas insulin secretion contribute to the development of hepatosteatosis and glucocorticoid induced insulin resistance[18]. Cortisol excess is known for glycemic regulation and recovery of hypercortisolism could provide remission insulin resistance parameters. Giardano et al.[19] showed significant reduction of 2-h glucose, LDL cholesterol and waist circumference measurements in patients

with CS after endocrine remission. But they did not find any change in mean BMI values in these patients before and after remission. Our study's results confirm significant decrease of weight, waist circumference, LDL cholesterol values after the endocrine remission. The follow-up period and patient demographic parameters such as gender, age or dietary habitus can play an important role in observing meaningful change in all metabolic parameters especially waist circumference and BMI measurements. We know younger age or strictly regulated diet content could be major factor to affect on metabolic parameters. Meanwhile reduction in weight and waist circumference measurements may have also affected long term follow up after endocrine remission.

Dyslipidemia secondary to hypercortisolemia has been reported in 12-72% of patients with CS[20-21]. Patients with CS have elevated total cholesterol, LDL cholesterol, triglyceride and decreased HDL cholesterol levels. While some studies have shown improvement in lipid profile with T-Cholesterol, LDL and triglyceride, some others have reported that lipid abnormalities, especially HDL cholesterol persist in patients with CS after endocrine remission[22-23]. Faggiano et al.[24] highlighted that one year after remission from hypercortisolism hyperlipidemia (increased LDL, decreased HDL), increased stiffness of vascular wall and atherosclerotic plaques as well persisted. Several studies on [25-28] have also shown only LDL cholesterol improvements took place after the hypercortisolism treatment and that changing HDL cholesterol levels can be slower. In the current study, during the long-term period, HDL levels were increased compared to preoperative values related to improvement of hypercortisolemia. In addition, LDL levels were also decreased during the endocrine remission, but this was not significant statistically. We argued that improvement of lipid parameters was related to the younger age of our patients, decreased of weight, probable short duration of hypercortisolism, favorable baseline values and longer follow up duration.

Hypertension is one of the major features of CS and a high level of cortisol values could lead to acting mineralocorticoid receptor to retain sodium, with consequent increases in intravascular volume, cardiac output and intravascular volume[29-32]. Although it is known that hypertension resolves after the remission of hypercortisolism, many predicting factors such as age, estimated duration of hypercortisolism, baseline BMI may affect decreasing blood pressure. Additionally, some studies[33-35] have highlighted that immediate resolution (10 days after surgery) of blood pressure was observed in patients with hypercortisolemia. But among these patients, those with long term follow-up did not complete resolution of hypertension. One possible reason for this failure to complete resolution of blood pressure is replacement of high dose glucocorticoid therapy. And the other possible reason is older individuals have arterial stiffness related to hypertension. In our study, all patients a mean age 35±9.5 had incredible loss of weight and weight circumference during the follow-up period without hormone replacement therapy. Otherwise, remission of hypertension was sustained in nearly all (63.6%) patients with a long term follow up period. We speculate younger age, shorter duration of hypercortisolism and not having hormone replacement therapy may influence the rates of remission of hypertension.

Glucocorticoid excess affects bone status through few different mechanisms by uncoupling bone turnover or alteration of calcium homeostasis[36]. In addition, catabolic effects on muscle might also have a role in developing osteoporosis. After the endocrine remission, improvement in BMD took place in most patients with hypercortisolism. Especially several studies[37-38] assessing bone status in patients' follow-up for at least 1 year after remission reported a progressive improvement in BMD, generally slower in the femoral neck than the lumbar spine. In a study with 68 patients, the patients were followed up for 4 years and BMD increased over lumbar spine and femur but decreased at the forearm. In our study, BMD of lumbar spine also improved in all patients after the long-term period (median 60 months), but we did not find any difference in the femoral neck. Studies have highlighted that stratification of patients should be done according to gender, age, presence of fracture, expected time of hypercortisolism and gonadal status[39-40]. Female patients, younger than 50 years, premenopausal period, short duration of having hypercortisolism and without fractures are predictive factors for the recovery of bone status[41]. And these factors also determine the needing bone active treatment such as bisphosphonates. In our study, all the patients were female, premenopausal and with mean age 35±9.5. In line with these results, it may be difficult to say improvement of bone health after the recovery of hypercortisolism in our patients. Long-term follow-

up, multicenter, large sample size can be more convenient.

Limitations, we know that our study was retrospectively designed therefore some data was missing. And we could not perform sample size analyses related to retrospective nature.

Since we include patients with adrenal cushing syndrome who admitted in our center, we observed these results in small sample size. And it was major limitation to affect result of our study. Duration of hypercortisolism could definitively factor influencing the outcomes of CS. Since some patients were admitted from other different centers, it was not known how long patients were under hypercortisolism before diagnosis of cushing syndrome. We did not have control subjects due to retrospective designed so it was difficult to clearly say improvement of metabolic parameters in patients with CS.

In conclusion, our data showed that younger age, most probable shorter duration of hypercortisolism, baseline BMI and long-term follow-up time can influence the improvement of metabolic diseases (hypertension, dyslipidemia and glucose tolerance) and bone health in patients with CS after endocrine remission. Age, duration of hypercortisolism and etiology of hypercortisolism are important factor for recovery all comorbidities related to high cortisol levels, so we need more comprehensive, large sample size studies. And patients with CS who achieved endocrine remission or not should be followed at regular intervals for a long time.

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