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Bone mineral density in patients with Cushing's syndrome

Aysun SEKER [1], Dilek GOGAS YAVUZ[2]

[1] Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey
[2] Divison of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey

Corresponding Author: Aysun SEKER
E-mail: dr.aysunozdemir@hotmail.com

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ABSTRACT

Objective: Cushing's syndrome is caused by the excessive secretion of cortisol or the intake of exogenous cortisol. Morbidity caused by osteoporosis is a major complication that cannot be ignored. We conducted a study to evaluate bone density and fracture risk factors in patients with Cushing's syndrome.

Patients and Methods: This retrospective case-control study involved 176 patients diagnosed with Cushing's syndrome [153 female and 34 male patients] and 84 controls [72 female and 12 male patients]. Patients admitted to the clinics within the last eight years were included in the analysis. We collected demographic, clinic laboratory data, and bone densitometry measurements from electronic patient files. The classification of patients into normal, osteopenia, or osteoporosis groups is determined by their Body Mineral Density measurements based on the World Health Organization criteria.

Results: Among the patients, 135 were diagnosed with Cushing's disease and 41 with adrenal adenomas. Patients with Cushing' syndrome showed a higher incidence of osteopenia (11.4%) and osteoporosis (2.8%) when compared to the control group. No osteoporosis cases were found in the control group, while nine cases of osteopenia were detected. Osteopenia was significantly more common in adrenal adenoma patients than in those with pituitary Cushing's disease. Osteopenia was present in 39.1% of adrenal Cushing's patients, with only 8.7% (n = 2) having osteoporosis. Osteopenia was observed in 11 patients (23.4%) with pituitary Cushing's disease, while only 4 patients (8.5%) had osteoporosis.

Conclusions: Osteopenia is more prevalent in patients with adrenal Cushing's syndrome.

Keywords: BMD, Bone, Cushing's syndrome, Low bone density, Osteopenia, Osteoporosis

1. INTRODUCTION

Cushing's syndrome (CS) is a pathological condition that is characterized by hypercortisolemia of various origins. Etiologic causes of the syndrome can vary from long-term glucocorticoid utilization (results with iatrogenic CS), corticotropin-releasing hormone (CRH), and adrenocorticotropic hormone (ACTH) secretion either from pituitary or non-pituitary sources (results with endogenic CS). Although, it is less common, excessive glucocorticoid secretion from the adrenal gland is also described in the disease pathophysiology [1].

Numerous complications and related treatments associated with hypercortisolism are well described. All discussion aside, today, early detection and intervention still weigh their importance in successfully managing long-term complications [2].

Osteopenia and osteoporosis are considered common comorbidities in Cushing's syndrome patients, with an estimated frequency between 60-80% and 30-65% of various Cushing's syndrome populations [3]. Skeletal complications manifesting with uncoupled suppressed bone formation and enhanced bone resorption contribute to distinct skeletal damage, accelerating the vertebral fracture risk. Bone mineral density (BMD) is a routine part of Cushing's patient evaluation. Vertebral fractures (VF) are frequently reported and may occur even in patients with mild reduction of BMD results [5,6].

Bone fractures caused by Cushing's syndrome are scarce, despite extensive literature [7-10]. These fractures most commonly occur in the thoracic and lumbar vertebrae, hip, ribs, and pelvis. Fracture development is not uncommon after spontaneous or low-energy trauma. Articles also mention that the risk of fracture increases two years prior to the diagnosis of Cushing's disease, and the risk can be normalized with appropriate treatment [11]. Routine thoracolumbar spinal radiographs in patients with Cushing's disease demonstrate that 76% of patients have vertebral fractures at any time of the disease, and 48% are reported as asymptomatic [8].

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In this study, we aimed to evaluate BMD measurements and bone metabolism markers in our group of patients diagnosed with Cushing's disease and cortisol-secreting adrenal adenoma.

2. PATIENTS and METHODS

Patients

The study protocol was approved by the Marmara University Medical School Ethics Committee (09.2017.118) and conducted following the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

One hundred seventy-six patients diagnosed with Cushing's disease, admitted to the Marmara University Pendik Training and Research Hospital between January 2010 to February 2018 were included in this retrospective study. A control group (n = 84) was selected by matching sex and age distribution with no Cushing's disease diagnosis, sourced from available study datasets from the same healthcare facility.

The sample size was calculated as 260 subjects prior to the study implementation. The 2:1 ratio resulted in 176 and 84 sample sizes in the case and control groups.

Methods

Data included demographic data (age, sex), laboratory tests performed within the diagnosis and treatment timespan, including basal cortisol, 1 mg dexamethasone suppression test, 24-hour urine-free cortisol, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone, (TSH), thyroxine (T4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), calcium (Ca), phosphorus(P), parathormone (PTH), 25-OH Vitamin D, fasting blood sugar, hemoglobin A1C (HbA1C), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) levels and radiological (adrenal and pituitary MRI findings, bone mineral densitometry) assessments.

Parameters and techniques used for each subject were confirmed solely. 24-hour urine-free cortisol, ACTH, TSH, T4, FSH, LH, PRL, and 25-OH vitamin D were studied by chemiluminescence immunoassay (CLIA). Ca was studied with Schwarzenbach by the o-cresolphthaleincomplexone. P level was studied by ammonium molybdate. HbA1C was studied by boranate affinity chromatography. Fasting blood sugar was studied by enzymatic UV test (hexokinase method).

Bone mineral density (BMD) was analyzed by dual-energy X-ray absorptiometry (DXA). Within DXA assessment, L1 – L4 was measured in anteroposterior projection (AP), additionally for right and left hip assessment Lunar DPX-L (GE-Lunar Corp., Madison, WI) was used. Coefficient of variation (CV) was set to 1.0%. According to World Health Organization criteria, osteopenia was defined as BMD values over 1.0 and less than 2.5 standard deviation from reference mean values. Osteoporosis was defined as 2.5 or more deviation from reference BMD values (T score less or equal to −2.5 SD).

Hypercortisolism was evaluated with 1 mg dexamethasone suppression test, 24-hour urine free cortisol and midnight cortisol levels. 2x2 mg dexamethasone suppression test and inferior petrosal sinus sampling were used to confirm both the diagnosis and detect the pathological location.

Statistical Analysis

IBM SPSS 23 software was used to analyze the collected data. Descriptive statistics were presented as mean and standard deviation for continuous variables. Categorical variables were interpreted as counts and percentages. Appropriate chi-square ($\chi 2$) test or Fisher's exact test were selected for categorical data analysis. Student's t-test used for parametric variables. Spearman rank correlation was utilized to reveal variable associations. The results were evaluated at a 95% confidence interval. Post hoc analysis based on contingency tables, using GPower (Version 3.1.9.7, HHU) found that the study power (1-β) was 0.986 (ω = 0.314, N = 176, df = 1). p

3. RESULTS

One hundred seventy-six patients with Cushing's syndrome were included in the study. Of the included subjects, 153 (86.9%) were female, and 23 (13.1%) were male. The mean age was calculated as 50.52 (± 0.97) in females, 51.65 (± 3.09) in males, and 50.66 (± 0.93) in the whole case group.

Table I. *Baseline characteristics of Cushing's patients*

	Total (n = 176)	Female (n = 153)	Male (n = 23)	p
Age	50.66 (± 0.93)	50.52 (± 0.97)	51.65 (± 3.09)	0.729
Age at diagnosis	44.96 (± 0.99)	44.74 (± 1.04)	46.43 (± 3.15)	0.563
Disease location				
Pituitary	76.3 % (n = 135)	77.4 % (n = 119)	68.2 % (n = 16)	0.266
Adrenal	23.1 % (n = 41)	21.9 % (n = 34)	68.2 % (n = 7)	
Pituitary Adenoma				
Macroadenoma	19.3 % (n = 26)	20.5 % (n = 24)	14.3 % (n = 2)	0.845
Microadenoma	62.2 % (n = 84)	60.3 % (n = 72)	71.4 % (n = 12)	
Comorbidities				
Diabetes Mellitus	47.2 % (n= 83)	47.7 % (n = 73)	43.5 % (n = 10)	0.440
Hypertension	57.9 % (n =102)	58.2 % (n = 89)	60.8 % (n = 14)	0.497
Hyperlipidemia	**59.1 % (n =104)**	**62.7 % (n = 96)**	**34.8 % (n = 8)**	**0.012**
Obesity	57.4 % (n =101)	56.9 % (n = 87)	60.9 % (n = 14)	0.449
Central Hypogonadism	13.7 % (n=24)	13.8 % (n = 21)	13.0 % (n = 3)	0.610
Physical Examination				
BMI	35.74 (± 0.99)	35.95 (± 1.09)	33.94 (± 1.10)	0.206
Systolic BP	136.47 (± 2.24)	136.30 (± 2.45)	138.0 (± 4.44)	0.746
Diastolic BP	86.27 (± 1.61)	86.21 (± 1.71)	86.83 (± 5.08)	0.911

BMI: Body Mass Index, BP: Blood Pressure

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Considering the pathologic aspects, lesions in pituitary gland were detected in 135 patients (76.3%) whereas, 41 (23.1%) patients had adrenal adenoma. In Cushing's disease with pituitary pathophysiology, macroadenoma was detected in 20.5% (n = 15) of female and 14.3% (n = 1) of male patients, and again, microadenoma frequency was 60.3% (n = 44) and 71.4% (n = 5) respectively. Macroadenoma and microadenoma were observed in 20% (n = 16) and 61.3% (n = 49) of the pituitary Cushing's patients, respectively. Although, microadenoma was more common in each group, no statistical significance could be shown between the sexes. A significant difference was observed in age at diagnosis (Adrenal: 44.96 vs. Pituitary: 43.63; p = 0.015). Student's t-test results revealed that patients with pituitary pathophysiology were diagnosed earlier. Except for the age of diagnosis, no significant difference was found between the sex of the patients, bone densitometry measurements, and other biochemical results (Table I).

The most common comorbidities in Cushing's group were hyperlipidemia (59.1%), hypertension (57.9%), obesity (57.4%), and diabetes mellitus (47.0%). Central hypogonadism (13.7%) was noted as the least frequent comorbidity. Analysis of demographic data revealed that the mean BMI was 35.74 (±0.99), and systolic and diastolic blood pressure were 136.47 (±2.24) and 86.27 (±1.61), respectively (Table I).

Table II. *Biochemistry and bone metabolism results of Cushing's patients*

	Total (n = 176)	Female (n = 153)	Male (n = 23)	p
Biochemistry Results				
ACTH	52.67 (± 4.58)	54.61 (± 5.00)	37.82 (± 9.99)	0.144
24 H Free Urine Cortisol	373.49 (± 39.58)	381.40 (± 43.69)	310.80 (± 70.80)	0.631
1 mg Dx Cortisol	10.36 (± 0.72)	10.44 (± 0.76)	9.88 (± 2.12)	0.804
2 mg Dx Cortisol	9.71 (± 0.99)	10.11 (± 1.09)	6.75 (± 1.89)	0.141
8 mg Dx Cortisol	5.41 (± 0.78)	5.37 (± 0.85)	5.76 (± 2.01)	0.859
TSH	**1.54 (± 0.10)**	**1.62 (± 0.11)**	**1.00 (± 0.20)**	**0.010**
T4	1.59 (± 0.19)	1.62 (± 0.22)	1.32 (± 0.16)	0.266
FSH	**16.92 (± 2.03)**	**18.01 (± 2.26)**	**8.89 (± 2.51)**	**0.010**
LH	**10.53 (± 1.20)**	**11.29 (± 1.34)**	**5.15 (± 1.28)**	**0.002**
PRL	**22.10 (± 3.98)**	**18.75 (± 1.78)**	**43.80 (± 27.54)**	**0.032**
FBG	111.46 (± 3.21)	112.44 (± 3.54)	104.96 (± 6.97)	0.345
HbA1C	6.28 (± 0.12)	6.31 (± 0.13)	5.99 (± 0.23)	0.224
Bone Metabolism Results				
Ca	9.40 (± 0.05)	9.40 (± 0.05)	9.39 (± 0.13)	0.926
P	3.50 (± 0.05)	3.55 (± 0.05)	3.19 (± 0.14)	**0.010**
PTH	57.87 (± 3.66)	56.13 (± 3.22)	71.07 (± 20.13)	0.192
25 – OH D Vitamin	18.67 (± 0.97)	18.70 (± 1.06)	18.47 (± 2.31)	0.928

ACTH: Adrenocorticotropic hormone, H: Hour, Dx: Dexamethasone, TSH: Thyroid stimulating hormone, T: Thyroid Hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PRL: Prolactin, FBG: Fasting blood glucose, HbA1C: Hemoglobin A1C, Ca: Calcium, P: Phosphor, PTH: Parathormone

Table II shows the differences between sexes in the biochemistry test results in Cushing's patients. TSH (p = 0.01), FSH (p = 0.01), LH (p = 0.002), and PRL (p = 0.032) levels varied between sexes. Cortisol levels in 1, 2, and 8 mg dexamethasone suppression tests were similar in both sexes. In contrast to cortisol values, 24-hour urinary-free cortisol levels were higher in women with 381.40 ug/day (± 43.69; p = 0.631). However, no significant difference has been shown between male and female patients.

Both biochemical tests and bone densitometry measurements were examined to analyze bone metabolism (Table II). Serum levels of Ca, P, PTH, and 25-OH vitamin D are given by age group. A significant difference was found only between P levels in sex groups. P levels were 3.55 mg/dL (± 0.05) in females, 3.19 mg/dL (± 0.14) in males, and 3.50 mg/dL (± 0.05) in the whole case group. P levels in male patients were significantly lower (p = 0.01).

Table III. *Bone marker results and interpretations of case and control groups*

	Case Group		Control Group		p
	Female (n = 85)	Male (n = 13)	Female (n = 72)	Male (n = 12)	
Bone Densitometry Results					
Femur Neck BMD	0.847 (± 0.017)	0.892 (± 0.036)	0.983 (± 0.155)	0.982 (± 0.143)	0.972
Femur Neck T Score	-0.399 (± 0.138)	-1.100 (± 0.297)	0.266 (± 1.281)	-0.383 (± 1.066)	0.810
Femur Neck Z Score	-0.343 (± 0.121)	-0.430 (± 0.175)	0.262 (± 1.097)	-0.025 (± 1.039)	0.844
L1 – L4 BMD	1.062 (± 0.040)	1.197 (± 0.773)	1.131 (± 0.153)	1.146 (± 0.144)	0.154
L1 – L4 T Score	-0.720 (± 0.149)	0.380 (± 0.586)	-0.117 (± 1.243)	0.267 (± 1.174)	0.801
L1 – L4 Z Score	-0.511 (± 0.182)	0.413 (± 0.672)	-	-	0.610
Patients based on Bone Density					
Low Bone Density*	5.9% (n = 5)	0.0% (n = 0)	0.0% (n = 0)	0.0% (n = 0)	0.160
Osteopenia	**16.5% (n = 14)**	**46.1% (n = 6)**	**11.1% (n=8)**	**8.3% (n = 1)**	**<0.001**
Osteoporosis	7.1% (n = 6)	0.0% (n = 0)	0.0% (n = 0)	0.0% (n = 0)	0.979

**Assessed by Z score, BMD: Bone mineral density*

Bone mineral density tests were encountered only in 98 patients in case groups, thus, we ran the analysis, considering this limitation. Although, high standard error occurred in BMD analysis, L1-4 T score differed in sex groups, being higher in males (p = 0.801). No significant difference was found in the femoral neck measurements (Table III).

Osteoporosis was less common than osteopenia in both sex subgroups. While, 16.5% of female patients had osteopenia, only 7.1% (n = 6) had osteoporosis. Similarly, 46.1% of male patients had osteopenia, and no patients with osteoporosis were recorded. In addition, low bone density was only found

in women at the rate of 5.9%. The chi-square test was used for osteopenia, and no statistically significant difference was found between the sex groups. Also, bone densitometry data of the patients in the control group revealed no significant difference between sex subgroups (Table III).

Table IV. *Bone marker results and interpretations of Cushing's syndrome patients by pathology locations*

	Adrenal (n = 41)	Pituitary (n = 134)	p
Femur Neck BMD	0.851 (± 0.350)	0.853 (± 0.279)	0.972
Femur Neck T Score	-0.888 (± 0.279)	-0.888 (± 0.141)	0.810
Femur Neck Z Score	-0.388 (± 0.249)	-0.339 (± 0.121)	0.844
L1 – L4 BMD	0.988 (± 0.088)	1.107 (± 0.039)	0.154
L1 – L4 T Score	-0.668 (± 0.375)	-0.581 (± 0.155)	0.801
L1 – L4 Z Score	-0.558 (± 0.450)	-0.326 (± 0.205)	0.610
Low Bone Density	11.1 % (n = 2)	3.4 % (n = 3)	0.160
Osteopenia	**39.1 % (n = 9)**	**23.4 % (n = 11)**	**< 0.001**
Osteoporosis	8.7 % (n = 2)	8.5 % (n = 4)	0.979

BMD: Bone mineral density

We also investigated low bone density, osteopenia, and osteoporosis in terms of Cushing's localization. In a similar fashion, osteoporosis was less common than osteopenia in both pituitary and adrenal groups. Osteopenia was present in 39.1% of adrenal Cushing's patients, with only 8.7% (n = 2) having osteoporosis. Whereas 23.4% of pituitary Cushing's patients had osteopenia, osteoporosis was recorded in 8.5%. However, low bone density is observed in 11.1% and 3.4% in adrenal and pituitary Cushing's patients. There was a statistically significant difference between the adrenal and pituitary Cushing's patients regarding osteopenia ($p < 0.001$) (Table IV).

In general, bone density measurements were lower in the case group compared to the control group. Within line with the study findings, osteoporosis was less frequent than osteopenia in both groups. While osteopenia was observed in 11.4% to 10.7% of the patients in the case and control groups, respectively, 2.8% (n = 5) of the case group had osteoporosis, and none encountered it in control. Also, low bone density appears to be around 2.8% in the case group, with none reported in the control.

Table V: *Correlations between bone narrow density biochemistry markers*

	Femur Neck BMD	p	L1 – L4 BMD	p
24 H Free Urine Cortisol	0.02	0.458	– 0.08	0.305
Basal ACTH	– 0.25	0.059	**– 0.28**	**0.039**
BMI	**0.45**	**0.002**	**0.29**	**0.036**
1 mg DST	**– 0.25**	**0.017**	-0.12	0.252

H: Hour, ACTH: Adrenocorticotropic hormone, BMI: Body mass index, DST: Dexamethasone

Collected data were further analyzed to reveal possible correlations in Table V. The analysis observed correlation between 24-hour urine cortisol, 1 mg dexamethasone suppression test results, and BMI and BMD values. Femur neck BMD and BMI indicated a moderate-to-high correlation. Also, an increase in BMI was aligned with an increase in both the femur neck and L1 L4 BMD values. The correlation between the suppression test of 1 mg dexamethasone and the femoral neck BMD was statistically significant ($p = 0.017$).

The mean 24-hour urinary cortisol level was 373.49 (± 39.58) in the whole case group, 381.40 (± 43.69) in females, and 310.80 (± 70.80) in male patients. Mean ACTH levels were 52.67 (± 4.58) in all patients, 54.61 (± 5.00) in females, and 37.82 (± 9.99) in males.

4. DISCUSSION

This study was conducted on a large group of Cushing's syndrome patients admitted to a single health facility. The ratio of female patients had a higher frequency of 3–8:1 compared to males [11,12]. Our findings were similar to other published findings. The female/male patient ratio in the study population was 6:1. Published papers stated that the community-based incidence of Cushing's disease is 2-3, and the prevalence is believed to be around 40 in 1.000,000 individuals.

The number of Cushing's patients investigated in this study was 176. This number can be considered relatively high compared to other studies on Cushing's disease published in the last five years. In our patient group, the average age at diagnosis was 44. Although, there was no significant difference between the sexes, women were diagnosed 1.5 years earlier. We had an elderly patient group when compared to the patient groups of published articles (44 vs 30-40 years of age); this can be attributed to the fact that our study center is positioned as a third-level treatment facility in current healthcare access policies [13]. We can assume that the patients we have encountered in our study either had an earlier final or differential diagnosis in low-level healthcare facilities. Patients may have to endure a lengthy process to receive an accurate diagnosis because of the current referral system. The older age of the study population may cause a bias in terms of bone density and comorbidity.

Pituitary Cushing's disease was diagnosed in 76.3% of the study patients and adrenal Cushing's disease in 23.1%. Only one male patient was diagnosed with ectopic Cushing's disease and the age at diagnosis was 55. Although, pituitary Cushing's disease was more common in both sexes, male patients had lower frequency than female patients. Previous studies reported the rate of pituitary Cushing's disease around 60-80% and adrenal Cushing's disease between 15-35% [14 – 17]. In this respect, our study was compatible with the literature.

Microadenoma was observed in 61.3% of the patients, with a higher incidence in males (71.4%). Some studies showed that the ratio of microadenoma / macroadenoma was 65 – 90% [17,18].

In general, articles reported hypertension frequency in Cushing's disease within the range of 45-100%. Diabetes was 25-68.8%, obesity was 32.1-75% and dyslipidemia was 9.1-71.4% among Cushing's patients [19]. Also, male sex had a higher risk of hypertension and dyslipidemia [20]. Data of our study showed that hyperlipidemia (59.1%) was the most common comorbidity in study cases. Hyperlipidemia was observed twice as often in women than in men. Our findings partially supported the recent literature.

Fasting blood sugar (FBS), HbA1c, and cholesterol were also examined in context with the study. Mean FBS (111.46 ± 3.21),

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mean HbA1C (6.28 ± 0.12), and mean total cholesterol (223.19 ± 4.06) levels were recorded for the case group. Measurements did not vary between the sexes. Liu's study with 73 Cushing's patients presented similar results, with no significant difference between males and females [21].

In our study, neither urinary cortisol nor ACTH levels differed between sexes. Contradictory data were published in 2014. A study on 67 Cushing's patients concluded that ACTH and urinary cortisol levels were higher in males [20].

Statistical analysis revealed a significant difference between the male and female case groups regarding L1-4 T scores. We concluded that the location of the mass in Cushing's disease patients and sex did not affect other measurements. The L1-4 BMD scores were the only measurement we found to be different between the case and control groups. The case group had lower scores in all parameters. The difference between the femur neck T score was especially higher than the other BMD scores. The femur neck T score average was – 0.836 (± 0.126) in the case group, while it was 0.172 (± 0.141) in the control.

A study by Apaydın et al., reported that femoral neck BMD (but not lumbar BMD) was independently associated with age, BMI, and PTH levels. Our findings regarding BMI association with BMD were compatible with the literature [22].

Mancini et al., in 2004, stated that osteoporosis caused by glucocorticoids might be reversible, but at least ten years of treatment was required for the normalization of BMD values [23]. Kawamata et al., observed an improvement in BMD values within three months after surgical intervention [24]. Di Somma and Colao suggested that alendronate treatment was more effective in improving BMD values than cortisol normalization [25].

We also investigated the bone densitometry measurements of the patients according to age. Although, patients with low bone density were more common in the our case group, the statistical inferences obtained were not considered strong enough to implement. Since, patients with low bone density and osteoporosis could not be detected in the control group, we hesitate to form a conclusion. Valassi et al., conducted a multicenter observational study in 620 Cushing's patients, which provides essential evidence regarding bone-related morbidities. In the study, osteopenic findings were detected in the spine at 40% and in the hips at 46% of the patients [26]. Our study results had a much lower rate (20.4%) of osteopenia. Another article published in 2010 reported that the prevalence of osteoporosis was between 30 and 67% in Cushing's patients [27]. Rates of osteoporosis / vertebral fracture varied between 24% and 68.8% in other studies in the literature [28]. In our patient group, osteopenia was observed more frequently in adrenal Cushing's patients than in pituitary Cushing's patients ($p = <0.001$).

A 2021 study conducted on 135 patients reported 75% vertebral fractures. In the same study, 40% of patients with vertebral fractures had normal bone mineral densitometry results [29]. Various studies reported that osteoporotic fracture prevalence was up to 50% and, in this setting, 15% of all patients with Cushing's syndrome also experienced non-traumatic peripheral fractures at the wrist, humerus, elbow, hip, patella, and ankle [11,30].

Miwa Kmura et al., in 2022, stressed that 24-hour urinary cortisol follow-up in patients with adrenal Cushing's disease had a significant and negative correlation with lumbar BMD [31]. Again in 2015, a study by Belaya et al., reported a significant association between plasma and urinary cortisol levels and osteoporosis and vertebral fracture [32]. In another study conducted in 2006 observed that more and more severe vertebral fractures were detected in cases with similar urinary cortisol excretion [33]. Our study also found the same interpretations in 24-hour urinary cortisol excretion and lumbar BMD ($p <0.05$).

Our study included 176 Cushing's patients who had been followed up in the Department of Endocrinology at Marmara University for the past 10 years. Compared to recent studies, our study had a high number of patients with Cushing's syndrome.

The age at diagnosis may be higher than what is described in the literature because our hospital is a third-level health center. The situation causes bias, particularly in regard to comorbidity and bone density. The patient and control groups both have missing data, which presents another challenge. Another limitation of this study is the low count of male patients and the presence of only one patient with ectopic Cushing's disease. The study's generalizability is limited by the retrospective nature of the study design.

Conclusion

In this study, our findings support the current literature that pituitary and adrenal Cushing's disease increases the risk of osteoporosis and osteopenia. Study analyses showed that osteopenia was more common in adrenal Cushing's patients than in pituitary Cushing's patients. Also, we encountered significant reverse correlations between femoral neck median BMD measurements, BMI, 24-hour urine cortisol level, and 1 mg dexamethasone suppression test. This correlation may be helpful in current clinical practice and in treating physicians to investigate possible fractures in relevant patients.

The study by design is limited to comprehensive interpretations. Writers suggest multicenter prospective studies with a larger sample size to gain strong evidence and better understand the disease.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, School of Medicine Clinical Research Ethics Committee (Reference no: 09.2017.118). The study was conducted in accordance with the World Medical Association Declaration of Helsinki and Good Clinical Practices Guidelines.

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Conflict of interest: Both authors have no conflict of interest to declare.

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of data, and/or analysis and interpretation of data, participated in drafting the article or revising it critically for important intellectual content, and gave final approval of the version to be submitted.

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