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RESEARCH

Comparison of visceral adipose tissue in patients with autonomous cortisol secretion and patients with the nonfunctional adrenal masses

Otonom kortizol sekresyonu olan hastalarda ve fonksiyonel olmayan adrenal kitleleri olan hastalarda viseral yağ dokusunun karşılaştırılması

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Abstract

Purpose: This study aimed to explore the impact of continuous autonomous cortisol secretion on visceral (VAT), abdominal subcutaneous (SAT) adipose tissue, and total body fat.

Materials and Methods: A total of 57 patients (36 female, 21 male) with adrenal masses, referred to our single center, were included in this study. Among them, 31 patients had adrenal cortical carcinoma (ACS) and 26 had nonfunctional adrenal mass (NFAM). Hormonal evaluation was conducted for all patients. Measurements of total, visceral, and subcutaneous adipose tissue were performed using 3.0 T magnetic resonance imaging (Ingenia, Philips Medical Systems, Best, The Netherlands).

Results: Mean age, gender distribution, and body mass index (BMI) were comparable between patients with ACS and NFAM. Patients with ACS exhibited higher volumes of both total (422.1±131.3 vs. 346.2±86.0 cm3) and visceral adipose tissue (199.9±77.3 vs. 160.6±60.8 cm3) compared to those with NFAM. Incidence rates of diabetes mellitus and hepatosteatosis were similar in both groups. Subcutaneous adipose tissue volumes, visceral-to-subcutaneous ratio, and visceral-to-total fat ratio showed no significant differences between the two groups.

Conclusion: Patients with ACS demonstrated increased total and visceral fat tissue volumes compared to NFAM patients matched for gender, age, and BMI. This observation may elucidate the potential influence of continuous mild autonomous cortisol secretion in ACS patients. Such findings could serve as indicators of heightened cardiovascular risk among ACS patients.

Keywords:. Autonomus cortisol secretion, nonfunctional adrenal incidentalomas, visceral adipose tissue, magnetic resonance imaging

Öz

Amaç: Bu çalışmada sürekli otonom kortizol sekresyonunun (OKS) viseral adipoz doku, abdominal subkutan yağ dokusu ve total vücut yağı üzerindeki etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Merkezimize sevk edilen adrenal kitlesi olan hastalar (n=57, kadın/erkek; 36/21) bu çalışmaya alındı. OKS'li otuz bir (n =31) hasta ve fonksiyonel olmayan adrenal insidentalomlu (FOAİ) 26 hasta dahil edildi. Hormonal değerlendirmeye yapıldı. Total, viseral ve subkutan yağ dokusu 3.0 T manyetik rezonans görüntüleme (Ingenia, Philips Medical Systems, Best, Hollanda) kullanılarak ölçüldü.

Bulgular: Ortalama yaş, cinsiyet ve vücut kitle indeksi ölçümleri OKS'li hastalar ile FOAİ'li hastalar arasında benzerdi. Toplam (422,1±131,3'e karşı 346,2±86,0 cm3) ve viseral yağ dokusu (199,9±77,3'e karşı 160,6±60,8 cm3) hacimleri, OKS'li hastalarda FOAİ'li hastalara göre artmıştı. Diabetes mellitus varlığı ve hepatosteatoz, OKS'li hastalar ile FOAİ'li hastalar arasında benzerdi. Deri altı yağ dokusu hacimleri, viseral/deri altı ve viseral/toplam yağ oranı iki grupta benzerdi.

Sonuç: OKS'li hastalarda total ve viseral yağ dokusu hacimleri cinsiyet, yaş ve BMI uyumlu FOAİ hastalarına göre daha yüksekti. Bu, OKS'li hastalarda sürekli hafif / hafif otonom kortizol sekresyonunun etkisini açıklayabilir.

Anahtar kelimeler: Otonom kortizol sekresyonu, fonksiyonel olmayan adrenal kitleleri, visceral yağ dokusu, manyetik rezonans görüntüleme

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INTRODUCTION

Autonomous cortisol secretion (ACS), previously referred to as subclinical Cushing syndrome, involves excessive cortisol secretion without the classical clinical manifestations of Cushing syndrome [1,2]. The latter definition was introduced and refined in the 2016 European guidelines to distinguish clearly between ACS and overt Cushing syndrome, as they exhibit distinct morbidity and mortality rates[3]. Specifically, the guidelines outline serum cortisol levels after 1-mg dexamethasone suppression: ≤1.8 μg/dL for nonfunctional adrenal incidentalomas, 1.9-5.0 μg/dL for possible ACS, and >5.0 μg/dL without overt Cushing syndrome manifestations for ACS. Up to now, a handful of studies[4-6] have established a definite association between ACS and metabolic syndrome, as well as a correlation with cardiovascular mortality. Moreover, a connection has been identified between subtle cortisol secretion and an increased risk of glycemic disregulation, atherosclerosis, and cardiovascular events.

In individuals with autonomous cortisol secretion, elevated levels of circulating cortisol can act as a driving factor for the presence of central adiposity due to glucocorticoid effects that stimulate adipocyte differentiation and triglyceride synthesis[7,8]. Prolonged hypercortisolism is primarily linked to the accumulation of visceral fat, although the mechanisms underlying this characteristic distribution of fat are only partially understood at present. It has been suggested that the overexpression of 11 beta-hydroxysteroid dehydrogenase in visceral compared to subcutaneous tissue could contribute to this fat distribution pattern, although data from human studies remain limited[9]. Furthermore, the preferential buildup of visceral fat in individuals with hypercortisolemia has been associated with the secretion of proinflammatory adipokines, potentially contributing to metabolic dysfunction[10-12].

Demonstrating the accumulation of adipose tissue in patients with ACS is important for understanding the clinical progression of the patients. And taking preventive measures against cardiovascular diseases, may be necessary in patients with ACS. For this reason, we aimed to compare the fat distribution pattern of patients with ACS with age sex and BMI matched patients with non-functional adrenal mass (NFAM).

MATERIAL AND METHODS

An Instutional Clinical Research Ethics Committee (decision number 114/10/24) approved this single-center retrospective study. Informed consent was obtained from patients according to the 1964 Helsinki Declaration principles before all diagnostic procedures.

In this study, patients followed due to adrenal incidentalomas in the endocrine outpatient clinic between January 2019 and January 2021 at Cukurova University Faculty of Medicine Hospital were analyzed retrospectively. Inclusion criteria were as follows: Only those patients who were between 18-70 years old with incidentally discovered unilateral and/or bilateral adrenal masses. Exclusion criteria were as follows: 1) lack of baseline or follow-up data, 2) active malignancy, 3) being dependent on alcohol or treated with steroids, estrogens or any drugs which could influence the steroid metabolism 4) diagnosed as Cushing syndrome, primary hyperaldosteronism, or pheochromocytoma. Between the specified dates, a total of 200 adrenal incidentaloma patients were identified. After applying exclusion criteria, one hundred eleven (ACS vs NFAM, 31 vs 80) patients were eligible but we random matched patients with ACS between the patients with NFAM (n=26) in case of age, gender, and body mass index (figure 1).

Endocrinological evaluation

All patients underwent baseline cortisol measurements (ranging from 6.7 to 22.6 mcg/dL), ACTH measurements (ranging from 10 to 60 pg/mL), and a 1 mg overnight dexamethasone suppression test. Patients with nonfunctional adrenal masses whose cortisol levels were suppressed (≤ 1.8 μg/dL) following the overnight dexamethasone suppression test, along with normal 24-hour urine levels of metanephrine-normetanephrine and a plasma aldosterone (ng/dL)/renin (ng/mL/h) ratio < 20, were categorized as "non-functional." The interpretation of the results of the 1 mg overnight dexamethasone suppression test was in accordance with the recent Clinical Practice Guidelines provided by the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ENSAT). Autonomous cortisol secretion was defined as serum cortisol levels after dexamethasone administration (1 mg on day 1 and 2 mg on day 2) exceeding 1.8 mcg/dL, along with additional measurements including 24-hour urinary free cortisol

excretion (UFC, ranging from 28.5 to 213 mcg/day), suppressed serum adrenocorticotrophic hormone (ACTH) levels (<10 IU/mL), and elevated midnight serum cortisol values in the absence of specific data for hypercortisolism. For the analysis of DHEAS (dehydroepiandrosterone sulphate), ACTH, and cortisol values, the enzymatic-labeled chemiluminescent immunometric assay method was used, and chemiluminescence was measured using the Beckman DXI 800 auto analyzer (Beckman Coulter Diagnostics, Fullerton, CA, USA). The high-performance liquid chromatography (HPLC) method was employed for the analysis of urine cortisol and metanephrine values. Endocrinological assessments were conducted by a specialist physician with over 10 years of experience in the field of endocrinology.

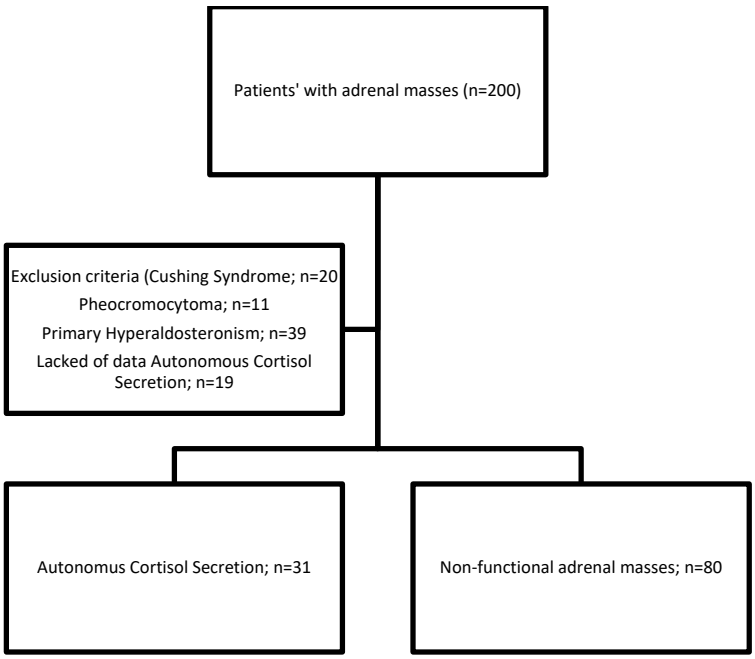

Figure 1. Flowchart of the study.

Adipose tissue measurement

In our hospital adrenal mass were evaluated with MRI. Therefore, MRI images were used for measuring patients' fat tissue volumes. Imaging was performed with a 3.0 T MRI (Ingenia, Philips Medical Systems, Best, The Netherlands) using a phased array body coil. The imaging were obtained as an axial T2 weighted without fat suppression. The imaging parameters were as follows:TR/TE of 1381 ms/62 ms;128 x 124 matrix size; 5 mm section thickness; 3.04 x 3.1 x5 mm measured voxel size; 1.52 x 1.52 x 5 mm reconstructed voxel size; sense acceleration factor of 2.5;34x34 cm field of view; number excitations = 3; and acquisition time of 1 min.

All measurements were performed by a board-certified radiologist with 8 years of experience in the field of abdominal radiology. For the measurement of fat thickness and the calculation of fat contents, the OsiriX software (OsiriX Foundation, Geneva, Switzerland) was employed. The sections at the L2-L3 intervertebral disc space were utilized for these measurements. Axial T2-weighted images without fat suppression were utilized for the current study. Initially, all adipose tissue was measured using a signal intensity index[13]. Subsequently, the volume of subcutaneous adipose tissue was measured by defining the boundary of the subcutaneous adipose tissue. The subcutaneous fat, which refers to the area of adipose tissue situated between the skin and the outermost aspect of the abdominal muscle wall, was isolated from the slice beyond this contour. The

calculation of visceral adipose tissue involved subtracting the total adipose tissue volume from the volume of subcutaneous adipose tissue. Muscular tissue volume was calculated using the same method (Figure 2). Measurements were performed in the first 20 patients as a training process. These results were not included in the study data. The same method was used for measurements in all patients.

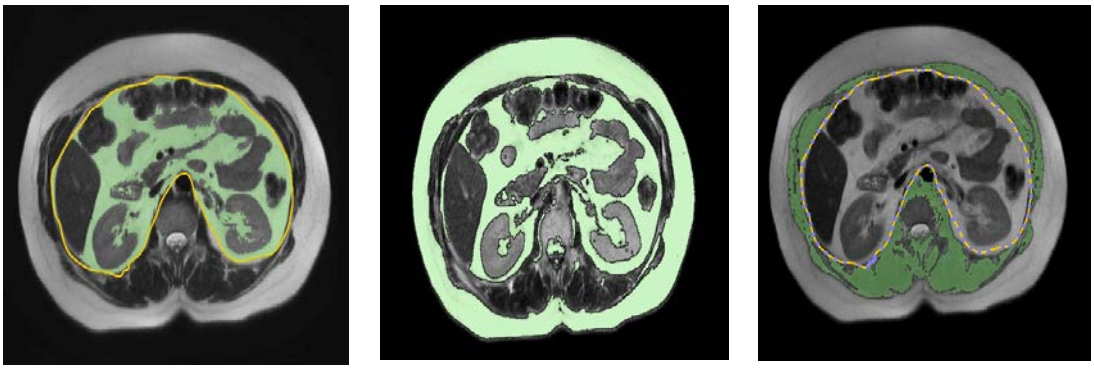

Figure 2. All fat (total, visceral, subcutaneous) measurements. 1a) Visceral fat tissue measurement 1b)Total fat tissue measurement 1c) Muscular tissue measurement

Statistical analysis

Patients with adrenal masses were categorized into two groups: those with non-functional adrenal masses and those with autonomous cortisol secretion, based on the outcomes of the 1 mg and 2 mg dexamethasone suppression tests, using the TURCOSA statistical software (Turcosa Analytical Ltd. Company, Turkey). Categorical variables were presented as counts and percentages, while continuous variables were summarized as means and standard deviations, or as medians and minimum-maximum values where appropriate. The chi-square test was employed to compare categorical variables between the two groups. The Shapiro-Wilk test was used to assess the normality of distribution for all parameters. Abnormal distributed parameters were compared by applying Mann-Whitney U test. Data that exhibited a normal distribution were compared using the Student's t-test. Correlations of the subcutaneous, visceral, and total fat measurement between all groups were calculated by using Spearman's test. The statistical level of significance for all tests was considered as 0.05.

RESULTS

The mean age of patients with non-functional adrenal masses (NFAM) (n=26) compared to those with autonomous cortisol secretion (ACS) (n=31) was 57.8±10.8 vs. 61±10.3, respectively (p=0.263). The female-to-male ratio between the two groups (NFAM vs. ACS, 15/11 vs. 21/10) was similar (p=0.4).

Baseline cortisol levels in patients with NFAM vs. ACS were 10.6±3.8 vs. 13.4±9.52 mcg/dL (p=0.165). The 24-hour urinary cortisol levels for patients with ACS were substantially higher at 317.8±361 mcg/day, compared to patients with NFAM (142.5±136 mcg/day, p=0.04). Cortisol levels following the 1 mg dexamethasone suppression test (DST) were 0.96±0.39 vs. 3.01±1.1 mcg/dL for patients with NFAM vs. ACS, respectively (p=0.015). Demographic, clinical, and laboratory characteristics of the patients are presented in Table 1.

The total fat content of patients with ACS measured 422.1±131.3 cm3 (range: 373.9-470.3 cm3), which was significantly higher compared to patients with NFAM (346.2±86.07 cm3, p=0.015).

Furthermore, a notable difference was observed in visceral fat volume between patients with ACS (199.9±77.3 cm3, range: 171.5-228.2) and those with NFAM (160.6±60.8 cm3, range: 136.1-185.2) (p=0.04). While the measurement of muscular tissue (psoas muscle) was similar between the two groups (ACS vs. NFAM, p=0.552), the ratio of total fat to muscle tissue tended to be higher in patients with ACS (p=0.056) (refer to Table 2).

Table 1. Baseline characteristics of the subjects

N=57	NFAM	ACS	P
Female/male	15/11	21/10	0.4
Age (year)	57.8±10.8	61±10.3	0.263
Presence of DM	67.3%	75.4 %	0.193
Presence of hepatosteatosis	42.3%	45.4%	0.829
Baseline cortisol (mcg/dL)	10.6±3.8	10.6±3.8	0.917
Cortisol after 1 mg DST (mcg/dL)	0.96±0.36	3.01±1.1	0.001
24-hour urine cortisol (mcg/day)	142.5±136	317.8 ±361	0.04
FPG (mg/dL)	155±65	170±30	0.9
Triglyceride (mg/dL)	185±35	205±35	0.7

NFAM: Non-functional adrenal masses, ACS: Autonomous cortisol secretion, DM: Diabetes Mellitus, DST: Dexamethasone supression test, FPG: Fasting Blood Glucose

Table 2. Fat area measurements of all subjects

N=57	NFAM (F/M; 15/11)	ACS (F/M; 21/10)	P
Total adipose tissue (cm^3)	346.2±86.0	422.1±131.4	0.015
Visceral adipose tissue (cm^3)	160.6±60.8	199.9±77.3	0.04
Subcutaneous adipose tissue (cm^3)	185.6±67.2	222.1±87.6	0.087
Muscular tissue (cm^3)	13.3±4.1	12.6±4.1	0.552
V/S	1.0±0.58	1.02±0.52	0.917
V/T	0.46±0.13	0.47±0.11	0.693
T/M	29.1±12.4	38.0±20.2	0.552

NFAI: Non-functional adrenal mass, ACS: Autonomous cortisol secretion, V/S: Visceral adipose/Subcutaneous adipose, V/T: Visceral adipose/total adipose, T/M: total adipose/muscular tissue

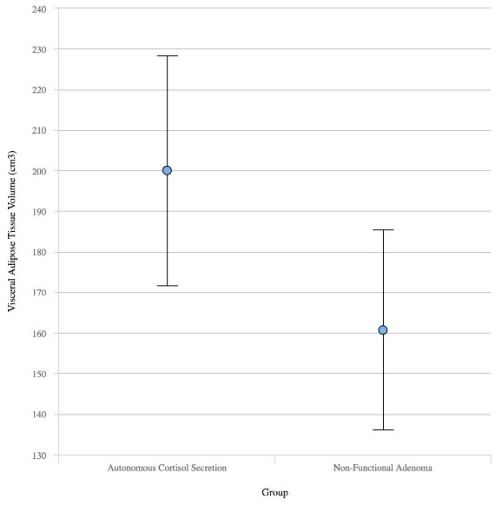

Figure 3. Comparison of visceral adipose tissue between the two groups

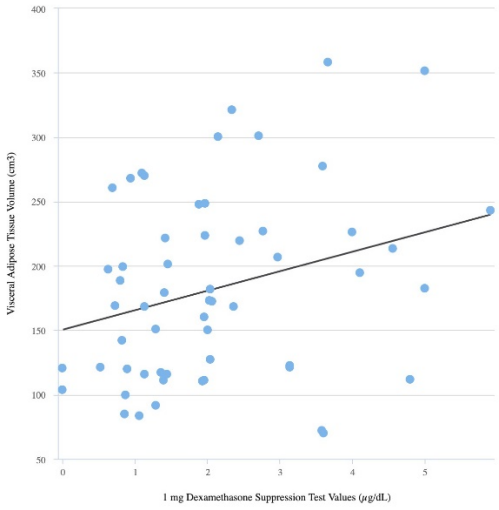

Figure 4. Correlation between serum cortisol levels after the 1 mg dexamethasone suppression test and measurement of visceral adipose volume

Moreover, a significant correlation was found between cortisol levels after the 1 mg DST and both total and visceral fat volume in all patients with adrenal masses (p=0.01, p=0.03) (refer to Figures 3 and 4).

DISCUSSION

There is compelling evidence indicating that hypercortisolemia is associated with severe morbidity, increased cardiovascular mortality, and metabolic abnormalities. Furthermore, autonomous cortisol secretion in adrenal masses has been linked to detrimental effects on the metabolic profile. In this study, we have demonstrated that patients with ACS exhibit higher volumes of both total and visceral adipose tissue compared to age-, gender-, and BMI-matched individuals with NFAM. Subcutaneous adipose tissue volumes, however, were similar between the two groups. Considering that visceral adipose tissue is an independent risk factor for the future onset of type 2 diabetes mellitus and cardiovascular disease, our findings suggest a potential association between ACS and the development of metabolic and cardiovascular disorders.

It is widely recognized that individuals with ACS do not exhibit specific signs or symptoms of hypercortisolism. Nonetheless, several studies have indicated an association between ACS and various metabolic disorders, including hypertension, type 2 diabetes, obesity, and increased mortality[14-16]. Some studies have reported increases in waist-to-hip ratio, visceral fat content, the prevalence and frequency of atheromatous plaques, and intima-media thickness within this context[17,18]. These parameters are well-established cardiovascular risk factors, as confirmed in patients with metabolic syndrome.

The effects of cortisol on adipose tissue are intricate, particularly in the case of visceral fat tissue, where glucocorticoid receptors are more abundant compared to subcutaneous fat tissue[19,20]. This abundance of receptors stimulates adipocyte differentiation and enhances triglyceride synthesis by activating lipoprotein lipase[21]. Visceral adipose tissue also releases proinflammatory and proatherogenic substances, including tumor necrosis factor-alpha and interleukin-6[22,23]. Additionally, visceral adipose tissue produces lower levels of adiponectin, a protective factor against cardiac remodeling[24]. Elevated visceral adiposity can contribute to the development of type 2 diabetes due to decreased adiponectin levels and the chronic inflammation associated with insulin resistance[25,26].

In our study, despite similar prevalence rates of diabetes mellitus and hepatosteatosis in both groups (p=0.191, p=0.829), patients with ACS had higher visceral fat tissue compared to patients with NFAM. Yener et al.[27] observed an increase in visceral adipose tissue thickness and visceral-to-total adipose tissue ratio in patients with ACS over a follow-up period of approximately three years. They also established correlations between post-DST cortisol levels, gender, and the increase in visceral adipose tissue. While visceral adiposity is closely linked to cardiovascular disease and diabetes, various confounding factors such as waist circumference, body mass index, and gender can influence the distribution of visceral and subcutaneous adipose tissue.

Debono and colleagues[28] demonstrated that patients with post-DST cortisol levels exceeding 1.8 mcg/dL had significantly higher visceral-to-subcutaneous and visceral-to-total fat ratios compared to those with serum cortisol levels below 1.8 mcg/dL. They further indicated that age and male sex were two factors positively correlated with the visceral-to-total fat ratio. In our study, following the matching of patients based on confounding factors including gender, age, and BMI, we observed higher total and visceral adipose tissue volumes in patients with ACS compared to patients with NFAMs. Similar to other studies' findings, we also identified correlations between post-DST cortisol levels and total and visceral fat measurements across all patients. However, the ratios of visceral-to-subcutaneous and visceral-to-total fat were not significantly different between the two groups (NFAM vs. ACS). This nonsignificant difference might be attributed to the limited number of patients in the study and the similarity in subcutaneous fat tissue thickness between both groups. Our study has several limitations. The sample size was small and, given that this concerns a retrospective study, we did not obtain the other allied parameters, such as measurements of waist circumference and waist to hip ratio. Due to insufficient data, patients could not be evaluated for cardiovascular disease. Radiological measurements might have been influenced by inter-observer

variability since they were conducted by a single radiologist.

In conclusion, it was observed that total and visceral fat tissues of ACS patients increased compared to patients with NFAM. This situation could be an indicator of elevated cardiovascular disease risk in ACS. However, to arrive at a definitive conclusion, there is a need for studies where these two groups of patients are subjected to long-term follow-up and evaluated in terms of cardiovascular diseases.

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Human and animal rights: No animals were used in this study. The research was performed in humans in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/)

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