Turk J Endocrinol Metab. 2020;24:277-283

A Slight Contribution of Retroperitoneal Fat Accumulation to the Metabolic Comorbidities of Patients with Autonomous Cortisol Production

Retroperitoneal Yağ Birikiminin Otonom Kortizol Üretimi Olan Hastaların Metabolik Komorbiditelerine Hafif Derecede Katkısı

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Abstract

Objective: Autonomous cortisol secretion (ACS) in the adrenal incidentaloma (AI) refers to an excess of low-grade autonomous cortisol without the clinical symptoms of Cushing's syndrome (CS), while ACS is shown to be related to the accumulation of visceral fat. To elucidate whether the accumulation of fat in different compartments, such as total adipose tissue (TAT), peritoneal adipose tissue (PAT), retroperitoneal adipose tissue (RPAT), and subcutaneous adipose tissue (SAT) could predict metabolic problems in patients with ACS. **Material and Methods:** We conducted a retrospective cohort study, including 74 patients diagnosed with ACS and 8 patients diagnosed with CS. 8 patients with ACS had also undergone adrenalectomy. Baseline (initial admission) and follow-up (most recent visit) data, including the clinical, laboratory, and radiological parameters, were evaluated. **Results:** Total adipose tissue (TAT), visceral adipose tissue (VAT), PAT, and RPAT increased significantly while the SAT remained stable in patients with ACS. Adrenalectomy in patients with CS resulted in a significant reduction of TAT, VAT, PAT, and RPAT while SAT was relatively preserved. However, no significant change was observed in surgically treated patients with ACS. The independent predictors of cardiovascular events, glucose intolerance, or elevated blood pressure were age, the level of cortisol post dexamethasone suppression test (DexF), and an increase in the RPAT. **Conclusion:** Visceral fat accumulation, particularly in the retroperitoneal area, slightly contributed to the development of metabolic problems in patients with ACS.

Keywords: Autonomous cortisol secretion; multidetector computed tomography; visceral fat; subcutaneous fat; abdominal adipose tissue; retroperitoneal fat

Özet

Amaç: Adrenal insidentalomalarda görülen otonom kortizol sekresyonu (OKS), visseral yağ akümülasyonuna neden olmakla birlikte, Cushing Sendromu (CS) klinik bulguları oluşturmadan, düşük dereceli otonom kortizol yüksekliğine yol açmaktadır. Çalışmamızda, total (TAT), peritoneal (PAT), retroperitoneal (RPAT) ve subkutanöz (SAT) gibi değişik kompartımanlardaki yağ akümülasyonunun OKS olan hastalardaki metabolik problemleri öngörme gücünün değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmamız, OKS tanılı 74 hasta ve CS tanılı 8 hastanın dâhil edildiği retrospektif kohort çalışmasıdır. OKS tanısı olan 8 hastaya adrenalektomi cerrahisi uygulanmıştır. İlk değerlendirme ve takip değerlendirmesine (en son gerçekleştirilen değerlendirme) ait klinik, laboratuvar ve radyolojik parametreler değerlendirilmiştir. **Bulgular:** OKS olan hastalarda total adipoz doku (TAT), visseral adipoz doku (VAT), PAT ve RPAT anlamlı şekilde artış gösterirken, SAT stabil kalmaktadır. CS hastalarda uygulanan adrenalektomi, anlamlı düzeyde TAT, VAT, PAT ve RPAT azalışına sebep olmakta iken, SAT rölatif olarak korunmuştur. Bununla birlitke, cerrahi olarak tedavi edilen OKS hastalarında anlamlı değişiklik izlenmemiştir. Yaş, deksametazon supresyon testi sonrası kortizol düzeyleri (DexF) ve RPAT daki artış, kardiyovaskuler olay, glukoz intoleransı ve yüksek tansiyon için bağımsız prediktörler olarak saptanmıştır. **Sonuç:** Özellikle retroperitoneal alandaki viseral yağ akümülasyonu, OKS'li hastalarda metabolik problemlerin gelişmesine az da olsa katkıda bulunmaktadır.

Anahtar kelimeler: Otonom kortizol sekresyonu; multidedektör bilgisayarlı tomografi; visseral yağ; subkutanöz yağ; abdominal yağ dokusu; retroperitoneal yağ dokusu

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Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 15 May 2020 **Received in revised form:** 12 Nov 2020 **Accepted:** 16 Nov 2020 **Available online:** 10 Dec 2020

DOI: 10.25179/tjem.2020-76323

Introduction

The visceral adiposity and ectopic fat accumulation pose a cardiometabolic risk. Visceral adipose tissue (VAT), measured by computed tomography (CT) or magnetic resonance imaging (MRI), is an independent marker for metabolic and cardiovascular morbidity and mortality (1-3). Visceral adipose tissue has distinctive properties not shared by subcutaneous adipose tissue (SAT), such as exacerbating hyperinsulinemia, increased hepatic production of triglyceride-rich lipoproteins and glucose, as well as increased production of inflammatory cytokines. In physiological conditions, subcutaneous adipose tissue serves as a metabolic pool for excess triglycerides. Several observations have shown that the accumulation of VAT occurs when the expandability and plasticity of SAT fail (3).
Endogenous hypercortisolism results in redistribution of fat tissue that leads to central obesity and metabolic complications such as glucose intolerance, elevated blood pressure, and future myocardial infarction. Exposure to chronic glucocorticoid is associated with the expansion of adipose tissue and a positive balance of lipid storage, suggesting an increase in the total body lipogenesis despite the increased lipolysis (4). The effects of cortisol on VAT result in different features. The mRNA expression of the glucocorticoid receptor is higher in omental fat than in the SAT; thus, glucocorticoids induce insulin resistance in human omental fat tissue but not in subcutaneous adipocytes (5-7). Glucocorticoid induces lipolysis that is prominent in SAT, while the overexpression of lipoprotein lipase induces increased uptake of triglyceride by the abdominal adipocytes, resulting in increased deposition of omental fat (4).
Autonomous cortisol secretion (ACS) in the adrenal incidentaloma (AI) refers to an excess of low-grade autonomous cortisol without showing any clinical symptoms of Cushing's syndrome (CS) (8). Previous studies have clearly demonstrated that patients with ACS have an increased rate of metabolic comorbidities and cardiovascular mortality compared to their non-functioning counterparts (9,10).
One retrospective cohort study by our group (11) along with one cross-sectional study (12) demonstrated significantly increased VAT at the time of admission and follow-up of patients with ACS. In this study, we hypothesized that the change of fat mass in different compartments of adipose tissue might contribute to the increased prevalence of metabolic and cardiovascular comorbidities in patients with ACS at the time of follow-up. For this purpose, we evaluated the AI patients with ACS, assessed their long-term comorbidities, and analyzed whether the alterations in different fat compartment areas had any impact on the development of metabolic and cardiovascular deteriorations.

Material and Methods

Data Collection

This retrospective study was approved by the ethics committee of Dokuz Eylül University Hospital (Dokuz Eylul Universitesi Girisimsel Olmayan Arastirmalar Etik Kurulu, file no: 2017/19-13, dated 27.07.2017) and was conducted as per the Helsinki Declaration Principles. The need for informed consent was waived by the ethics committee. We used the data of 74 patients diagnosed with ACS and 8 patients diagnosed with CS. We used data of all eligible patients who attended the routine follow-up between January 2017 and January 2019. We also recruited 8 patients having ACTH-independent overt hypercortisolism (CS) with follow-up scans performed due to unrelated conditions. The exclusion criteria were as follows: suppressed levels of DexF during admission and follow-up, non-adenoma appearance on computed tomography (CT), primary hyperaldosteronism, pheochromocytoma, adrenalectomy without prior follow-up, active malignancy, and lack of baseline and/or follow-up evaluation.

Hormonal Assessment of Participants

The hormonal evaluation of the participants included the measurement of corticotrophin (ACTH) and dehydroepiandrosteanadione (DHEAS), overnight 1 mg dexamethasone suppression test (DST), urinary metanephrine, normetanephrine, and plasma aldosterone to plasma renin activity ratio. Autonomous cortisol production (ACS) was defined in the thresholds of post-DST

cortisol which was recommended by the ESE-ENSAT guidelines (8).

Routine Follow-up Protocol

We suggest an annual follow-up to all the AI patients for the first three years, and then the duration may depend on the individual. At each follow-up visit, the physical examination, imaging, hormonal evaluation, routine laboratory tests with investigations on metabolic comorbidities are carried out.

Measurements and Routine Laboratory Investigations

The Adrenal incidentaloma (AI) patients underwent clinical evaluation at each visit, where concomitant type 2 diabetes mellitus, arterial hypertension, and cardiovascular events were tested. Clinical symptoms and signs of hypercortisolemia, along with weight, height, waist circumference, and blood pressure (Erka, Bad Tölz, Germany), were noted. A systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher was used to diagnose hypertension. Also, the diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association (ADA) at the time of assessment. The current smokers were defined as individuals who were currently smoking any type of tobacco, whereas former smokers were people who had ceased smoking at least six months before the assessment, and non-smokers were patients who had never smoked.

Measurement of the Fat Compartment Areas

One investigator who was blinded to the biochemical data measured the fat compartment areas during the routine follow-up CT scans. Until 2008, CT imaging in our institute was performed through an Mx8000 Quad scanner (Philips Medical Systems), which was subsequently replaced by a Philips Brilliance 64 scanner (Philips Medical Systems). An axial view was used with the subject lying in the supine position. The fat compartments were measured on Philips Extended Brilliance Workspace (software version V3.5.0.22.54) using QCT (quantitative computed tomography) software. A single slice was evaluated at the level of L1/2 disk space, which was identified for fat measurements because the VAT at the T12-L1 and L1-L2 landmarks had much stronger associations with metabolic syndrome than those at the other sites. The fat area measurement method was described in our previous study (11). Additionally, we further divided the visceral fat into peritoneal and retroperitoneal areas along the boundary, which was comprised of the posterior surface of small bowels, the anterior wall of the aorta, medial border of the spleen, posteromedial border of liver, anterior border of the vertebral column, and inner-most wall muscles of the posterior abdomen. The interfascial planes, anterior perirenal fascia (Gerota fascia), and posterior perirenal fascia (Zuckerkandl fascia) were visible in most of the participants, which was also used to outline the boundary (Figure 1). Peritoneal adipose tissue (PAT) was calculated by subtracting the retroperitoneal adipose tissue (RPAT) from visceral adipose tissue (VAT). Subcutaneous fat was defined as the adipose tissue area between the skin and the outermost abdominal muscle wall. The SAT area was calculated by subtracting the VAT area from the TAT area. The ratio of VAT to SAT area (V:S) and VAT to TAT (V: T) area were also calculated to eliminate the possible bias, which was secondary to the differences found in individual body size.

Statistical Analysis

Statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Illinois, USA). The distribution of variables was assessed using The Kolmogorov Smirnov test. Variables with asymmetric distribution were presented as median values and (min-max) values. For continuous variables with asymmetric distribution, differences between the groups were analyzed using the Mann-Whitney *U* test or the Independent samples *T*-test. Changes in the measurements of the fat area between the baseline and follow-up were analyzed using the Wilcoxon signed-rank test for repeated measurements. Logistic regression analysis models were used to investigate the impact of the fat compartment-specific changes on the development of metabolic comorbidities. Two-tailed tests were conducted, and the results of all statistical analyses were considered significant if $P<0.05$.

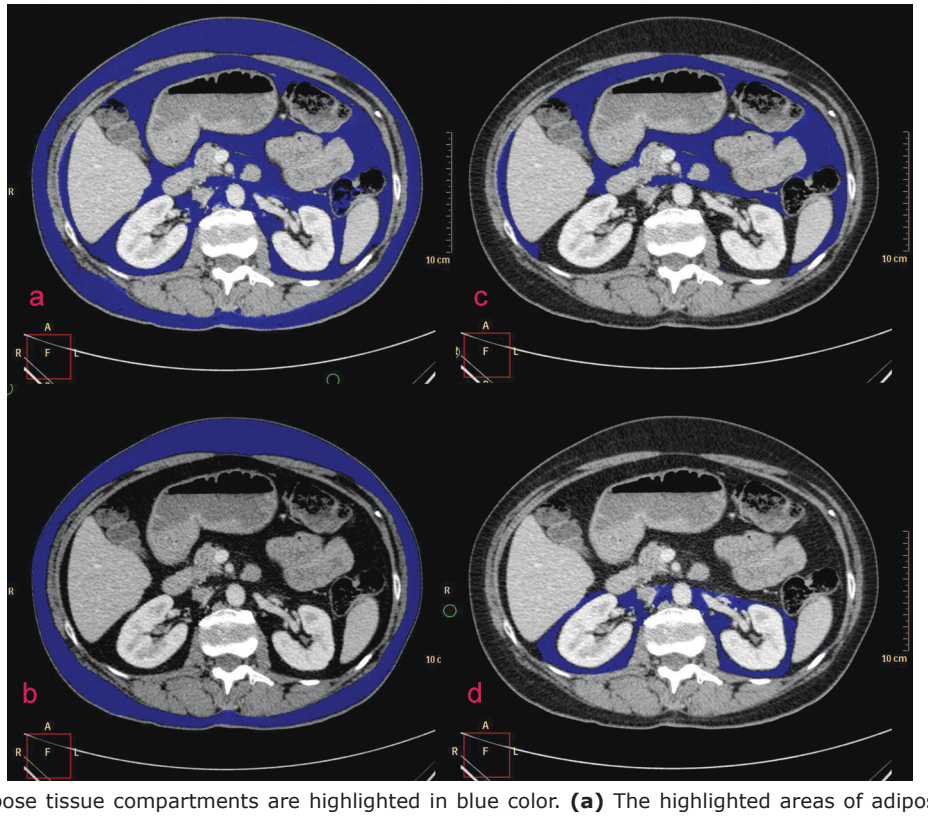

Figure 1. Adipose tissue compartments are highlighted in blue color. **(a)** The highlighted areas of adipose tissue were measured to calculate TAT, **(b)** Blue colored areas show the measurement of the SAT, **(c)** and **(d)** highlight PAT and RPAT, respectively.
TAT: Total adipose tissue; SAT: Subcutaneous adipose tissue; PAT: Peritoneal adipose tissue; RPAT: Retroperitoneal adipose tissue.

Results

Baseline Characteristics of Patients

The baseline demographic and endocrine data of patients with ACS (n=74) is described in Table 1. Additionally, 8 patients with CS were also recruited. Out of the 74 patients with ACS, 8 patients underwent adrenalectomy because of the tumor size and CT appearance (n=3) or worsening of the metabolic profile during follow-up (n=5).

Changes in the Measurement of the Fat Area During Follow-up

Fat area measurements during follow-up are described in Table 2. The total adipose tissue, VAT, PAT, and RPAT showed a significant increase while the SAT remained stable in patients with ACS. Adrenalectomy in CS patients resulted in a significant reduction of TAT, VAT, PAT, and RPAT while SAT was relatively preserved. However, no significant change was observed in surgically treated patients with ACS.

Association Between Fat Accumulation and Metabolic Comorbidities

Fat compartment-specific changes and their impact on the development of metabolic comorbidities were investigated in patients with ACS (Table 3). We conducted several logistic regression analysis models for this purpose, where all the models included independent variables such as age, gender, follow-up DexF, and fat mass change in different compartments (deltaRP, deltaP, and deltaSC separately in each model) for the development or deterioration of metabolic comorbidities (AHT, DM, CVD).
Age was the sole independent variable that predicted Cardiovascular disease (CVD) with an odds ratio (OR) of 1.18, 1.32, and 1.44 ($p<0.05$ in all models). The contribution of the DexF, gender, or fat mass change in different compartments was not significant. Delta RP was the only significant independent predictor of glucose tolerance deterioration, recording an OR of 1.02 ($p=0.038$). The assessment of factors that predicted the

Table 1. Baseline characteristics of participants.

	ACS
Total number	74
Female, n	61
Age	53.5 (9.8)
Menopause,%	54.1
BMI, kg/m^2	29.9 (5.6)
Bilateral adenoma, %	35.1
Adenoma size, mm	30 (12-65)
Dex F, µg/dL[a,b]	2.8 (1.3-21.7)
ACTH, pg/mL	7.6 (1.8-36.7)
Adrenalectomy, n	8
Diabetes Mellitus, %	20.3
IFG+IGT, %	14.9
Arterial Hypertension, %	45.9
CVD, %	2.8

[a]Two patients with ACS had marginal baseline Dex F values. Patient #1 with a baseline Dex F of 21.7 µg/dL has been on routine follow-up for nine years without having Cushing's syndrome stigmata. Patient #2 with a baseline Dex F of 14 µg/dL underwent adrenalectomy due to metabolic comorbidities. [b]Seven patients had discordant baseline and follow-up Dex F.
Dex F: Post dexamethasone cortisol; ACTH: Corticotropin; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; CVD: Cardiovascular disease.

worsening of blood pressure control also revealed the significant contribution of DexF, DeltaP, and Delta RP. Odds ratios for DexF were found to be 1.33, 1.37, and 1.49, whereas for Delta RP and delta P the OR was found to be 1.02 and 1.01, respectively ($p<0.05$ in all models).

Discussion

Our study shows that the metabolic comorbidities observed in patients with ACS are strongly related to DexF and age but only slightly related to the accumulation of retroperitoneal fat mass.

The abdominal cavity consists of 3 different adipose tissues, namely omental, mesenteric, and retroperitoneal, and the term visceral fat applies to the sum of these compartments. The visceral fat accumulation predicts metabolic and cardiovascular risks, along with mortality (13-15). Centripetal obesity is a frequent feature of hypercortisolism, where glucocorticoids induce key adipogenic transcription factors (16) and regulate 20% of the expressed genes in adipose tissues (17). Visceral adipose tissue

Table 2. Analysis of fat compartment areas at follow-up.

	ACS (follow-up)		ACS (adrenalectomy)		CS (adrenalectomy)	
	Baseline	Follow-up	Baseline	Post-operative	Baseline	Post-operative
Number of Patients, n	66		8		8	
Follow-up duration, m	35 (12-156)		24 (12-60)		31 (9-132)	
TAT (cm^2)	269.1 (52-719)	293.2 (115-161)*	334.4 (92-854)	291 (101-718)	368.8(161-616)	233.7 (31-396)
VAT (cm^2)	85.8 (10-337)	115.7 (9-526) **	88.6 (21-361)	88.7 (39-298)	153.6 (70-397)	121.7 (8-149) *
RPAT (cm^2)	28.9 (2-129)	40.9 (3-187) **	23.7 (9-114)	23.7 (7-120)	47.4 (29-153)	44.9 (2-49) *
PAT (cm^2)	59.6 (8-207)	76.1 (6-339) *	71.2 (12-246)	61 (31-178)	106.4 (40-244)	76.2 (6-100) *
SAT (cm^2)	165.5 (36-557)	161.1 (38-557)	245.8 (71-494)	209.2 (62-421)	189.3 (69-306)	131.6 (21-248)

TAT: Total adipose tissue; SAT: Subcutaneous adipose tissue; PAT: Peritoneal adipose tissue; RPAT: Retroperitoneal adipose tissue.
* $p<0.05$, ** $p<0.01$ vs. Baseline.

Table 3. Metabolic and cardiovascular complications during the follow-up visit.

	ACS (follow-up)	ACS (adrenalectomy)	CS (adrenalectomy)
Number of Patients, n	66	8	8
Follow-up duration, m	35 (12-156)	24 (12-60)	31 (9-132)
New-onset or poor DM,%	15.2	-	-
Improved DM control,%	-	42.9	100
New-onset or poor AHT,%	17.5	-	-
Improved AHT control,%	-	14.3	100
New CV event	7.8	-	-

DM: Diabetes mellitus; AHT: Arterial hypertension; CV: Cardiovascular.

is a key target for glucocorticoid effects. It allows the binding of glucocorticoid and mRNA expression of the glucocorticoid receptor, which is more prominent (5). The induction of insulin resistance by glucocorticoids is observed in the VAT but not in the SAT (18).

Two previous studies have also shown the accumulation of visceral fat in patients with ACS. Additionally, a cross-sectional study has demonstrated significantly increased VAT in patients with ACS (12). Another study from our group showed that a non-suppressed DexF at both baseline and follow-up of ~3 years was associated with a significant increase in the visceral fat (11). The novelty of the present study was that for the first time, we found that both peritoneal and retroperitoneal fat mass was found significantly increased in patients with ACS during follow-up, but in CS patients, it was found to be significantly decreased after adrenalectomy. Interestingly, among fat compartment parameters, only retroperitoneal fat accumulation was an independent predictor of metabolic problems in patients with ACS, which could be linked to diverse features of visceral fat compartments. The venous drainage and adipocytokine secretion pattern of retroperitoneal fat were shown to be different from that of the omental and mesenteric fat (19,20).

We also showed that age and DexF levels were other independent predictors of metabolic problems in patients with ACS. This observation is parallel to the current knowledge as well. The magnitude of the autonomous cortisol production in an AI can be extrapolated by interpreting DexF values. Both DexF and the presence of ACS is linked to unfavorable metabolic profiles and increased cardiovascular risk (21,22).

Conclusion

In conclusion, the unfavorable metabolic outcomes observed in the patients with ACS are strongly related to the magnitude of hypercortisolism and age, along with the encountered visceral fat compartment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mustafa M. Barış, Ahmet Peker, Serkan Yener; Design: Mustafa M. Barış, Ahmet Peker, Serkan Yener; Control/Supervision: Mustafa M. Barış, Serkan Yener, Mustafa Seçil; Data Collection and/or Processing: Mustafa M. Barış, Ahmet Peker, Serkan Yener, Ozan Bozkurt; Analysis and/or Interpretation: Mustafa M. Barış,

Serkan Yener, Ozan Bozkurt; Literature Review: Writing the Article: Ahmet Peker, Serkan Yener, Ömer Demir; Critical Review: Mustafa Seçil, Ömer Demir; Materials: Serkan Yener, Ozan Bozkurt, Ömer Demir.

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