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CT-based Abdominal Adipose Tissue Area Changes in Patients Undergoing Adrenalectomy Due to Cushing's Syndrome and Non-functioning Adenomas

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ABSTRACT

Background The majority of Cushing's syndrome (CS) cases constitute patients with functional adrenal adenomas. In adrenal CS, visceral adipose tissue (VAT) area, VAT/subcutaneous adipose tissue (SAT), and VAT/total adipose tissue (TAT) ratios are expected to decrease in response to adrenalectomy, although no change is expected in non-functioning adrenal adenomas (NFA).
Objective To evaluate the changes in VAT, SAT, TAT areas and VAT/SAT, VAT/TAT ratios using computed tomography (CT) in patients who underwent adrenalectomy due to adenomas.
Methods Preoperative and postoperative CT of 32 patients (16 with CS and 16 with NFA) were retrospectively evaluated. The VAT, SAT, TAT areas were obtained from CT at the level of L1–2 intervertebral disc space, and the VAT/SAT, VAT/TAT ratios were calculated. The postoperative parameter changes in both groups were evaluated compared to the preoperative values. The level of statistical significance was considered as $p < 0.05$.
Results The time interval between preoperative and postoperative CT measurements were 10.37 months (6–17) in CS and 9.75 months (7–15) in NFA groups ($p = 073$). Preoperative CT indicated that the patients with CS had larger VAT and TAT areas ($p = 0.03$, $p = 0.02$) but SAT remained unchanged ($p = 0.08$). However, postoperative CT revealed that there was no difference between the two groups in terms of VAT, TAT, and SAT areas ($p = 0.87$, $p = 0.36$, $p = 0.14$). Postoperatively, in patients with CS, there was a decrease in VAT and TAT areas ($p = 0.01$ for both) and VAT/SAT and VAT/TAT ratios ($p = 0.03$, $p = 0.02$) but SAT remained unchanged ($p = 0.10$). In patients with NFA, no change was detected in the postoperative SAT, TAT, and VAT areas ($p = 0.12$, $p = 0.40$, $p = 0.99$) or the VAT/SAT and VAT/TAT ratios ($p = 0.38$, $p = 0.62$).
Conclusions Adrenalectomy is an effective treatment method leading to a decrease in the VAT, TAT areas, and VAT/SAT and VAT/TAT ratios in patients with cortisol producing adrenocortical adenoma. Thus, CT facilitates quantitative demonstration of the changes while evaluating the response of these patients to treatment.

Introduction

Adrenal adenomas are the most common adrenal lesions found incidentally when performing abdominal imaging usually for other reasons [1–4]. The vast majority of adrenal adenomas are not hormonally active, and therefore they are often asymptomatic [2, 4–7]. On the other hand, functional adenomas produce excess hormones and can present with clinical symptoms [6]. In patients with functional adrenal adenomas, a majority of cases are of Cushing's syndrome (CS) [6]. Fifteen percent of adrenal incidentalomas show hypersecretion of hormones. The reported prevalence of

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hypercortisolism is between 1 – 29 % (average 9 %) and that of hyperaldosteronism is 1.5 – 3.3 % [8].

Non-functioning adrenal adenomas (NFA) are usually asymptomatic and discovered incidentally on abdominal imaging. Rarely, large-sized adenomas may cause a local mass effect. Cortisol producing adrenocortical adenomas can present with the symptoms of CS including obesity, hypertension, hyperglycemia, fatigue, depression, menstrual irregularities, proximal muscle weakness, acne, facial plethora, striae, fractures, and osteopenia [9].

In CS and possible autonomous cortisol production (the latter being those with adrenal adenomas but low-grade excess cortisol production without obvious clinical signs of hypercortisolism), a negative metabolic profile, increased cardiovascular risk, and mortality are observed [2, 7, 10, 11], which have been attributed to increased visceral adipose distribution indicated by computed tomography (CT) studies [12, 13]. The preferred method of treatment in adrenal CS cases is unilateral removal of the adrenal gland with the lesion [6, 14]. In NFAs, follow-up is mostly preferred; however, diagnostic adrenalectomy can be undertaken in certain cases with non-specific findings of adenomas, such as > 4 cm lesion size, new emergence or increased lesion size during the follow-up, and a density of > 10 Hounsfield units (HU) or absolute/relative washout values of < 60/40 % on non-contrast-enhanced CT [3, 6, 14]. Nevertheless, there is limited study on this subject.

Hong et al. evaluated changes in CT determined visceral adipose tissue (VAT) area and VAT/ subcutaneous adipose tissue (SAT) ratio after adrenalectomy in patients with CS and NFA [15]. In patients with successful adrenalectomy due to NFA, no change is expected in the VAT, SAT and total adipose tissue (TAT) areas or the VAT/SAT and VAT/TAT ratios. However, in adrenal CS, VAT area, VAT/SAT and VAT/TAT ratios are expected to decrease in response to adrenalectomy. Based on this hypothesis, in this study, we evaluated the changes in the VAT, SAT, and TAT areas and the VAT/SAT and VAT/TAT ratios in patients with adrenal CS and those with NFA.

Materials and Methods

Before initiating the study, the approval of the local ethics committee was obtained (date: 10.12.2019, no:25403353–050.99-E.145728). The study was conducted in accordance with the principles of the Declaration of Helsinki. All image data used in this study were obtained from routine imaging at our institution. Datasets were evaluated retrospectively, therefore, approval and informed consent were not necessary and waived by our local institutional review board.

The study was conducted at a tertiary university hospital. All the CT imaging (pre and postoperative) and adrenalectomy were done in the same hospital.

Study participants

The files of 109 patients who underwent adrenalectomy due to adrenal masses between January 1, 2016, and January 1, 2020, were retrospectively examined. Based on the pathology reports, 61 patients with non-adenoma lesions (malignancy, pheochromocytoma, adrenocortical carcinoma, myelolipoma, cyst, ganglioneuroma, oncocytic tumor, lymphoma, and tuberculosis) were excluded from the study. In addition, 10 patients without a postoperative CT examination, four patients with their CT images covering only the adrenal gland and retroperitoneum but not the entire skin surface section, and two patients with Conn's syndrome were also excluded from the study. However, CT is not routinely performed in clinical practice, therefore, post-operative CT examinations were performed for reasons such as post-operative pain or hernia. The remaining 32 patients in this study underwent CT examination. All the adrenal incidentalomas are evaluated at our tertiary university hospital, according to recommendations of the European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors [14]. These 32 patients in our study with adrenal incidentalomas were also evaluated according to the above-mentioned guideline (patients underwent a 1 mg dexamethasone suppression test overnight to exclude excess cortisol). Post dexamethasone test, serum cortisol level ≤ 50 nmol/L (≤ 1.8 µg/dL) was accepted as a diagnostic criterion for the exclusion of autonomous cortisol secretion, and the level > 138 nmol/L (> 5.0 µg/dL) was considered as evidence of autonomous cortisol secretion and CS. The levels between 51 and 138 nmol/L (1.9–5.0 µg/dL) were considered as evidence of possible autonomous cortisol secretion. Among 32 patients, 16 had CS; in the remaining sixteen patients, no endocrinological pathology of adrenal origin was detected according to the hormone analysis. These patients were categorized into two groups as those with CS (Group 1) and those with NFA (Group 2). A flowchart for the categorization is presented in ▶ **Fig. 1**. The patients in group 1 were operated on for high cortisol levels and those in group 2 were operated on because of a lack of typical CT findings for adenomas.

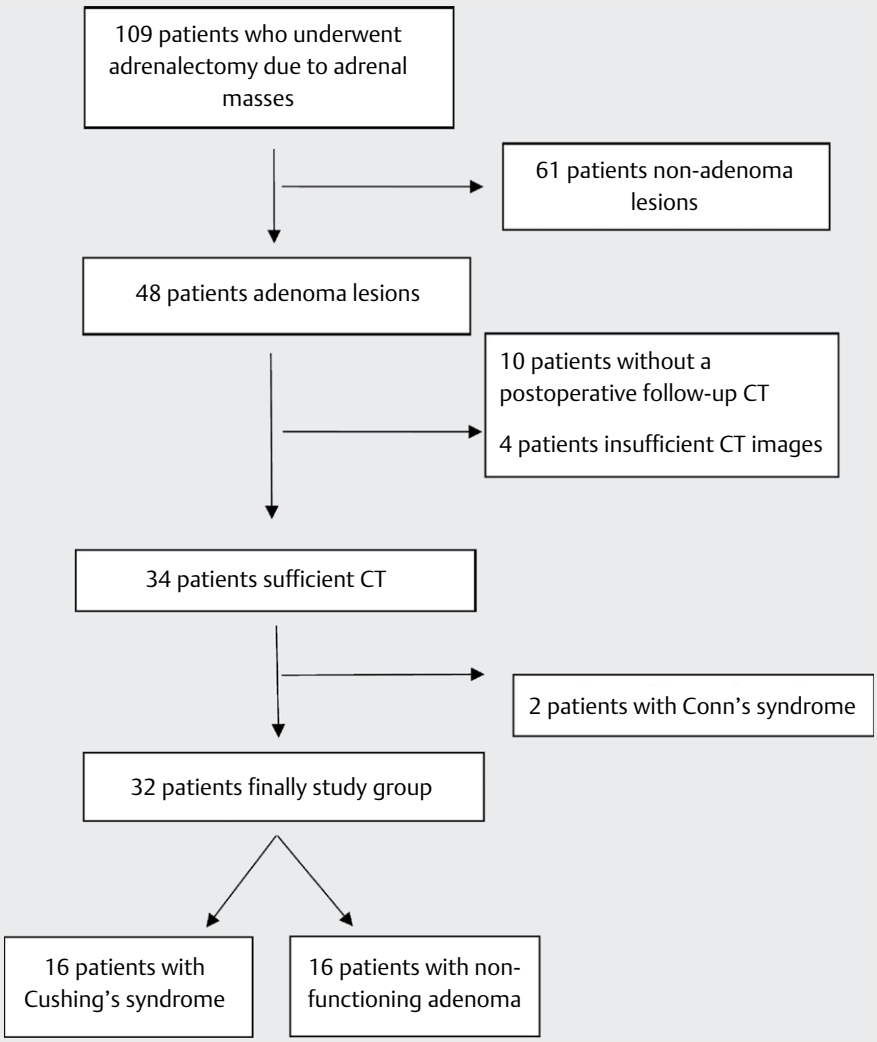
Computed tomography protocols

CT imaging was performed using 64-slice (Toshiba, Aquillon 64, Japan) or 128-slice (GE, Revolution EVO, USA) multidetector CT scanners. For examination, the subjects lay in a supine position with their arms extended above their heads. All preoperative CT examinations were performed using a standard adrenal CT protocol. The lesions with a density of >10 HU on non-contrast CT were also examined using dynamic contrast-enhanced CT. In dynamic contrast-enhanced CT imaging, in addition to non-contrast scanning, a two-phase examination protocol of early (65 s) and late (15 min) phase images were applied after the intravenous bolus administration of an iodinated contrast agent. All post-operative CT examinations were performed using a routine abdominal CT protocol after the intravenous bolus administration of an iodinated contrast agent (65 s). For both preoperative and postoperative CT examinations, the intravenous contrast agent (1.5 mL/kg; iopromide 370, Bayer Schering Pharma AG, Germany or iohexol 350, GE Healthcare, USA) was administered through the antecubital veins using an automatic injector at a rate of 3 mL/sec. The CT parameters were as follows: 1:1 pitch, 200–250 mAs, 120 kVp, and 0.5–0.625 isotropic spatial resolution.

Computed tomography image analysis and measurement of fat

The preoperative CT images were evaluated by two radiologists, blinded to the clinical, pathology, and laboratory results of the patients. In the preoperative CT, all the investigated parameters were

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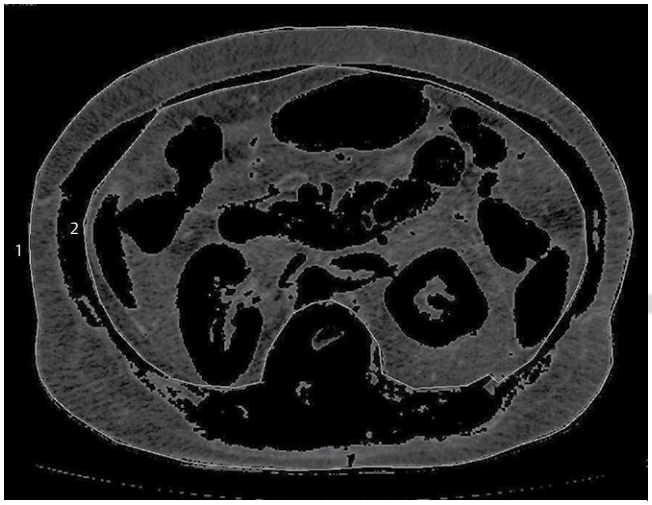
▶ **Fig. 1** A schema of the recruitment of the participants.

measured twice and averaged. To obtain the size of the lesion, the widest diameter in the axial plane was measured. A circular or elliptical region of interest (ROI) was used to measure CT attenuation. The ROI was placed in the central region away from the periphery to prevent a partial volume effect, covering 1/2 to 2/3 of the mass. In the evaluation of dynamic contrast-enhanced CT, ROI was placed in the same location in all phases. The absolute and relative washout values were calculated. For both preoperative and postoperative CT, an axial view was used to measure the areas with fat content. A single slice at the level of L1–2 intervertebral disc space was evaluated. The L1–2 intervertebral disc space was identified for the measurements because VAT at the T12-L1 and L1-L2 landmarks has been reported to have a much stronger association with metabolic syndrome than adipose tissue on other sites [16]. Using a dedicated workstation (GE, Advantage Workstation 4.3, USA), the TAT and VAT ROI were delineated by manually tracing a contour of each region (▶ **Fig. 2**). Fat pixels, i. e., areas with fat were identified based on the threshold attenuation values between−190 and−30 HU, as described by Yoshizumi et al. [17]. TAT was measured by drawing a contour around the skin. Another contour was drawn around the visceral fat by identifying the innermost part of the abdominal wall muscles and the anterior aspect of the vertebral column. SAT was defined as the area of adipose tissue between the skin and the outermost aspect of the abdominal muscle wall. The SAT area was calculated by subtracting the values of the VAT area from that of the TAT area.

Statistical analysis

SPSS software v.22.0 (Chicago, IL) was used for statistical analysis. The normality analysis was performed using the Shapiro-Wilk test. Descriptive statistics were presented as mean, standard deviation, median, minimum and maximum values for the continuous data, and percentage values were used for discrete data. The Student's t-test was used to compare the parameters between groups 1 and 2. Preoperative and postoperative VAT, SAT, and TAT areas were compared using the paired samples t-test. The level of statistical significance was considered as $p<0.05$.

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▶ **Fig. 2** TAT was measured by drawing a contour around the skin, while VAT was measured by drawing around the visceral fat by identifying the innermost part of the abdominal wall muscles and anterior aspect of the vertebral column manually. The SAT area was calculated by subtracting the value of the VAT area from that of the TAT area.

▶ **Table 1** Characteristics of the patients in group 1 (CS) and group 2 (NFA).

	Group 1 (CS)	Group 2 (NFA)
Number of patients (n)	16	16
Age (y)	51.50 (34–63)	53.75 (41–68)
Male/female	2/14	8/8
Adenoma localization Right/left	8/8	2/14
Non-contrast enhanced/ dynamic CT	12/4	8/8
Adenoma size (mm)	36.37 (24–72)	30 (17–48)
Postoperative time to follow-up CT (months)	10.37 (6–17)	9.75 (7–15)

*CS, Cushing's syndrome; NFA, Non-functioning adenomas; CT, Computed Tomography. *The continuous data are expressed as mean and respective ranges are presented in parentheses.

Results

The patients included in the study were categorized into either of the two groups, those with CS (group 1) and those with NFA (group 2). The demographic data, CT characteristics, and the time from the operation to the postoperative CT are mentioned in ▶ **Table 1**.

There was no significant difference between groups 1 and 2 in terms of age, lesion size, and postoperative time to CT (p = 0.60, 0.36, and 0.73, respectively). The diagnosis of adenoma was made in all patients by the preoperative CT examination. Pre-contrast lesion density was < 10 HU in 75 % (12/16) of the group 1 patients and 50 % (8/16) of the group 2 patients; the adenoma diagnosis was performed based on non-contrast-enhanced CT. The male/female ratio was equal in group 2 while the percentage of females was higher (87.5 %) in group 1. The incidence of lesions in the right and left glands was equal in group 1 whereas left adrenal gland lesions were more common in group 2 (87.5 %).

In the preoperative CT examination, the patients in group 1 had significantly larger VAT and TAT areas than those in group 2 (p = 0.03 and 0.02, respectively), but there was no significant difference between the groups in terms of the SAT area (p = 0.08). In postoperative CT, no significant difference was observed between the two groups in VAT, TAT, or SAT (p = 0.87, 0.36, and 0.14, respectively).

There was a significant decrease in the postoperative VAT and TAT areas in group 1 patients (p = 0.01 for both) compared to the preoperative values; however, no significant change was observed in the SAT area (p = 0.10). The postoperative VAT/SAT and VAT/TAT ratios of group 1 decreased significantly (p = 0.03 and 0.02, respectively). The decrease in postoperative SAT and TAT areas of the patients in group 2 was slight and non-significant (p = 0.12 and 0.40, respectively), while there was no change in the VAT area (p = 0.99). No significant change was detected in the postoperative VAT/SAT and VAT/TAT ratios of group 2 (p = 0.38 and 0.62, respectively). The data of the preoperative and postoperative adipose areas and the ratios are summarized in ▶ **Table 2**. The changes at pre and postoperatively in groups are shown in ▶ **Fig. 3**.

Discussion

In this study, we evaluated the preoperative and postoperative VAT, SAT, and TAT areas and VAT/SAT and VAT/TAT ratios in patients who underwent adrenalectomy due to CS and NFA. To the best of our knowledge, only a few related studies have been reported. In the current study, adrenal CS was observed to be more common in female patients, and adrenal adenomas located on the left size caused CS more frequently. The preoperative VAT and TAT areas were significantly larger in the patients with CS compared to those with NFA while the SAT area did not differ between the two groups. Post-operation, there was no difference in any of the three adipose areas, while there was a decrease in the VAT and TAT areas and VAT/SAT and VAT/TAT ratios in cases with CS, while the SAT area remained the same. In patients with NFA, no significant change was observed in any of the adipose areas or ratios. Similar to the findings of ours study, Hong et al. [15] also observed a larger VAT area in CS patients preoperatively and a significant decrease in VAT area one year after adrenalectomy.

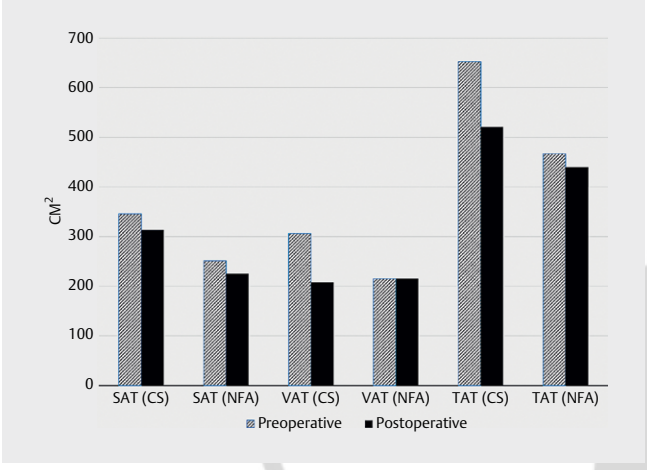
As in many other endocrine disorders, the occurrence of CS is more frequent in females [18]. This was the case in the current study with 14 of 16 adrenal CS cases being in women. In their study evaluating the etiology and epidemiology of CS in 1652 cases, Zhou et al. [19] reported that females accounted for 91.3 % of the patients with CS originating from adrenal adenomas. In another study on the incidence of endogenous CS, 93 % of CS cases due to adrenal adenomas were in women [20]. The rate in our study (87.5 %) is nearly similar to those reported in earlier studies. We also observed an equal incidence of NFA in both genders; however, Çömlekçi et al. [2] observed that NFA was 2.7 times more frequent in women. Giordano et al. [21] evaluated 102 patients with NFA, of which 61 were women (59 %), and reported nearly similar results to that observed in our patient population. The small number of patients in our study population and the evaluation of only surgical adenomas may have affected our results. Thus, there is a need

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▶ **Table 2** Preoperative and postoperative adipose tissue areas and ratios in the patients of group 1 (CS) and group 2 (NFA).

	Group 1 (CS)	Group 2 (NFA)	P-value
Preoperative VAT area (cm^2)	306.28 (232.74–417.28)	215.09 (108.55–363.94)	**0.03**
Postoperative VAT area (cm^2)	207.56 (69.56–305.13)	214.94 (75.59–374.56)	0.87
P-value for pre and post-operative analyses	***0.01***	*0.99*	
Preoperative SAT area (cm^2)	345.97 (177.28–517.62)	251.66 (126.0–336.67)	0.08
Postoperative SAT area (cm^2)	313.21 (100.36–523.52)	224.81 (63.26–318.84)	0.14
P-value for pre and post-operative	*0.10*	*0.12*	
Preoperative TAT area (cm^2)	652.25 (447.10–826.57)	466.75 (257.57–683.13)	**0.02**
Postoperative TAT area (cm^2)	520.77 (169.92–724.16)	439.75 (255.36–693.40)	0.36
P-value for pre and post-operative analyses	***0.01***	*0.40*	
Preoperative VAT/SAT	0.97 (0.59–1.42)	0.87 (0.35–1.17)	0.51
Postperative VAT/SAT	0.70 (0.38–0.88)	0.92 (0.30–1.17)	0.28
P-value for pre and post-operative analyses	***0.03***	*0.38*	
Preoperative VAT/TAT	0.48 (0.37–0.60)	0.45 (0.26–0.54)	0.55
Postoperative VAT/TAT	0.40 (0.27–0.46)	0.47 (0.23–0.81)	0.34
P-value for pre and post-operative analyses	***0.02***	*0.62*	

* CS, Cushing's syndrome; NFA, Non-functioning adenomas; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue. * The continuous data are expressed as mean and respective ranges are presented in parentheses.



▶ **Fig. 3** A graph presenting pre and postoperative changes in groups. CS, Cushing's syndrome; NFA, Non-functioning adenomas; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue.

for larger patient populations or studies based on a meta-analysis on this subject.

CS hypercortisolemia is known to cause visceral fat accumulation. Several studies have shown that the VAT/SAT and VAT/TAT ratio of cases with CS and subclinical CS (sCS) is high [11]. Yener et al. [10] evaluated patients with sCS rather than those with NFA and found an increase in their VAT areas and VAT/SAT and VAT/TAT ratios over a three-year follow-up. Likewise, Debono et al. [22] observed an increase in VAT, and VAT/SAT and VAT/TAT ratios in patients with sCS similar to those in CS cases while these values were low in adrenal incidentalomas without high cortisol levels. Similar to the findings of previous studies, in our study, the VAT and TAT areas, and VAT/SAT and VAT/TAT ratios were higher in the CS group than in the NFA group.

The majority of adrenal CS cases are caused by benign adenomas but adrenocortical carcinomas can also lead to the development of this disease, albeit rarely [23]. In CS cases associated with adrenal glands, unilateral adrenalectomy is the appropriate treatment choice [6]. After treatment, an immediate decrease in the cortisol level is observed, and clinical symptoms specific to CS generally disappear within months. One of the most important clinical findings of CS is central obesity due to the increase in the VAT area. Central obesity can be confirmed by anthropometric techniques and skinfold thickness measurements [24, 25]. However, cross-sectional imaging methods are needed to quantitatively determine the fat distribution in the subcutaneous and visceral compartments. CT is considered the gold standard for this purpose [17, 26]. In the postoperative period, anthropometric measurements can be performed in the follow-up, but it is not possible to evaluate the distribution of fat among different compartments. CT is the preferred imaging method in the preoperative evaluation and postoperative follow-up of adrenal gland pathologies. It is possible to measure adipose areas and determine their distribution in compartments using preoperative and postoperative CT images without the need for additional radiation doses or contrast media. In our study, we quantitatively detected a decrease in the VAT and TAT areas and VAT/SAT and VAT/TAT ratios in the postoperative period in patients with CS caused by adrenal adenomas and found that the increase in the VAT area was reversible when adenoma disappeared. On average, 10.37 months after the operation, we observed similar VAT, TAT, and SAT areas in the operated CS and NFA patients. Clinical findings are known to improve within months after adrenalectomy. Accordingly, in our study, the clinical findings improved in not more than 10 months on average. However, to generalize our data, our results should be supported by further studies on

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larger patient populations. Despite the small number of patients in this study, our findings will contribute to the existing literature.

Our study has certain limitations. These include the retrospective design and the relatively small sample size. However, the vast majority of CS is caused by exogenous hypercortisolism while only a few are of endogenous origin associated with adrenal adenomas. In addition, NFA rarely requires surgery; thus, the number of patients in both the CS and NFA groups in our study was small is due to the rarity of these cases in the general population. Because of the relatively small sample size, a separate analysis according to sex was not possible. Other limitations of the study include the varying time elapsed from the surgery to the postoperative CT in all patients, the evaluation was based on a single postoperative CT examination, and the changes in the postoperative findings over time could not be assessed due to the unavailability of a postoperative CT scan for all patients. Besides, the clinical and laboratory findings of the patients could not be evaluated and correlated with those of CT data.

Conclusion

In conclusion, in patients with CS due to adrenal adenomas, adrenalectomy causes a decrease in the VAT and TAT areas and VAT/SAT and VAT/TAT ratios. This data is important for evaluating the efficacy of treatment. In addition to clinical examination and laboratory findings, it is possible to quantitatively demonstrate the changes in the VAT and TAT areas and VAT/SAT and VAT/TAT ratios in the evaluation of the response of the patients to treatment and follow-up.

Conflict of Interest

The authors declare that they have no conflict of interest.

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