Effect of mild cortisol cosecretion on body composition and metabolic parameters in patients with primary hyperaldosteronism

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Abstract

Objective: To investigate the effects of simultaneous cortisol cosecretion (CCS) on body composition in computed tomography (CT)-imaging and metabolic parameters in patients with primary aldosteronism (PA) with the objective of facilitating early detection.

Design: Retrospective cohort study.

Patients: Forty-seven patients with PA and CCS confirmed by 1-mg dexamethasone suppression test (DST) with a cutoff of ≥1.8 µg/dL were compared with PA patients with excluded CCS (non-CCS, n = 47) matched by age and sex.

Methods: Segmentation of the fat compartments and muscle area at the third lumbar region was performed on non-contrast-enhanced CT images with dedicated segmentation software. Additionally, liver, spleen, pancreas and muscle attenuation were compared between the two groups.

Results: Mean cortisol after DST was 1.2 µg/dL (33.1 nmol/L) in the non-CCS group and 3.2 µg/dL (88.3 nmol/L) in the CCS group with mild autonomous cortisol excess (MACE). No difference in total, visceral and subcutaneous fat volumes was observed between the CCS and non-CCS group (p = .7, .6 and .8, respectively). However, a multivariable regression analysis revealed a significant correlation between total serum cholesterol and results of serum cortisol after 1-mg DST (p = .026). Classification of the patients based on visible lesion on CT and PA-lateralization via adrenal venous sampling also did not show any significant differences in body composition.

Conclusion: MACE in PA patients does not translate into body composition changes on CT-imaging. Therefore, early detection of concurrent CCS in PA is currently only
attainable through biochemical tests. Further investigation of the long-term clinical adverse effects of MACE in PA is necessary.

**KEYWORDS**
body composition, cortisol cosecretion, primary hyperaldosteronism

## 1 | INTRODUCTION

Primary aldosteronism (PA) is the leading cause of endocrine hypertension resulting from mostly renin- and sodium-independent aldosterone secretion.\(^1\) PA is traditionally classified into unilateral and bilateral disease which prioritises appropriate management in regard to therapy.\(^2\) Patients with PA usually present with high blood pressure that does not improve with antihypertensive medication due to aldosterone oversecretion. Recent studies have proven a broader metabolic influence of PA than previously suggested including impaired insulin-secretion and sensitivity\(^3,4\) and type 2 diabetes mellitus (T2DM) in PA patients.\(^5\)

Large multi-centre cohort studies revealed that glucocorticoid cosecretion is a much more prevalent phenotype found in PA that might contribute to a higher incidence of cardiovascular risk factors and events (e.g., left ventricular hypertrophy, obesity, T2DM and dyslipidemia).\(^6,7\) The estimated prevalence of cortisol cosecretion (CCS) in PA patients is between 5% and 21%.\(^8,9\) However, further investigations of the underlying mechanisms have not yet uncovered the pathophysiology of CCS in this entity.

It is known that overt hypercortisolism results in an increased visceral adiposity\(^10\) and muscle loss,\(^11\) which are known to be independent cardiovascular risk factors associated with increased mortality.\(^12\) However, little is known about cortisol-induced changes in body composition of patients with PA and CCS. The effects of hypercortisolism on body composition, including skeletal muscle mass and adipose tissue mass in patients with adrenal hypercortisolism were repeatedly shown in analyses of abdominal computed tomography (CT) in multiple studies performed by Delivanis et al.\(^13,14\) Studies comparing the effects of mild autonomous cortisol excess (MACE) in comparison with patients with nonfunctioning adrenal tumours (NFATs) yielded contradicting results regarding differences in visceral adiposity.\(^15,16\) CT-imaging is an integral part of the diagnostic cascade in patients with PA\(^17\) offers an attractive approach for body composition measurements as it is reproducible, reliable and noninvasive.

Early identification of CCS in patients with PA is important, since the concurrent secretion of cortisol is associated with an increased risk of metabolic as well as cardiovascular diseases. Moreover, the removal of an adenoma could potentially lead to a higher risk of adrenal insufficiency if CCS is not detected. A study by Wang et al.\(^18\) has shown a potential link between CCS and adrenal insufficiency following adrenalectomy (ADX). Adrenal insufficiency has been reported in up to 27% of patients with PA after ADX, and even though adrenal crisis rarely occurs, it is an issue that should be considered.\(^19\) Diagnosing CCS is the first important step to assess the additional risk.

In this explorative study, we sought to investigate the effects of prevalent CCS on the distribution of visceral and subcutaneous fat in patients with diagnosed PA of the German Conn’s Registry compared with matching PA patients (by age and sex) with excluded CCS via 1-mg dexamethasone suppression test (DST). We hypothesized that because of the known effects of cortisol on metabolism,\(^20\) patients with PA and concurrent autonomous cortisol secretion might display differences in their body composition possibly detectable in non-contrast-enhanced CT-imaging, compared to patients with PA and excluded CCS.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

Out of the 269 patients with diagnosed PA included in the German Conn’s registry between the years 2013 and 2022 with non-contrast enhanced CT-imaging, we identified 47 patients from two centres with confirmed CCS (University Hospital of the Ludwig Maximilians University Munich and University Hospital of the University of Würzburg). They were subsequently matched with patients with excluded CCS (non-CCS group) by age and sex (total of \(n = 94\) subjects). Medical records were reviewed for clinical information pertinent to the presentation, laboratory measurements and therapy. All patients gave written informed consent. The protocol of the German Conn’s Registry was approved by the Ethics Committee of the Medical Faculty of the Ludwig Maximilians University Munich.

### 2.2 | Clinical and biochemical data

The procedures of PA diagnosis were performed according to the Endocrine Society Practice Guidelines\(^21\) after positive confirmatory testing either through saline infusion testing or captopril challenge test. The absolute aldosterone cut-off for diagnosing PA was 60 pg/mL (166.5 pmol/L). Before testing, the antihypertensive medication was adapted according to the guidelines.\(^22\) According to the guidelines, confirmatory testing was performed in cases where aldosterone concentrations were above 200 pg/mL (554.9 pmol/L) with spontaneous hypokalemia and non-detectable renin concentrations (<2 mU/L or 0.0284 pmol/L). For lateralization of the source of aldosterone overproduction, adrenal venous sampling (AVS) was performed.
To test for hypercortisolism, we performed a single 1-mg DST in all patients at the baseline visit. Autonomous cortisol secretion was confirmed when cortisol following DST was equal or greater than 1.8 µg/dL (49.7 nmol/L). In case of an elevated 1 mg DST, a second test is usually done using 24 h urinary-free cortisol or midnight salivary cortisol. Reference values were determined following the practice guidelines of the Endocrine Society for the diagnosis of Cushing’s syndrome and recently updated guidelines of the Pituitary Society. We determined serum cortisol levels using a commercially available chemiluminescence immunoassay (Liaison; DiaSorin, Würzburg: Siemens Immulite). Performed at our institution, intra-assay and interassay variability was <10%, with a lower limit of quantification at 0.2 µg/dL (5.5 nmol/L). We measured serum aldosterone with a chemiluminescence immunoassay (LIAISON, CLIA, DiaSorin, at the Munich centre, WÜRZBURG: IDS-iSYS, IDS). Body mass index (BMI) was calculated as body weight (kilograms)/height (square metres).

2.3 | Adrenal venous sampling

In all cases, AVS was performed without adrenocorticotropic hormone stimulation in a sequential manner. During AVS, both plasma cortisol and plasma aldosterone concentration were determined in blood collected selectively from the adrenal veins and simultaneously from the inferior vena cava (IVC). To evaluate the success of adrenal vein catheterization, selectivity index (SI) was defined as the ratio of plasma cortisol concentration for each adrenal vein and IVC. The lateralization index (LI) is defined as the aldosterone to cortisol ratio (ACR) on the dominant side with excess aldosterone secretion over ACR on the nondominant side. If the LI exceeded 4, the patient was judged to have unilateral PA. Otherwise, a diagnosis of bilateral disease was made.

2.4 | CT protocol and body composition analysis

Non-contrast enhanced CT imaging of the abdomen was obtained as part of the diagnostic workup of patients with PA after laboratory confirmatory testing. CT images were uploaded into a dedicated segmentation software (3D-Slicer). One radiologist with extensive experience in abdominal imaging reviewed the scans from three levels: lumbar vertebral bodies L1, L2 and L3. For each patient, we identified the single axial image at the level of the third lumbar vertebrae (L3) on which both transverse processes were fully visible. After establishment of the correct level (L3), volume rendering and volume cropping were then performed to obtain an axial slice with a standard thickness of two millimetres for further analysis.

2.5 | Adipose and muscle tissue measurements

Measurement of body composition data such as visceral to total fat (V/T) and visceral to subcutaneous fat V/S ratios and abdominal muscle mass via CT imaging is an established measuring method. A semi-automated quantification of the total fat area (subcutaneous and visceral) at the particular slice was performed with the help of thresholding of Hounsfield units (HU) and a set range of −190 to −30 HU for fat and −30 to 150 HU for muscle tissue (Figure 1), as previously established. The following parameters were calculated for each patient in the respective slice: skeletal muscle area (cross-sectional area of all skeletal muscles at the L3 level); total fat tissue volume rendering and volume cropping were then performed to obtain an axial slice with a standard thickness of two millimetres for further analysis.

**FIGURE 1** Quantification and density analysis via 3D-Slicer. HU-Thresholding for automated segmentation (areas marked in green) of the total fat volume at the third lumbar region with a range of −190 to −30 HU (A). The red arrows indicate low-density intestinal contents that were then manually removed (blue arrows in B). After quantification of the total fat volume, the visceral fat was then manually removed for the quantification of the subcutaneous and visceral fat compartments (C). For quantification of the muscle volume, a threshold of −29 to 150 HU was used (D) and manual corrections were also performed.

(TAT); visceral (VAT) and subcutaneous adipose tissue (SAT) and median density of fat and muscle tissue. After applying the corresponding thresholds, careful review of the marked areas was conducted and marked segments which contained non-desirable areas (e.g., fatty intestinal contents) were manually removed (Figure 1, red and blue arrows in A and B).

2.6 Measurements of organs and muscle attenuation

For the measurement of attenuation in the liver, spleen and pancreas, nine regions of interest (ROIs) circles were placed in each organ parenchyma in the same CT scans of the upper abdomen used for body composition analysis. Confounding structures like vessels were carefully avoided and the circles were placed in the upper, mid and lower sections of the respective organ (three rings per section) for the spleen and liver. As for the pancreas, the ROIs were placed at the tail, body and head sections (three rings per section). The median attenuation was then calculated automatically by the segmentation programme.

2.7 Statistics

The CCS-group (cutoff ≥1.8 µg/dL/49.7 nmol/L cortisol after 1-mg DST) was identified and randomly matched by age and sex with same-aged PA-patients with biochemically excluded cosecretion (<1.8 µg/dL cortisol after 1-mg DST). Statistical analysis was performed using R statistical software (R version 3.6.3). Descriptive statistics were used to determine mean and standard deviation (SD) or median and ranges depending on data distribution, while categorical data are shown as a number (%). Associations between variables were assessed using one-way ANOVA for continuous variables and we adjusted for multiple comparisons using Bonferroni corrections. p Values less than .05 were considered significant. Baseline differences in body composition measurements in between the groups were performed using linear regression analysis adjusting for sex and BMI. Additionally, to investigate the relationship between morning cortisol concentrations after overnight DST and body composition and clinical data, we performed a multivariable linear regression analysis while controlling for confounding factors including sex and BMI.

3 RESULTS

3.1 Clinical characteristics

The 94 PA patients included had a median age of 60 years and a male predominance (n = 65, 69%). Forty-seven patients had confirmed CCS by a pathological 1-mg DST that was then matched by age and sex with patients with excluded CCS (non-CCS, range 0.1–1.7 µg/dL/2.8–46.9 nmol/L). Mean cortisol after DST was 1.2 µg/dL (33.1 nmol/L) in the non-CCS group and 3.2 µg/dL (88.3 nmol/L) in the CCS group. In the CCS group, all patients were within the range of MACE (1.8–12.6 µg/dL), as none met the biochemical and clinical criteria for overt Cushing syndrome.31 As seen in Table 1, there was no difference in median concentration of triglycerides and cholesterol between the groups (p = .2 and .11, respectively). A multivariable regression analysis after controlling for confounding factors (age, sex and BMI) showed a significant positive correlation between total serum cholesterol and results of serum cortisol after DST, as displayed in Figure 2 (p = .026, multiple R² = .846). Forty-seven patients had a visible and measurable adrenal gland lesion on non-contrast-enhanced CT. By means of AVS, 36 patients had lateralized disease and 58 had bilateral disease.

3.2 Measurements of visceral and subcutaneous fat area

No difference in median total, visceral and subcutaneous fat volumes was observed between the groups (p = .7, .6 and .8, respectively). Furthermore, no differences were found in volumetric measurements of the muscle area at L3 between CCS and non-CCS (30 vs. 31 cm², p = .4). Multivariable regression analysis while controlling for confounding factors (sex and BMI) displayed no significant correlation between visceral and subcutaneous fat ratio (V/S ratio) and results of cortisol levels after 1-mg DST (Figure 2, p = .27). Classification of the patients based on visible lesion on CT and PA-lateralization via AVS also did not show any significant differences in body composition (Table 2).

3.3 Measurements of organs and muscle attenuation

No significant differences in attenuation of the liver, spleen and pancreas between CCS and non-CCS were observed. Furthermore, with a higher cutoff for cortisol after DST the diagnosis of hypercortisolism being set to >5.0 µg/dL (138 nmol/L), no significant differences between the groups were observed (n = 5 CCS with >5.0 µg/dL/138 nmol/L vs. 47 non-CCS < 1.8 µg/dL/49.7 nmol/L), limited by the low number of patients with higher cortisol secretion. Classification of the patients based on visible lesion on CT and PA-lateralization via AVS also did not show any significant differences in organ and muscle attenuation (Table 2).

4 DISCUSSION

We found that cortisol levels above a threshold of 1.8 µg/dL (49.7 nmol/L) after overnight 1-mg DST neither correlated with increased visceral fat volumes nor affected the visceral to subcutaneous fat ratio compared to non-CCS patients with the same age and sex. Furthermore, no significant differences in muscle volume or
Muscle attenuation were observed between the two groups. Multivariable regression analysis after adjustment for confounding factors (age, sex and BMI) revealed that total serum cholesterol correlated significantly and positively with cortisol levels after 1 mg overnight DST. This finding is in line with recent data from Arlt et al. in 2017 linking CCS with metabolic risk factors such as increased insulin resistance and higher waist circumference. Nevertheless, in the case of MACE, these findings did not translate into changes in body composition that are detectable by non-contrast-enhanced CT imaging.

Imaging based body composition analysis with standardized measurements of VAT, SAT and skeletal muscle in CT and magnet
resonance imaging (MRI) is an established method which is increasingly employed in the clinical routine. Furthermore, multiple studies comparing Dual-energy X-ray absorptiometry (DEXA) with cross-sectional imaging (CT and MRI) found CT and MRI to be more accurate regarding adipose tissue and skeletal muscle measurements. Although CT inevitably exposes patients to ionizing radiation, standardized CT-based analysis of body composition parameters can be performed opportunistically from images obtained during a clinical work-up as performed in this study.

Numerous proposed mechanisms account for the predominant development of visceral fat tissue in the context of hypercortisolism. This predominance may be attributed to the higher presence of glucocorticoid receptors (GR) in visceral fat compared to subcutaneous fat tissue. The heightened expression of GR is thought to make visceral fat adipocytes more responsive to cortisol. This ultimately leads to an increased synthesis of triglycerides through the activation of lipoprotein lipase, particularly in visceral fat tissue. Consequently, patients with overt Cushing's disease exhibit higher levels of visceral adiposity. A recent multicenter cohort study has additionally disclosed a link between glucocorticoid cosecretion and elevated CYP11B1 enzyme activity in adenoma tissue in patients with PA. However, further investigations into the underlying mechanisms have yet to be undertaken.

In a study conducted by Delivanis et al., the severity of hypercortisolism correlated with lower muscle mass and increased visceral adiposity in CT-imaging in patients with cortisol-producing adenomas. Contrary to our design, this study comprised a high number of patients with clinically overt Cushing syndrome (n = 25/105, 24%) and nonfunctioning adrenal tumours (NFATs, n = 32/105, 31%). This likely resulted in the inclusion of patients with less favourable baseline body composition and higher cardiovascular risk profiles. On the contrary, the measurements of the fat compartments (V/T and V/S) were decreased in patients with MACE compared to patients with NFAT. This may explain the insignificant differences found in this study, as all of the PA patients had only MACE.

In the study, a cutoff of 1.8 µg/dL (49.7 nmol/L) for 1-mg DST was used for the diagnosis of CCS in accordance with current guidelines for the diagnosis of Cushing's disease. As more evidence is emerging about the relatively high prevalence of mild CCS in PA and often the absence of typical metabolic signs of hypercortisolism (subclinical Cushing's disease), further studies are needed to clarify whether there are clinically useful cut-off points for CCS in PA patients in regard to adverse health outcomes.

4.1 | Strengths and limitations

A clear strength of this study is the 1:1 matching cohorts of PA patients with and without MACE and the standardized semi-automated analyses of body composition parameters in non-contrast-enhanced CT imaging at the third lumbar region. A study limitation is the low proportion of patients with overt hypercortisolism with highly elevated cortisol values after DST exceeding 5.0 µg/dL (137.93 nmol/L). Any findings regarding this subgroup might not be representative due to the small sample size. An additional limitation is the absence of an NFAT group for general comparison. Another possible limitation is that due to the retrospective nature of this analysis, it is difficult to account for pseudo-Cushing's syndrome due to physiological and non-neoplastic activation of the Hypothalamic-Pituitary-Adrenal axis, such as depression and alcoholism. Analysis of the available adrenocorticotropic hormone levels in 83 included patients did not display an abnormal activation of the Hypothalamic-Pituitary-Adrenal axis.
TABLE 2  Body composition.

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<tr>
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<td>Yes, n = 47&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Total fat volume [cm²]</td>
<td>78 (58, 101)</td>
<td>82 (58, 102)</td>
</tr>
<tr>
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<td>43 (21, 59)</td>
<td>44 (28, 57)</td>
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<tr>
<td>Muscle volume [cm²]</td>
<td>30 (23, 34)</td>
<td>31 (26, 36)</td>
</tr>
<tr>
<td>V/T ratio</td>
<td>1.12 (0.55, 1.73)</td>
<td>1.13 (0.68, 1.60)</td>
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<td>Liver attenuation [HU]</td>
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<td>55 (46, 58)</td>
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<td>48 (43, 51)</td>
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<td>77 (58, 96)</td>
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<td>36 (25, 53)</td>
<td>31 (25, 42)</td>
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<td>41 (24, 56)</td>
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<tr>
<td>Muscle volume [cm²]</td>
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<td>31 (25, 35)</td>
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<tr>
<td>Liver attenuation [HU]</td>
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<td>Pancreas attenuation [HU]</td>
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<table>
<thead>
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<td>Total fat volume [cm²]</td>
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<td>75 (58, 95)</td>
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<tr>
<td>Visceral fat volume [cm²]</td>
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<td>Muscle volume [cm²]</td>
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<td>Liver attenuation [HU]</td>
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<tr>
<td>Muscle attenuation [HU]</td>
<td>36 (30, 39)</td>
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Note: All segmentations of the fat compartments and muscle area were performed at the third lumbar region on non-contrast-enhanced CT images. CCS was confirmed by 1-mg DST with a cutoff of ≥1.8 µg/dL. A lateralization index for AVS greater than 4.0, or a lateralization index between 3 and 4 together with a contralateral index below 1.0 were considered to be compatible with unilateral disease.

Abbreviations: AVS, adrenal venous sampling; CT, computed tomography; HU, Hounsfield units; V/T ratio, visceral to total fat ratio.

<sup>a</sup>Median (IQR); <sup>b</sup>n (%).

<sup>b</sup>Wilcoxon rank-sum exact test; Wilcoxon rank-sum test; Pearson’s Chi-squared test.

5  CONCLUSION

PA patients with simultaneous CCS do not display significant differences in body composition when analyzed in CT imaging compared to patients without CCS. With little data on the influence of simultaneous mild hypercortisolism on the clinical outcome of patients with PA and lack of prospective studies examining CCS after specific treatment of PA, further investigations are necessary.

AUTHOR CONTRIBUTIONS
Nabeel Mansour and Daniel Heinrich: Conception and design of the study; Generation, collection, assembly, analysis and/or interpretation of data; Drafting or revision of the manuscript; Approval of the
final version of the manuscript. Denise Bruedgam, Ulrich Dischinger, Lydia Kürzinger, Christian Adolf, Roman Walter, Osman Öcal, Vanessa F. Schmidt, Jan Rudolph, Jens Ricke, Nicole Reisch, Martin Reincke and Moritz Wildgruber: Generation, collection, assembly, analysis and/or interpretation of data; Drafting or revision of the manuscript: Approval of the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data collection was according to the protocol of the German Conn’s Registry approved by the Ethics Committee of the Medical Faculty of the Ludwig Maximilians University of Munich.

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