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Body Composition in Pituitary, Adrenal and Iatrogenic Cushing's Syndrome and Effects of DHEAS Levels

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Introduction

Hypercortisolemia is associated with abdominal adiposity. Prior studies have quantified visceral adipose tissue (VAT) versus subcutaneous adipose tissue (SAT) accumulation as assessed by CT and MRI in patients with pituitary Cushing's disease (1–3) but not of other etiologies. Hormone differences in women with Cushing's syndrome due to pituitary versus adrenal and iatrogenic etiologies, including differences in DHEA production, may affect body composition. Although effects of circulating androgen precursors are likely modest in men in whom testosterone production is high, the increased generation of androgens from adrenal precursors in pituitary Cushing's could exert significant effects on body composition in women.

We hypothesized that there would be a predominance of VAT versus SAT in patients with Cushing's syndrome of three etiologies: 1) pituitary adenomas 2) adrenal adenomas and 3) iatrogenic glucocorticoid administration. Furthermore, we hypothesized that Cushing's patients with relatively higher DHEAS levels would demonstrate an attenuation of these body composition abnormalities.

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Author Contributions

All authors contributed to manuscript preparation. In addition, LED, MAB, MS and KKM contributed to the design of the study and interpretation of data, AVG contributed to data collection, CMG completed radiologic measurements, and KPE, BS and RH contributed to subject identification.

Competing Interests: No authors have disclosures to report.

Methods

The study was IRB approved. Consent was obtained from all prospectively studied subjects. Three groups of women with Cushing's syndrome who underwent CT while hypercortisolemic were identified: pituitary (n=25), adrenal (n=13) or iatrogenic (n=12). All iatrogenic Cushing's subjects received oral prednisone (5 mg daily; mean ($\pm$ SD) 12.5 $\pm$ 10mg daily). Control subjects were 1:1 matched for age ($\pm$ 2 years) and BMI ($\pm$ 2 kg/m²), with menstrual status matching in most cases. Total abdominal adipose tissue (TAT), VAT and SAT were quantified on CT at L4 (Osirix software version 3.2.1) in all cases and controls. Urine free cortisol (UFC) and DHEAS (available in 15/25 of pituitary and 6/13 adrenal subjects) were extracted from the medical record. Duration of hypercortisolemia was estimated from the date of symptom onset or biochemical diagnosis until the date of the CT scan. UFC equivalency for iatrogenic subjects was calculated based on Gagliardi *et al.*: hydrocortisone dose of 21.7 mg daily = UFC 195 nmol/24 hours (4) and 1:4 prednisone:hydrocortisone potency.

Statistical Methods

JMP Pro Statistical Software (version 11.0.0; SAS Institute) was used. Paired t-testing was used to compare each group with its matched controls. ANOVA was used for non-paired 2-group comparisons, and Fisher's Least Significance Test for 3-group comparisons to control for multiple comparisons (5). Multivariable regression models were performed.

Results

Cushing's Groups versus Age and BMI-Matched Controls

Mean age and BMI were comparable between the Cushing's groups and their matched controls (pituitary: 41 $\pm$ 15 versus 41 $\pm$ 15y, 33 $\pm$ 7 versus 33 $\pm$ 7 kg/m²; adrenal: 48 $\pm$ 13 versus 48 $\pm$ 13y, 32 $\pm$ 6 versus 32 $\pm$ 5 kg/m²; iatrogenic: 66 $\pm$ 11 versus 66 $\pm$ 12y, 31 $\pm$ 7 versus 31 $\pm$ 7 kg/m²). The pituitary group had higher mean VAT (207 $\pm$ 89 versus 78 $\pm$ 42 cm², p<0.0001) and VAT/TAT (0.35 $\pm$ 0.10 versus 0.17 $\pm$ 0.09, p<0.0001) than controls (Figure 1A). The adrenal group had significantly higher mean VAT (190 $\pm$ 86 versus 138 $\pm$ 81 cm², p=0.02) and VAT/TAT (0.34 $\pm$ 0.07 versus 0.24 $\pm$ 0.10, p=0.05) than controls (Figure 1A). Mean VAT was 2.7 times higher in pituitary Cushing's and 1.4 times higher in adrenal Cushing's subjects than in their respective controls. There were no differences in mean VAT, TAT or VAT/TAT between the iatrogenic group and its controls.

Cushing's Between Group Comparisons

BMI did not differ between the three Cushing's groups. All analyses were adjusted for age and BMI. VAT, TAT and VAT/TAT were all significantly higher in pituitary versus iatrogenic Cushing's subjects (p<0.05). VAT SAT, TAT and VAT/TAT were not different between pituitary and adrenal Cushing's groups. There were no differences in any body composition variables between adrenal and iatrogenic Cushing's subjects.

Hormonal Determinants of Body Composition

ACTH and Urine Free Cortisol—The pituitary group had significantly higher median ACTH than the adrenal group [52 (13–300) versus 4 (2–12) pg/ml, $p<0.0001$]. Median duration of hypercortisolemia was 38 (18–122) months in the pituitary, 4 (0–47) months in the adrenal and 20 (11–25) months in the iatrogenic group. Within the iatrogenic group, the integrated cortisol exposure (UFC equivalent $\times$ duration of glucocorticoid treatment) correlated positively with the VAT/TAT ratio ($r=0.80$, $p=0.003$).

DHEAS—The adrenal Cushing's group had significantly lower median DHEAS levels [28 (14–40) versus 226 (17–679) mcg/dL, respectively, $p=0.0001$] and DHEAS Z-scores [−2.0 (−2.2 to −1.6) versus 1.3 (−1.0 to 3.1), $p=0.005$] than the pituitary Cushing's group. DHEAS was inversely associated with VAT adjusted for BMI (Figure 1B). 21% of the variability in VAT was attributable to DHEAS Z-scores. DHEAS remained significantly correlated with VAT after controlling for age and estimated cortisol exposure. DHEAS Z-score ($r=-0.50$, $p=0.03$) was also a significant negative determinant of VAT/TAT, which remained significant when controlled for age and estimated cortisol exposure.

Discussion

We demonstrate that patients with Cushing's syndrome due to pituitary and adrenal etiologies have more VAT and higher VAT/TAT than BMI-, age- and sex-matched controls. While we did not detect a difference in mean VAT between subjects taking low-dose glucocorticoids versus controls in this study, the study was not powered to detect a small difference, and we did find that the duration and intensity of steroid exposure within this group were associated with an increase in relative visceral adiposity. Therefore, minimizing overall exogenous steroid exposure may mitigate deleterious body composition effects of supraphysiologic glucocorticoids.

Additionally, we found that higher DHEAS levels are correlated with a lower VAT when controlled for BMI in patients with endogenous Cushing's and that 21% of the variability in VAT was attributable to DHEAS levels. However, this limited effect of DHEAS was not sufficient to result in a protective effect against the accumulation of VAT in these patients, as mean VAT did not differ between the pituitary and adrenal Cushing's groups. This may be due to a tendency for pituitary Cushing's patients to experience a protracted course before diagnosis, while adrenal Cushing's patients in our study may have been more likely to be diagnosed based on incidental abdominal imaging. However, such factors are difficult to estimate accurately. Therefore, we are limited in the conclusions that we can draw regarding the impact of DHEAS on VAT.

Limitations of this study include the small size, retrospective design and lack of DHEAS levels in all subjects.

In conclusion, our study suggests that Cushing's patients of pituitary and adrenal etiologies have higher VAT and VAT/TAT than BMI-, age- and sex-matched controls. Additionally, our data suggest that higher DHEAS levels may make a small and perhaps clinically insignificant contribution to the regulation of VAT in these patients. Finally, limited low-

dose glucocorticoid administration appears to have limited deleterious consequences on development of visceral adiposity.

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Fig. 1.

A: VAT for each Cushing's Group (black) versus matched controls (white). *Denotes $p < 0.0001$ and **denotes $p < 0.05$.

B: Correlation between VAT versus DHEAS controlled for BMI (whole model $r = -0.73$, partial correlation coefficient for DHEAS $r = -0.39$ $p = 0.05$).