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CLINICAL STUDY

Computed tomography assessment of fat distribution in male and female patients with Cushing's syndrome

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Abstract

Objective: Our aims were to describe the abdominal fat distribution in male patients with Cushing's syndrome (CS) on computerised tomography (CT), to compare our findings with non-cushingoid patients, to validate previous reports of increased visceral fat in female patients with CS and to identify any correlations between fat distribution and biochemical findings.
Design: Retrospective and observational.
Patients: Appropriate CT scans were identified in 31 patients (seven male) with active CS.
Measurements: Total, visceral and subcutaneous fat areas were obtained. The percentage of visceral fat and the visceral to subcutaneous fat ratio (V:S ratio) were calculated. Biochemical data were recorded. Control data of fat distribution were obtained from the literature.
Results: There was a significant increase in the V:S ratio in male patients with CS when compared with non-cushingoid controls (1.175±0.59 vs 0.77±0.39, 95% confidence interval (CI) 0.0817–0.728). There was a significant increase in the V:S ratio in female patients with CS (0.845±0.53 vs 0.38±0.19, 95% CI 0.269–0.661). There was no difference in the V:S ratio between male and female patients with CS (1.175±0.59 vs 0.845±0.53, 95% CI −0.144–0.804). No significant correlations between fat distribution and glucose levels, circulating cortisol, ACTH or lipids were found.
Conclusions: Our data demonstrate an increase in visceral fat distribution in both male and female patients with CS, with the abolition of the normal male to female difference in visceral fat. Increased visceral fat may increase the risk of the metabolic syndrome in this group of patients.

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Introduction

It has long been recognised that there is a major redistribution of body fat in patients with Cushing's syndrome, in whom clinically there is a pattern of central obesity. Patients with Cushing's syndrome often present with obesity and it may be difficult to differentiate between patients who have simple obesity, and those with hypercortisolaemia. In simple obesity, the distribution of fat in the subcutaneous and visceral compartments is different between men and women: in men, there is a greater proportion of fat in the visceral compartment compared with women (1).

Several studies have demonstrated that in women with Cushing's syndrome there is an increase in the proportion of fat in the visceral compartment compared with non-hypercortisolaemic controls (2, 3). This has been demonstrated using anthropometric techniques such as waist-to-hip ratio (WHR) as well as with computerised tomography (CT), the technique currently considered the 'gold standard' for multi-compartment fat measurement (4, 5). Thus, there is objective radiological evidence of fat redistribution in women with Cushing's syndrome. However, there are very limited published data describing the fat distribution in male patients with Cushing's syndrome, with only a single male patient described in the literature, to our knowledge (6). The question thus arises as to whether there is an increase in visceral fat in men with Cushing's syndrome.

Increased visceral fat distribution has been correlated with a group of metabolic abnormalities known as the metabolic syndrome or syndrome X (7). The metabolic syndrome is characterised by impaired glucose tolerance or diabetes, hyperlipidaemia, hypertension and atherosclerosis. There is an associated increase in cardiovascular and cerebrovascular disease and mortality (7–10). An increase in the proportion of visceral fat

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in Cushing's syndrome may exacerbate the insulin resistance and increased atherogenesis which characterise the condition.

In this study, our aims were (i) to document the distribution of fat in men with Cushing's syndrome, using CT, and to compare this with male non-hypercortisolaemic control data in the literature; (ii) to document the distribution of fat in women with Cushing's syndrome, to compare this with the male patients with Cushing's syndrome and also with the previously published data of women with or without Cushing's syndrome; and (iii) to identify any correlations between fat distribution and biochemical findings. As CT scanning involves ionising radiation, it was not considered ethical to recruit an age- and sex-matched cohort of controls, and we therefore relied upon previously published data in non-hypercortisolaemic patients.

Patients and methods

CT scans appropriate for the measurement of visceral and subcutaneous fat (see scan technique below) were available in 37 patients with Cushing's syndrome between 1989 and 2001. Analysis of the records revealed that 31 patients (seven male) were considered to have clinically active Cushing's at the time of scanning (mean serum cortisol of >300 nmol/l on a 5 point day-curve). Six patients were excluded who were considered to be biochemically inactive or were on treatment with ketoconazole or metyrapone for 3 months or longer. The mean age of the patients was 45 years (range 17–79 years). Twenty patients had Cushing's disease, five had primary adrenal Cushing's syndrome, three had a proven ectopic source of adrenocorticotrophin (ACTH) causing Cushing's syndrome, whilst in three patients the cause of the Cushing's syndrome remains unknown. The body mass index (BMI = weight in kg/height in m^2) was available in all seven male patients (mean$\pm$S.D. $= 26.2\pm2.3$) and 21 of the 24 female patients (mean$\pm$S.D. $= 29.6\pm6.9$). Five patients had impaired glucose tolerance or diabetes.

Scan technique and measurement of fat

Patients were scanned in the supine position using a GE 9800 scanner up to 1993, and a GE Hi-Speed Adv RP (General Electric, Milwaukee, USA) scanner from 1993 onwards. A single 10 mm thick slice at the L4 vertebral level was used for fat analysis. Patients were excluded from the fat distribution analysis if the entire skin surface was not included in the scan area as, in some cases, the CT field of view was reduced to include only the adrenal glands and retroperitoneum. Using GE software, the total fat area and visceral fat area regions of interest (ROIs) were delineated by manually tracing a contour of each region, as demonstrated in Fig. 1. Fat pixels and therefore fat area were identified

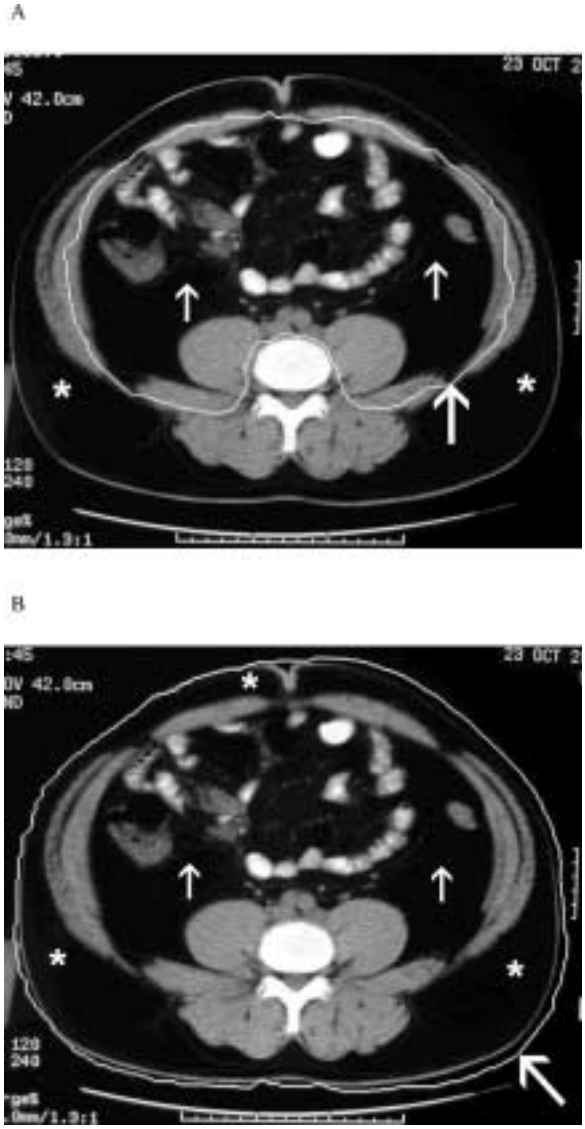

Figure 1 CT scan of regions of interest at the L4 level. (A) This scan demonstrates a hand-drawn region of interest (ROI) curve (hand drawn white line, indicated by the large arrow) around the visceral fat (small arrows). (B) This scan demonstrates a hand-drawn ROI around the total fat area (large arrow). The area of the pixels with a Hounsfield unit of -50 to -250 was measured within each ROI. Subcutaneous fat area (*) was calculated by subtraction of the visceral fat area (small arrows) from the total fat area.

with threshold attenuation values between -50 and -250 Hounsfield units, as described by Borkan *et al.* (4). The subcutaneous fat area was then calculated by subtracting visceral from total fat area. In order to compare our data with that quoted in the literature, several different expressions of the fat distribution were used: (i) total, visceral and subcutaneous fat area; (ii) percentage of visceral fat expressed as the ratio of visceral fat to total fat; and (iii) the ratio of visceral to subcutaneous fat (V : S ratio).

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Inter-observer and intra-observer variability for the CT fat area measurements were calculated as follows: measurements were repeated by the same observer and a second observer and then the coefficient of variation was calculated using the formula: coefficient of variation = (standard deviation/mean) × 100%.

Biochemical data

The results of biochemical investigations within 4 weeks of the CT date were obtained, including mean serum cortisol levels measured at five points throughout the day from 0900 h to 2100 h (cortisol day-curve), plasma ACTH levels at 0900 h, mean plasma ACTH levels (from the day-curve), fasting glucose and fasting lipids.

All hormonal assays were performed at the Department of Chemical Endocrinology at St Bartholomew's Hospital. Serum cortisol was measured by an in-house unextracted non-chromatographic RIA from 1982 until 2000: the coefficient of variation at 100 nmol/l and 1000 nmol/l is 6%. From the year 2000 serum cortisol was measured by a competitive immunoassay format on the fully automated Bayer Technicon Immuno-1 analyser, using an immunomagnetic particle separation step and alkaline phosphatase for enzymatic generation of a coloured complex quantified using absorbance at 405 nm. The lower limit of detection of serum cortisol concentration was set at < 50 nmol/l. Plasma ACTH was measured by our validated routine in-house Vycor (Socite-A.T.A. Geneva, Switzerland) glass-extracted RIA; inter- and intra-assay coefficients of variation are $< 8\%$ for both. Fasting cholesterol and triglycerides were measured using enzymatic analysis on a Monarch centrifugal analyser (Instrumentation Laboratory, Warrington, UK). The between-batch imprecision for cholesterol was 2.5% coefficients of variation at a concentration of 6.0 mmol/l; that for triglycerides was 3.0% coefficients of variation at a concentration of 1.5 mmol/l. High density lipoprotein (HDL) cholesterol was analysed following dextran sulphate precipitation. Low density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. Plasma glucose was measured by a hexokinase method.

Historical control data

A literature search was performed using PubMed and Ovid to identify publications that provided data concerning fat distribution in non-cushingoid and cushingoid patients.

Statistical analysis

Data are expressed as means ± 1 standard deviation. The difference of means between two groups was assessed by Student's *t*-test after confirmation of normality or near normality of distribution using the Kolmogorov–Smirnov test. Significance was taken as $P < 0.05$. The difference of means between our data and the data obtained from the literature was assessed using confidence interval analysis software, with a 95% confidence interval. We have assumed normal distribution of data in the literature. In some cases, this statistical comparison is not valid due to the small number of patients and the wide differences in the variabililty of the measurements. Spearman's correlation was applied to assess correlations between continuous variables. SPSS V. 11 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Results

The results of fat measurements are shown in Table 1, together with the previously published data obtained from the literature search (2, 3, 11–14). The data are presented graphically in Fig. 2A and B. The coefficients of variation for intra-observer measurements were 0.38% for total fat, 1.2% for visceral fat and 0.25% for subcutaneous fat measurements. The coefficients of variation for inter-observer measurements were 0.13% for total fat, 0.6% for visceral fat and 0.4% for subcutaneous fat measurements.

Male patients

There was a significant increase in the V:S ratio in the male patients with Cushing's syndrome when compared with the male patients undergoing routine CT in Siedell's study from 0.77±0.39 to 1.175±0.593 (95% confidence interval (CI) 0.0817–0.728) (12). There appeared to be a significant increase in the V:S ratio between the male Cushing's patients and the male unselected volunteers from Lemieux's study, from 0.48 to 1.175, but no standard deviations are available for the percentage of visceral fat or V:S ratio in Lemieux's publication so this cannot be tested statistically (13). No significant difference in the percentage of visceral fat was identified between male Cushing's patients and the unselected men undergoing CT in Dixon's study (11).

Female patients

The results demonstrated an increase in the percentage of visceral fat and the V:S ratio in female patients with active Cushing's syndrome compared with non-cushingoid historical controls. There was no statistical difference in fat distribution between the men and women with Cushing's syndrome included in the current study (1.175±0.59 vs 0.845±0.53, 95% CI −0.144–0.804).

Comparison between fat distribution and biochemical findings

The percentage of visceral fat was higher in patients with impaired glucose tolerance or diabetes ($n = 5$,

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Table 1 Fat distribution in patients with Cushing's syndrome at St Bartholomew's Hospital compared with studies in the published literature (reference in parentheses). Bart's, patients with active Cushing's syndrome at St Bartholomew's Hospital; 1, female Cushing's patients (2); 2, female Cushing's patients (3); 3, unselected volunteers (13); 4, random CT patients (11); 5, routine CT patients, mainly oncology (12); 6, healthy female volunteers (2); 7, non-obese healthy female volunteers (3); 8, obese female women (3); 9, obese female patients with non-visceral fat distribution (14); 10, obese female patients with visceral fat distribution (14). Data are expressed as means (one standard deviation).

	Study										
	Bart's	1	2	3	4	5	6	7	8	9	10
Female											
No. of patients	24	7	8	75	25	34	39	6	10	52	61
Age (years)	47.25 (15.6)	34 (13)	34.7 (9.2)	35.4 (4.9)*	49 (19)	52.4 (13.4)	26 (4.8)*	36.7 (6.4)	39.6 (6.6)	48.1 (8.2)	53 (6.2)*
BMI	29.6 (6.9)	*27.1*	30.2 (3.6)	29.9 (7.5)		26 (5)*	*22.4*	21.2 (1.1)*	32.1 (3.3)	40.1 (5.9)*	38 (4.6)*
Total fat	452.4 (211.6)	398 (227)	*647.3*	*531.6*	214 (115)*	347.9 (169.5)*	191 (76)*	*151*	*433*	*562*	*522*
Visceral fat	199.7 (125.7)	141 (116)	196.9 (54.9)	103.7 (53.8)*	54 (39)*	91.8 (52.7)*	25.5 (13.6)*	23.9 (14.7)*	88.5 (47.1)*	117.7 (44)*	190.4 (57)
Subcut. fat	252.7 (130.2)	257 (130)	450.4 (155.8)*	427.9 (200.5)*	159 (91)*	256.2 (130)	166 (70)*	127.0 (45.5)*	344.4 (121.5)	444.7 (136)*	331.3 (100)*
% visceral fat	42.4 (13.1)	34 (12)	*30*	*20*	25 (14)*	*26*	14 (7)*	*16*	*20*	*21*	*36*
V : S ratio	0.845 (0.525)	*0.549*	0.47 (0.16)*	*0.24*	*0.34*	0.38 (0.19)*	*0.15*	0.18 (0.1)*	0.28 (0.17)*	0.27 (0.08)*	0.59 (0.16)*
Male											
No. of patients	7			89	25	71					
Age (years)	37.3 (11.5)			36.1 (3.3)	50 (16)	51.5 (17)*					
BMI	26.2 (2.3)			27.6 (3.8)		23.4 (3.1)*					
Total fat	365.1 (183.5)			*377*	227 (103)*	220.2 (113)*					
Visceral fat	204.3 (146.1)			122.9 (49)*	93 (49)*	89.9 (53)*					
Subcut. fat	160.8 (42.5)			253.9 (101)*	133 (70)	130.3 (71)					
% visceral fat	49.5 (12.9)			*32.6*	42 (11)	*40.8*					
V : S ratio	1.175 (0.593)			*0.48*	*0.699*	0.77 (0.39)*					

BMI, body mass index; subcut. fat, subcutaneous fat; V:S, visceral to subcutaneous fat ratio.
* Denotes a significant difference between the Bart's patients with active Cushing's syndrome and the data from the study indicated, using 95% confidence intervals for the difference between the means. Numbers in italics were not provided in the original reference but were calculated using the data provided; standard deviations are therefore not available for these data.

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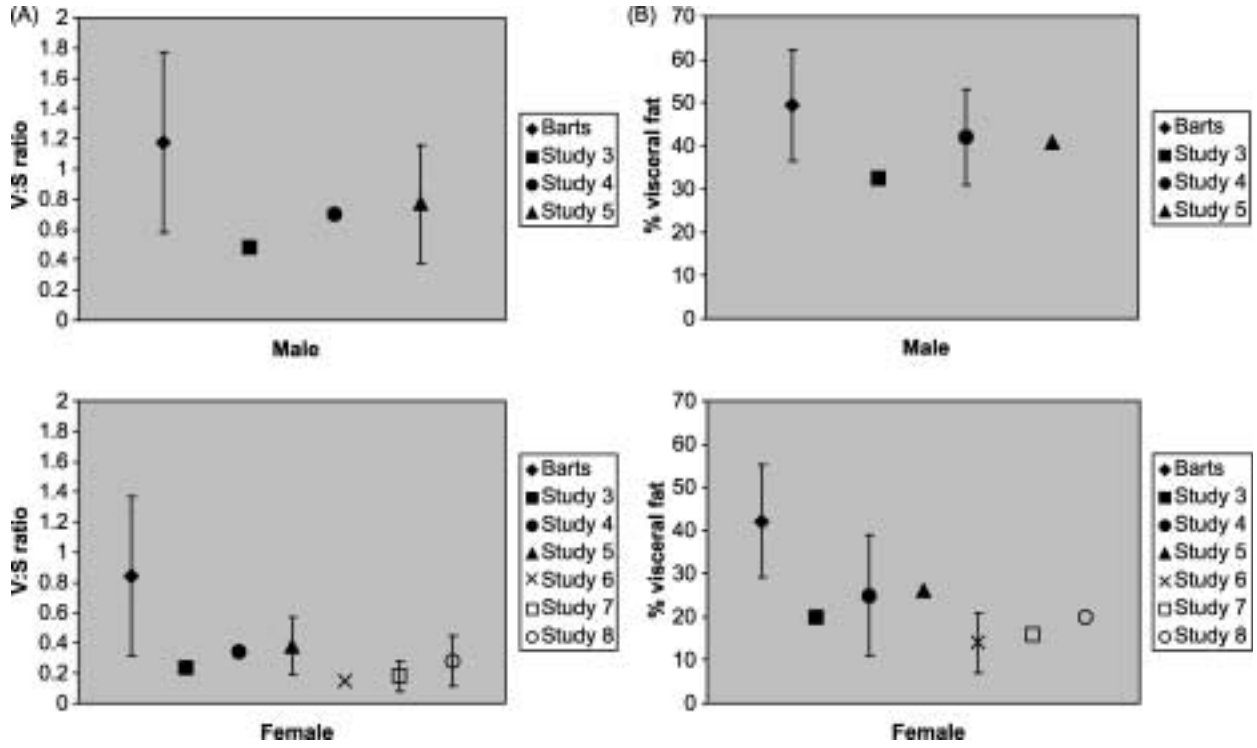

Figure 2 Graphical representation of fat distribution in patients with active Cushing's syndrome compared with studies in the published literature. (A) V:S ratios in cushingoid patients (Bart's) and non-cushingoid controls, shown as the mean±one standard deviation (data from Table 1). (B) Percentage of visceral fat in cushingoid patients (Bart's) and non-cushingoid controls, shown as the mean±one standard deviation (data from Table 1). Where 'whiskers' are not drawn, standard deviations are not available for some studies. Barts, patients with active Cushing's syndrome at St Bartholomew's Hospital; study 1 (reference no. 2), female Cushing's patients; study 2 (3), female Cushing's patients; study 3 (13), unselected volunteers; study 4 (11), random CT patients; study 5 (12), routine CT patients, mainly oncology; study 6 (2), healthy female volunteers; study 7 (3), non-obese healthy female volunteers; study 8 (3), obese female women.

mean±S.D. = 48.7±14.6) compared with non-diabetic patients ($n = 17$, mean±S.D. = 40.3±10.9), but this did not reach statistical significance. In those patients in whom data were available, serum cholesterol was elevated (>5.2 mmol/l) in 15/26 (58%), and serum triglycerides were elevated (>2.1 mmol/l) in 6/24 (25%) patients. No significant correlation was identified between fat distribution measurements and any of the biochemical markers tested: the cortisol day-curve, 0900 h plasma ACTH, ACTH mean or fasting lipids (Table 2).

Spearman's correlation demonstrated a positive correlation with age and the percentage of visceral fat (rho = 0.439, $P = 0.014$, $n = 31$) and the V:S ratio (rho = 0.423, $P = 0.018$, $n = 31$).

Discussion

It is recognised from epidemiological studies that obesity is associated with an increased risk of cerebrovascular and cardiovascular disease, and that there is a greater risk in patients where the regional fat distribution is in a central or abdominal type of distribution (15, 16). A central fat distribution is also known as the 'android' pattern, and it is now well established that men are more likely to have a central fat distribution than women, in whom a greater percentage of fat is deposited in the subcutaneous compartment. This central fat distribution is more commonly associated with diabetes, hyperlipidaemia, hypertension and atherosclerosis, a group of features known collectively as the metabolic syndrome.

Early studies using anthropometric techniques such as WHR and skinfold thickness confirmed this finding (7, 9, 10). However, cross-sectional imaging techniques are required to quantify the multi-compartmental fat distribution between the subcutaneous and visceral compartments in the abdomen. CT is established as the gold standard technique and has been used to confirm the association between visceral fat and the metabolic syndrome (17).

The classical cushingoid fat distribution is that of central obesity. A significant increase in visceral fat has been demonstrated using CT in female patients with Cushing's syndrome compared with non-hypercortisolaemic controls in two studies: one with seven patients with Cushing's syndrome and another

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Table 2 Spearman's correlations table of fat distribution. The correlation coefficient (rho), the significance level (*P*) and the number of patients (*n*) are shown.

		Total fat	Visceral fat	Subcut. fat	% V fat	V:S ratio
Age	rho	0.448*	0.526*	0.279	0.439*	0.423*
	P	0.011	0.002	0.129	0.014	0.018
	n	31	31	31	31	31
Weight	rho	0.725**	0.695**	0.628**	0.218	0.222
	P	0.000	0.000	0.002	0.343	0.334
	n	21	21	21	21	21
BMI	rho	0.722**	0.578**	0.744**	0.070	0.084
	P	0.000	0.001	0.000	0.722	0.673
	n	28	28	28	28	28
CDC	rho	−0.100	0.134	−0.189	0.289	0.324
	P	0.627	0.514	0.356	0.152	0.107
	n	26	26	26	26	26
ACTH (a.m.)	rho	−0.254	−0.141	−0.294	0.232	0.191
	P	0.211	0.492	0.144	0.253	0.351
	n	26	26	26	26	26
ACTH (mean)	rho	−0.196	−0.071	−0.297	0.289	0.243
	P	0.349	0.736	0.149	0.161	0.241
	n	25	25	25	25	25
Cholesterol	rho	0.648*	0.709*	0.552	0.491	0.491
	P	0.043	0.022	0.098	0.150	0.150
	n	10	10	10	10	10
TG	rho	0.569	0.494	0.586	0.276	0.276
	P	0.110	0.177	0.097	0.472	0.472
	n	9	9	9	9	9
LDL	rho	0.400	0.500	−0.200	0.700	0.700
	P	0.505	0.391	0.747	0.188	0.188
	n	5	5	5	5	5
HDL	rho	0.154	0.667	−0.359	0.359	0.359
	P	0.805	0.219	0.553	0.553	0.553
	n	5	5	5	5	5

*Correlation is significant at the 0.05 level (2-tailed); **correlation is significant at the 0.01 level (2-tailed).
% V fat, percentage of visceral to total fat; V:S ratio, visceral to subcutaneous fat ratio; BMI, body mass index; CDC, cortisol day-curve; TG, triglycerides; LDL, low density lipoproteins; HDL, high density lipoproteins.

with eight patients (2, 3). Our data support these findings; indeed, in our group of patients there was an even greater increase in visceral fat compared with one of the previous studies on women with Cushing's syndrome (3). This may reflect the larger sample size or possibly be related to a selection bias in our group of patients who attend a tertiary referral centre. We have also demonstrated an increase in the proportion of visceral fat in male patients with Cushing's syndrome compared with non-hypercortisolaemic controls (12). Furthermore, we have demonstrated that the normal male-to-female difference in fat distribution is abolished in Cushing's syndrome.

There was a higher percentage of visceral fat in the Cushing's patients with impaired glucose tolerance; however, this did not reach statistical significance, which may be due to the small sample size. This is expected in view of the recognised relationship between increased visceral fat and glucose intolerance as part of the metabolic syndrome.

The correlation which we found between age and increasing percentage of visceral fat and V:S ratio has also been demonstrated in previous studies of fat distribution but has not previously been demonstrated in Cushing's patients (1, 18, 19). In these cross-sectional studies, the visceral fat increases with age in both men and women, in lean as well as in obese patients. To our knowledge, there is no published longitudinal data on changes to visceral fat with age. The mechanism for increase in visceral fat with age may therefore be the same as in other types of obesity.

Several studies have demonstrated abnormalities of the hypothalamic–pituitary–adrenal axis (HPA axis) in patients with an increased proportion of visceral fat. These studies suggest that, in patients with visceral obesity, there is a hyper-responsiveness of the HPA axis to a variety of stimuli (20), which is probably a consequence of increased net conversion of cortisol to cortisone in hepatic tissue. Understanding the changes in fat distribution seen in men and women with Cushing's syndrome may improve our understanding of the mechanisms of the development of visceral fat distribution and the metabolic syndrome. It may also contribute to diagnostic and prognostic information in patients with Cushing's syndrome, and be useful in assessing follow-up (21).

Many of the patients in our study will have been growth hormone (GH) deficient, secondary to either pituitary disease or reversible suppression by cortisol. GH deficiency can also lead to accumulation of central

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fat, which may contribute to the change in fat distribution in patients with Cushing's syndrome (22, 23). The relative contributions of excess cortisol and GH deficiency in the redistribution of body fat, however, are currently unclear.

Our study has a number of limitations. There is no control group of non-hypercortisolaemic patients matched for age and BMI. Recruitment of normal controls was not possible due to the ethical problems involved in the use of an ionising radiation dose associated with CT scanning. We therefore used a variety of historical controls from other publications. Clearly, this is not ideal but, nevertheless, there were significant differences between our patients and the control subjects which appeared to be reproducible. The number of male patients with active Cushing's syndrome in whom an appropriate CT scan was available was small. This reflects the epidemiology of the disease, which is more common in women than in men.

In conclusion, we have demonstrated an increase in the visceral fat in both men and women with Cushing's syndrome and the abolition of the normal male to female difference in fat distribution. Thus, in both males and females, fat redistributes to a central, visceral location in Cushing's syndrome, as demonstrated on CT. Finally, age appears to be an important factor in the visceral distribution of fat.

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