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Effect of fat distribution on the pharmacokinetics of cortisol in obesity

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Abstract. *Objective:* Patients with predominantly upper body obesity are at greater risk for developing diabetes mellitus, hyperlipidemia, hypertension, and cardiovascular disease. Little is known about the mechanisms involved in the regulation of regional body distribution. It has been accepted that the accumulation of fat into adipose tissue depends on regional metabolic regulation of adipocytes and that glucocorticoids play a role in this mechanism. The aim of the present study is to investigate how the pharmacokinetics of cortisol correlate to intraabdominal and subcutaneous fat distribution in obese patients. *Methods:* A group of 24 obese patients (13 males and 11 females) were submitted to a CT scan for intraabdominal and subcutaneous fat area evaluation. A 30-min cortisol infusion (0.25 mg/kg) was administered and plasma cortisol was measured over 6 hours. *Results:* Patients with larger intraabdominal fat areas were found to have a higher cortisol clearance than those with lower intraabdominal fat areas. Cortisol clearance (both, absolute and body-weight corrected) showed a statistically significant correlation with intraabdominal fat area, either expressed by waist-hip ratio or obtained by computerized tomography. *Conclusions:* These findings indicate a more effective clearance capability for cortisol in patients with central obesity resulting in lowered cortisol plasma levels despite an increased cortisol secretion observed in this patient group.

Key words: cortisol – obesity – pharmacokinetics – fat distribution

Introduction

Regional fat distribution is critical in the clinical assessment of obese people. Patients with predominantly upper body obesity (i.e. increased fat in the neck, shoulder area, and abdomen) are at greater risk for developing diabetes mellitus, hyperlipidemia, hypertension, and cardiovascular disease [Bjorntorp 1988, Després et al. 1990, Donahue et al. 1987, Kissebah et al. 1989]. On the other hand, patients with predominantly lower body obesity (i.e. increased fat in the hips, thighs, and buttocks) are metabolically stable and not at greater risk for such diseases [Evans et al. 1983, Krotkiewski et al. 1993]. Association of abdominal obesity and cardiovascular disease can be partially explained by derangement of glucose homeostasis and insulin, as well as lipids and related lipoproteins [Bjorntorp 1988, Després 1991]. Computerized tomography (CT) studies have demonstrated that intraabdominal fat area (IAFA) correlated with glucose intolerance and plasma lipids [Fujioka et al. 1987, Sparrow et al. 1986].

Little is known about the mechanisms involved in the regulation of regional fat body distribution. It has been accepted that fat accumulation into adipose tissue depends on regional metabolic regulation of adipocytes and that glucocorticoids play a role in this mechanism [Rebuffé-Scrive et al. 1990]. Specific regional differences in the content of glucocorticoid receptor mRNA have been disclosed in human adipocytes [Bronnegard et al. 1990].

It has been shown that patients with upper body obesity have increased cortisol secretion associated with increased number of glucocorticoid receptors in intraabdominal fat. Despite the involvement of hyperinsulinemia, the hypercortisolism of patients with Cushing's syndrome leads to an increased activity in the lipoprotein lipase in adipose tissue associated with decreased lipid mobilization [Rebuffé-Scrive et al. 1988].

Steroid metabolic clearance is defined as the equivalent volume of plasma totally and irreversibly cleared of this steroid per unit time at steady-state [Gulprid and Mann 1970]. Isotopic studies have been considered an important tool in assessing adrenal steroid secretion and clearance.

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However, non-isotopic methods can also be useful in the evaluation of these parameters in clinical studies.

The aim of this investigation was to determine the pharmacokinetic parameters of cortisol in obese patients and investigate their correlations to the intraabdominal fat and subcutaneous fat areas evaluated by CT scan as well to demographic data, plasma lipids, glucose and insulin profiles.

Subjects, material and methods

The investigated subjects were 24 obese patients: 13 males (age: 12 – 57 years) and 11 females (age: 17 – 53 years) registered at the Outpatient Clinic of the Division of Endocrinology of the Hospital das Clinicas of University of São Paulo. The study was properly approved by the Hospital Ethical Committee and a written consent was obtained from all subjects included in this study. As shown in Table 1, all patients were obese with body mass index (BMI) greater than 30 kg/m^2 without any other clinical symptoms as evidenced by physical examination. Weight, height, BMI, blood pressure (BP), and waist-hip ratio (WHR) were obtained.

Abdominal CT scan examination was performed on *patients positioned at dorsal decubitus.* Images were generated at the level of the periomphalic region, and the intraabdominal (IAFA) and and subcutaneous fat areas (SCFA) were determined in cm^2. The tomographs employed were a CE 12000 of CGR (Paris, France) or a PACE from General Electric (Milwaukee, USA).

Cortisol (0.25 mg/kg, flebocortid, Merrell Lepetit Farmaceutica Ltda. São Paulo, Brazil) was infused over 30 minutes in 250 ml of 5% dextrose. Infusions were started at 8.00 h and blood samples for plasma cortisol were withdrawn 30 min before and 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min after beginning of the cortisol infusion.

Plasma glucose and insulin were also determined in samples obtained during an oral glucose tolerance test (75 g of glucose in 300 ml of water p.o.) performed in all patients. Plasma total cholesterol and lipoproteins were determined in basal samples.

Plasma cortisol and immunoreactive insulin were determined by commercial RIA kits (Diagnostic Products Corporation, USA). Plasma glucose, total cholesterol, HDL-cholesterol, and triglycerides were determined by enzymatic methods routinely employed at the clinical chemistry laboratory of the Hospital. LDL cholesterol and VLDL cholesterol were calculated by routine methods [Friedwald 1982].

The cortisol data were subjected to non-compartmental pharmacokinetic analysis. Cortisol baseline data were estimated from a regression line based on cortisol concentrations predose (0 h) and at the end of experiment (6 h) and were substracted from the measured values.

Non-compartmental pharmacokinetic parameters were obtained as follows: The half-life ($T_{1/2}$) was calculated from the terminal slope (β) of a semilogarithmic concentration-time plot as ln $2/\beta$. The area under the plasma cortisol concentration-time curve (AUC) was calculated using the trapezoidal rule. The total body clearance (CL) was calculated as dose divided by AUC. Mean residence time (MRT) was calculated as the area under the first moment curve (AUMC) divided by AUC minus the mean absorption time ($T_{inf}/2 = 15$ min). AUMC was determined using a plot of plasma cortisol concentration × time (Cp*t) versus time and calculation of its area under the curve calculated by the trapezoidal rule. The volume of distribution at steady-sate (Vd_{ss}) was determined as the product of total body clearance and mean residence time (CL*MRT). The volume of distribution during the elimination phase (Vd_{area}) was calculated as CL/β [Derendorf et al. 1991].

Student t-test and multiple regression analysis were employed for statistical analysis with a statistical significance of $p < 0.05$ (Primer of Biostatistics: The program, McGraw-Hill, Inc., Blue Ridge Summit, PA).

Results

Table 1 shows the demographic and biochemical data when the studied group was split into 2 based on IAFA as a cut-off value. Group A comprised of obese patients with

Table 1 Demographic and biochemical characteristics (mean ± SD) of the investigated group of obese patients. Group A (IAFA < 107 cm^2), group B (IAFA ≥ 107 cm^2); * denotes statistically significant differences between the 2 groups ($p < 0.05$).

	Group A (IAFA < 107 cm^2)	Group B (IAFA ≥ 107 cm^2)
Sex	3 Males, 7 Females	10 Males, 4 Females
Age (years)	17 – 53	12 – 57
Weight (kg)	93.4 ± 8.2	100.9 ± 12.4
Height (m)	1.58 ± 0.09	1.68 ± 0.10*
BMI (kg/cm^2)	38.0 ± 5.1	35.8 ± 5.1
DBP (mmHg)	87.0 ± 10.6	90.4 ± 16.0
SBP (mmHg)	130.0 ± 12.5	132.9 ± 17.3
Total cholesterol (mg/dl)	172.6 ± 29.3	194.2 ± 33.6
HDL cholesterol (mg/dl)	46.1 ± 9.8	35.7 ± 6.9*
LDL cholesterol (mg/dl)	102.3 ± 22.7	122.2 ± 33.7
VLDL cholesterol (mg/dl)	22.3 ± 11.0	37.2 ± 13.3*
Triglycerides (mg/dl)	111.2 ± 54.7	186.5 ± 67.5*
Fasting plasma glucose (mg/dl)	98.5 ± 15.1	97.8 ± 11.0
2-h oGTT plasma glucose (mg/dl)	115.4 ± 23.7	139.4 ± 43.1
Fasting insulin (μIU/ml)	6.4 ± 5.0	20.4 ± 15.1*
2-h oGTT insulin (μIU/ml)	53.4 ± 52.9	100.4 ± 70.8

IAFA = intra-abdominal fat area, BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure

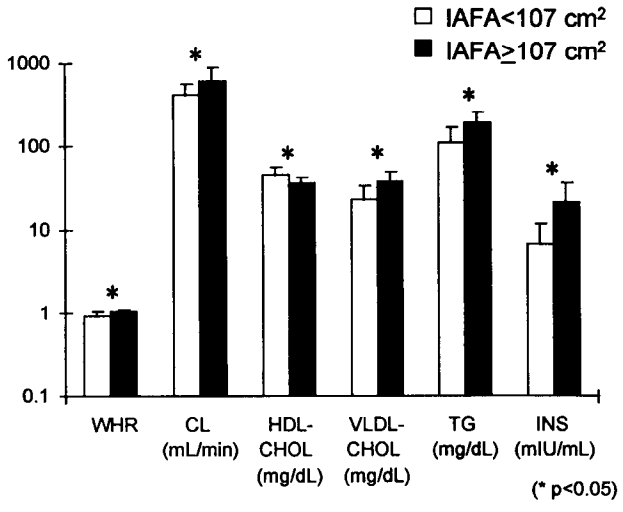

Fig. 1 Comparison between groups A (intraabdominal fat area < 107 cm^2) and B (intraabdominal fat area ≥ 107 cm^2) with respect to waist-hip ratio (WHR), plasma cortisol clearance (CL), HDL cholesterol (HDL-CHOL), VLDL cholesterol (VLDL-CHOL), triglycerides (TG), and fasting insulin (INS).

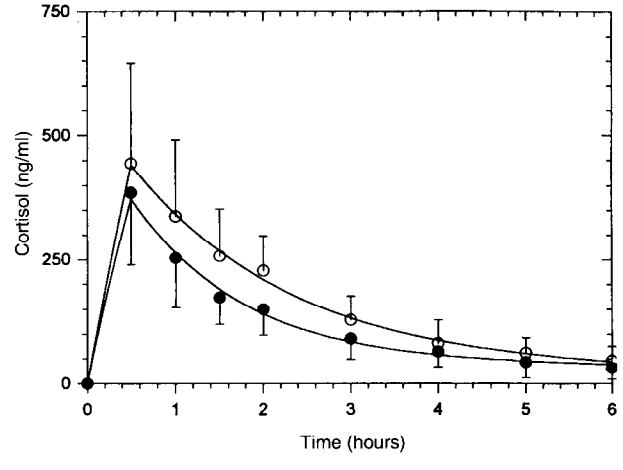

Fig. 2 Plasma concentrations (mean ± SD) after a 30-minute infusion of cortisol (0.25 mg/kg) in groups A (○ intraabdominal fat area < 107 cm^2) and B (● intraabdominal fat area ≥ 107 cm^2).

IAFA < 107 cm^2 and group B with IAFA ≥ 107 cm^2. There were no differences between the 2 groups regarding age, weight, BMI, diastolic or systolic blood pressure (DBP and SBP, respectively), total cholesterol, LDL cholesterol, fasting and 2-h after glucose challenge plasma glucose and insulin. Group B patients showed greater mean concentrations of triglycerides and VLDL cholesterol than patients of group A and lower mean concentrations of HDL cholesterol (Figure 1). Mean fasting insulin concentrations were statistically greater in group B than in group A. The mean cortisol plasma concentrations are shown in Figure 2, the

Table 2 Pharmacokinetic parameters (mean ± SD) of the investigated groups of obese patients. Group A (IAFA < 107 cm^2), group B (IAFA ≥ 107 cm^2); * denotes statistically significant differences between the 2 groups ($p < 0.05$).

	Group (IAFA < 107 cm^2)	Group B (IAFA ≥ 107 cm^2)
Fasting plasma cortisol (ng/ml)	97.1 ± 46.1	92.9 ± 41.3
$T_{1/2}$ (min)	93.1 ± 18.4	92.5 ± 30.3
AUC (μg×min/ml)	64.5 ± 24.1	48.1 ± 20.5
CL (ml/min)	408.2 ± 160.2	614.8 ± 256.7*
MRT (min)	141.3 ± 25.5	123.4 ± 30.3
Vd_{area} (l)	56.7 ± 23.2	77.0 ± 30.5
Vd_{ss} (l)	55.8 ± 31.5	73.4 ± 27.8

$T_{1/2}$ = half life, CL = clearance, MRT = mean residence time, AUC = area under the plasma concentration-time curve, after baseline correction, Vd_{area} = volume of distribution during the elimination phase, Vd_{ss} = volume of distribution at steady-state

respective pharmacokinetic parameters calculated for the 2 groups are listed in Table 2. There were no statistically significant differences between groups A and B regarding fasting plasma cortisol, $T_{1/2}$, AUC, MRT, Vd_{area}, and Vd_{ss}, even when the parameters were corrected for body weight, except for cortisol plasma clearance, which was found to be significantly higher in group B. IAFA, either indicated by WHR or as the area (cm^2) obtained from the abdominal CT, showed a statistically significant correlation with cortisol clearance ($r = 0.44$ or $r = 0.53$, respectively) even when corrected for body weight ($r = 0.48$, Figure 3). The ratio IAFA/SCFA showed a statistically significant correlation with the volume of distribution of plasma cortisol at steady-state (IAFA/SCFA vs. Vd_{ss}: $r = 0.43$, Figure 4). Furthermore, IAFA correlated with total cholesterol ($r = 0.48$), HDL cholesterol ($r = 0.45$), LDL cholesterol ($r = 0.48$), VLDL cholesterol ($r = 0.53$), triglycerides ($r = 0.53$), and fasting plasma insulin ($r = 0.59$).

Discussion

The pathophysiologic mechanisms involved in central obesity, particularly visceral, is of great interest due to the increased cardiovascular disease risk in obese patients. Many investigators have demonstrated lipid profile alterations, e.g. increased cholesterol, LDL cholesterol, and triglycerides associated with decreased plasma HDL cholesterol, related to visceral obesity [Bjorntorp 1988, Després 1991]. Insulin resistance with basal hyperinsulinemia in patients with predominantly upper-body obesity has been reported previously [Kissebah et al. 1989, Stern and Haffner 1986]. All of these findings are consistent with the results from this study.

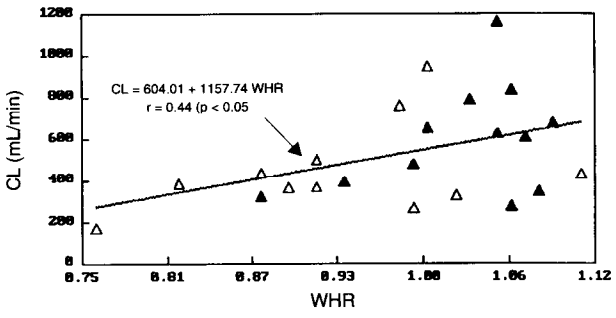

Fig. 3a

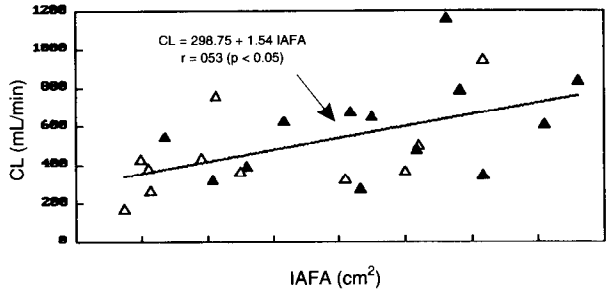

Fig. 3b

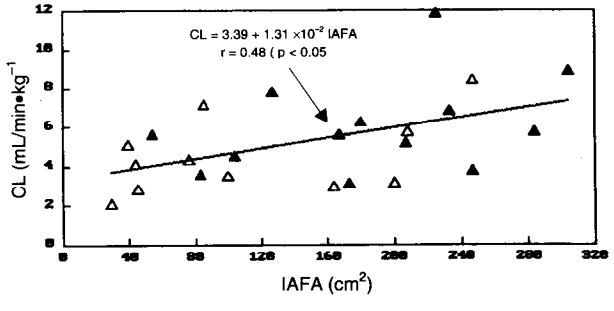

Fig. 3c

Fig. 3 Correlation analysis between waist-hip ratio (WHR) – and cortisol clearance (A), intraabdominal fat area (IAFA) and cortisol clearance (B), and intraabdominal fat area (IAFA) and weight-corrected cortisol clearance (C) (▲ = male, Δ = female).

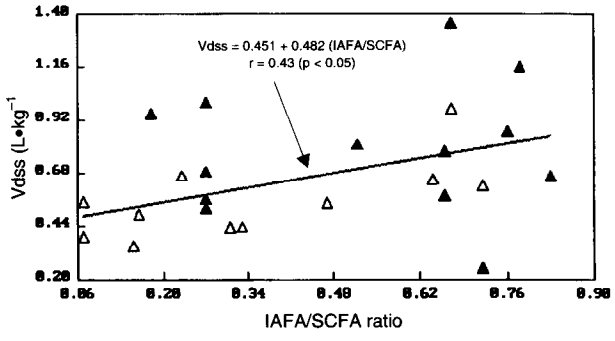

Fig. 4 Correlation analysis between the ratio of intraabdominal : subcutaneous fat areas (IAFA/SCFA) and the volume of distribution at steady-state for cortisol when corrected by body weight ($Vd_{ss} \times kg^{-1}$), (▲ = male, Δ = female).

The role of glucocorticoids in the pathogenesis of visceral obesity is made evident by the predominantly centripetal obesity observed in patients with Cushing's syndrome who also show insulin resistance and hyperlipidemia. Increased concentrations of 17-hydroxycorticosteroids and 17-ketosteroids in urine of patients with central obesity have been reported before. Our observation of increased clearance associated to normal plasma cortisol concentrations could be explained by a concomitant increase in cortisol secretion in visceral obesity. It is well established that a significant number of obese subjects have an increased secretion rate and enhanced turnover of cortisol. Nevertheless, plasma cortisol concentrations are usually within the normal range, the normal diurnal variation of cortisol is maintained. Urinary free cortisol data have been inconclusive [Marin et al. 1992, Pascuali et al. 1993, Zamboni et al. 1994]. Since there appears to be no major alteration in protein-binding, the enhanced production of cortisol has to be balanced by accelerated metabolism [Bjorntorp 1991, Schteingart et al. 1969]. Recently, a study of a group of women aged below 45 years demonstrated an increased cortisol secretion related to visceral adiposity with a decrease in basal plasma cortisol concentration [Marin et al. 1992]. Adipocytes isolated from intraabdominal fat present a greater number of glucocorticoid receptors than other tissues. Furthermore, increased metabolism has been reported in adipocytes [Rebuffé-Scrive et al. 1985]. Such a more effective clearance capability of the visceral adipose tissue may result in a decreased basal plasma cortisol concentration despite the increased cortisol secretion observed in those patients.

Many authors have considered the usefulness of non-isotopic methods in the evaluation of hormone pharmacokinetic parameters. Our data showed, in a well-characterized and homogenous group of obese patients, that plasma cortisol clearance correlates to the amount of visceral fat represented either as intraabdominal fat area or as waist-hip ratio without any relationship with the total body weight. This group of patients also showed an increased volume of distribution of cortisol (Vd_{ss}) which correlated positively with the intraabdominal to subcutaneous fat area ratio. The greater the amount of visceral fat the greater the volume of plasma cortisol distribution. It is conceivable that this increment in the volume of distribution may be due to a larger number of glucocorticoids receptors in the adipocytes of the intraabdominal fat of the centripetal type of obesity. Further investigations should be carried out to explore whether the increased number of glucocorticoid receptors could be responsible for a hypersensitivity of the intraabdominal fat adipocytes to cortisol leading to accumulation of visceral adiposity.

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