Anthropometric, computed tomography and fat cell data in an obese population: relationship with insulin, leptin, tumor necrosis factor-alpha, sex hormone-binding globulin and sex hormones

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Abstract

Objective: To correlate anthropometric, computed tomography and fat cell data from abdominal regions with the levels of serum insulin, C-peptide, leptin, tumor necrosis factor-alpha (TNF-α), testosterone, 17β-estradiol, androstenedione, dehydroepiandrosterone sulphate (DHEA-S) and sex hormone-binding globulin (SHBG).

Design and methods: The sample consisted of 84 obese patients (29 men, 22 premenopausal women and 33 postmenopausal women) who had undergone abdominal surgery. Weight, height, percentage of body fat by skinfolds, waist, hip and thigh circumferences, sagittal and coronal diameters, visceral and subcutaneous area, serum hormones and fat cell data were studied.

Results and conclusions: Premenopausal women showed the lowest values in most abdominal distribution parameters, although, depending on the waist circumference criteria at the umbilicus level perimeter (W1) or midway between lower rib margin and iliac crest perimeter (W2), the population was classified differently, as gynoid or android. Although there were no differences in fat cell size between genders, gynoid women had smaller and more numerous fat cells than the android type. Perivisceral fat cell size was significantly smaller than subcutaneous fat cell size. In women, central obesity was significantly correlated with an increase in serum insulin, leptin, TNF-α, testosterone and androstenedione levels, and a decrease in 17β-estradiol and DHEA-S, while in men significant correlations were positive with insulin and negative with testosterone and androstenedione. Fat cell size was positively correlated with serum levels of leptin, insulin, DHEA-S, androstenedione and inversely correlated with SHBG. These data indicate that hormones seem to interact not only with body fat distribution but also with fat cell size. This interaction differs between genders and between the different abdominal adipose tissue regions.

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Introduction

Epidemiological data suggest that adipose tissue distribution per se might be an indicator of cardiovascular diseases, with intra-abdominal obesity being more detrimental than peripheral obesity (1). It is known that body fat distribution is related to insulin resistance (2) and that adipose tissue, besides playing an endocrine role as a target for sex hormones, produces modulator substances such as leptin, tumor necrosis factor-alpha (TNF-α) with endocrine, autocrine and paracrine effects (3). Changes in sex steroids, whose metabolism is influenced by adipose tissue, have a strong influence on regional development of this tissue, and play a primordial role, together with other factors, in the expansion of abdominal adipose tissue (4). However, a comparison of several studies in which the relationship between the distribution of adipose tissue and different hormones was investigated (5–8), reveals discrepancies, perhaps because of differences in study populations and in methods used to assess hormone levels and fat distribution. These studies used the waist/hip ratio as a measure of fat distribution. Imaging techniques, such as computed tomography and magnetic resonance imaging, give more accurate information about the separate fat depots, visceral and subcutaneous, than anthropometric data.

Regional growth of adipose tissue is mainly dependent
on the metabolism of mature adipocytes and is determined by the capacity of the adipocytes to accumulate and mobilise triacylglycerides i.e. adipocyte size. Previous studies on the relationship of hormones and the function and morphology of adipose tissue have shown the influence of these hormones on the accumulation of fat in the adipocytes of different adipose regions (9, 10). Although recent adipocyte culture studies provide valuable information on the relationship between hormones and adipose tissue (11, 12), including the possible differences in the way this tissue behaves depending on the adipose area studied (13), the very complexity of obesity and the large number of factors which intervene in fat accumulation make it necessary to conduct complete clinical studies in obese individuals. Such studies will include anthropometric data, computed tomography studies, analysis of adipocyte size in different abdominal regions and serum levels of different hormones and cytokines such as insulin, leptin, TNF-α, sex hormones and sex hormone-binding globulin (SHBG), with the aim of determining whether hormones and adipose tissue do interact and, if so, how these interactions differ depending on the different abdominal adipose tissue regions, i.e. omental, subcutaneous and perivisceral as studied in an obese subject.

**Subjects and methods**

**Subjects**

Eighty-four patients between 30 and 70 years of age were selected from the outpatient clinics of the University ‘Virgen de la Arrixaca’, the General University and the ‘Morales Meseguer’ hospitals in Murcia, Spain. All the patients were obese, grades I and II, body mass index (BMI) 27–35 kg/m² and were going to be admitted for abdominal surgery or laparoscopy for reasons that did not interfere with the study: gall bladder, ulcer or umbilical hernia. Patients who were on a special diet, who were under treatment with caloriogenic, lipogenic or contraceptive drugs, or were diagnosed with diabetes mellitus, chronic renal failure, chronic hepatopathy, or cancer, were excluded from the study. Patients were divided into groups of men ($n = 29$), premenopausal women ($n = 22$), and postmenopausal women ($n = 33$). The definition of menopausal status was in accordance with the following criteria: women in amenorrhea for at least 12 months, having 17β-estradiol levels lower than 150 pmol/l and follicle-stimulating hormone levels higher than 15 IU/l. Women presenting normal menses or who in any case reported at least 10 menopausal cycles in the previous year, and without climacteric-related symptoms such as hot flushes, bleeding irregularities and fluctuation in mood, were included in the premenopausal group (14). Informed consent was required for the study, which was approved by the Ethics Committee of the ‘Virgen de la Arrixaca Hospital’.

**Anthropometric measurements**

The evaluation of obesity was carried out according to the methods proposed by the Spanish Society for the Study of Obesity (15). Weight was determined in subjects wearing light clothes and bare-footed, using a digital electronic weighing scale. Height was determined using a Harpenden digital stadiometer (range 0.7–2.05 m), with the subject upright and the head in the Frankfurt plane. From these data, the body mass index (BMI) was calculated.

Total body fat (%) was derived by using Siri’s equation (16) and was based on body density as determined from the following skinfolds: biceps, triceps, suprailiac and subscapular. All measurements were obtained following standard protocols, on the right side, with the subject in an upright and relaxed position. Measurements were taken 1 cm from the position of the fingers and perpendicular to the anatomic region using a Harpenden lipocaliper (Holtain Ltd, Bryherian, Crymmych, Pembs, UK) with a constant pressure of 10 g/mm². Body fat distribution was assessed using the following circumferences: waist1 (W1), at the level of the iliac crest, passing through the umbilicus; waist2 (W2), midway between the lower rib margin and the iliac crest; hip, the widest circumference over the great trochanters; and oblique thigh perimeter. Anthropometric measurements were carried out three times by a single tester. The following ratios were calculated: waist1/hip (WHR1), waist2/hip (WHR2), waist/thigh, (WTR) and conicity index (CI) (17). Android women were defined as those with WHR > 0.9 (15).

**Computed tomography**

All subjects underwent computed tomography (CT). Measurements of visceral and subcutaneous adipose tissue areas were performed according to Sjöström (18) using a Toshiba CBCT007A Scanner (Toshiba Corporation 1385–1. Shimoshiqiu, Otowawara, Japan). A single 10 mm scan at the L4-L5 level was performed with a 512×512 matrix, a window size of 300 Hounsfield units (HU) and a centre of 40 HU. To obtain high accuracy and reproducibility of these measurements, a skeleton radiograph was used as the reference to establish the position of the scans to the nearest 1 mm. The subcutaneous (SA) and visceral (VA) abdominal fat areas were determined from a tomodiagram section by image analysis using a MIP-Micron Image Processing System (Micron, Barcelona, Spain) based on the BMIO 10 (Kontron, Eching, Germany). After both areas were evaluated, the VA/SA index was calculated (19). Sagittal and coronal diameters were determined directly in the CT scan (20).

**Adipose tissue examinations**

Abdominal adipose tissue samples were obtained during surgery. Subcutaneous samples were taken from the
periumbilical region, and intra-abdominal samples from perivisceral fat surrounding the gall bladder and omental fat. Samples were stored in Ringer solution at −70 ºC until just before analysis. Adipocyte sizes of different regions were determined according to Sjöström et al. (21). All measurements were conducted by the same operator. Intra-operator variability was examined from duplicate measures in several subjects by the same operator. Intra-operator variability was 0.99 and 0.94 respectively.

The total fat cell number was calculated by dividing the weight of total body fat by the average of the mean fat cell weights of the three adipose tissue regions studied: subcutaneous, omental and perivisceral.

**Blood analysis**

Blood samples were collected the day before surgery following an overnight fast. Serum was separated after centrifugation and stored at −20 ºC until analysed. Insulin, TNF-α and SHBG were determined by IRMA with reagents from Biosource (Fleurus, Belgium), Medgenix Diagnostics (Fleurus, Belgium) and Orion Diagnostica (Espoo, Finland) respectively. The sensitivity of the method was 1 μIU/ml for insulin, 5 pg/ml for TNF-α and 0.5 nmol/l for SHBG. The intra-assay coefficient of variation (CV) was 4.5% at a serum insulin concentration of 6.6 μIU/ml and 2.1% at 53 μIU/ml; 6% at a serum TNF-α concentration of 67.4 pg/ml and 2.2% at 1328.0 pg/ml; and 5.3% at a serum SHBG concentration of 17.7 nmol/l and 5.6% at 156.8 nmol/l. 17β-Estradiol and testosterone were determined by ELISA/competition with biotine/estreptavidine technology with reagents purchased from Boehringer Mannheim Immunodiagnostics (Meylan, France). Androstenedione, leptin, C-peptide and dehydroepiandrosterone sulphate (DHEA-S) were determined by RIAs with reagents purchased, respectively, from Immunotech (Marseille, France), Linco Research (St Charles, MO, USA), Byk-Santeg Diagnostic Systems Laboratories Inc. (Webster, TX, USA) and Diagnostic Systems Laboratories Inc. (Meylan, France). Androstenedione, leptin, C-peptide and Diagnostic Systems Laboratories Inc. determined by ELISA/competition with biotine/estreptavidine technology with reagents purchased from Boehringer Mannheim Immunodiagnostics (Meylan, France). Androstenedione, leptin, C-peptide and Diagnostic Systems Laboratories Inc. were determined by RIAs with reagents purchased, respectively, from Immunotech (Marseille, France), Linco Research (St Charles, MO, USA), Byk-Santeg Diagnostic Systems Laboratories Inc. (Webster, TX, USA). The assays had sensitivities of 0.1 ng/ml for androstenedione, 0.5 ng/ml for leptin, 0.05 ng/ml for C-peptide and 1.7 μg/dl for DHEA-S. The intra-assay coefficients of variation (CV) were 8.9% at a mean androstenedione concentration of 0.58 ng/ml and 4.1% at a mean value of 6.68 ng/ml. 8.3% at a mean leptin concentration of 4.9 ng/ml and 3.4% at 25.6 ng/ml. 4.8% at a mean C-peptide value of 0.76 ng/ml and 2.9% at 12.53 ng/ml. 9.4% at a mean DHEA-S concentration of 20.3 μg/dl and 6.3% at 593.3 μg/dl. The normal ranges according to the hospital standards were: insulin: 5–25 μIU/ml; C-peptide: 0.3–2.5 ng/ml; leptin: 7.5 ± 9.3 ng/ml; TNF-α: 0–20 pg/ml; 17β-estradiol: 10–39 pg/ml in males and 10–147 pg/ml in females in the follicular phase, 110–338 during menses. 27–247 in the luteal phase and 0.01–46 in the postmenopausal state; androstenedione: 0.61–3.71 ng/ml in males and 0.46–3.39 ng/ml in females; testosterone: 2–8.5 ng/dl in males and 0.01–0.86 ng/dl in females; DHEA-S: 281–606 μg/dl in males from 17 to 50 years, 117–342 μg/dl in males > 50 years, 195–507 μg/dl in females, and 7–348 μg/dl in the
postmenopausal state; SHBG: 10–50 nmol/l in males, and 30–90 nmol/l in females.

**Statistical analyses**

Results are reported as means ± s.d., unless otherwise indicated. The comparisons between different groups were analysed by means of one-way ANOVA. The paired t-test was used to compare two adipose samples from different areas in the same subject. Pearson’s correlation coefficients were used to quantify the relations between variables.

**Results**

Table 1 shows anthropometric and computed tomography data in the studied population.

Fat cell data are presented in Table 2. Results indicate that premenopausal women had a higher number of fat cells than men and postmenopausal women. After dividing the females into gynoid and android types, the results indicate that gynoid women had a significantly higher number of adipocytes than their android counterparts. $7.3 \times 10^{10}$ vs $5.6 \times 10^{10}$ ($P < 0.05$), although the size was significantly smaller 0.43 $\mu$m vs 0.53 $\mu$m ($P < 0.05$). Mean differences in adipocyte sizes among different adipose tissue regions indicate that perivisceral fat cells (0.45 ± 0.03 $\mu$m) are significantly smaller than subcutaneous fat cells (0.53 ± 0.03 $\mu$m) ($P < 0.05$). There were no significant differences between subcutaneous and omental fat cell size.

Plasma concentrations of circulating hormones, SHBG and TNF-α are reported in Table 3. Leptin, TNF-α, and C-peptide values were all above the normal range and insulin values were at the upper limit of the reference range, according to local hospital standards. Values of the sex hormones were all within normal limits, except for DHEA-S, which was low, especially in men and premenopausal women. When different groups were compared, significant differences were observed in every hormone except androstenedione and C-peptide. Insulin, leptin, TNF-α and SHBG plasma values were significantly higher and testosterone mean values were significantly lower in women than in men. As expected, 17β-estradiol and DHEA-S mean values were significantly higher in premenopausal than in postmenopausal women. No significant differences were found in testosterone plasma levels between pre- and post-menopausal women.

The interrelationships among BMI, fat distribution, circulating hormones, SHBG and TNF-α are described in the following paragraph. In male and female populations, fasting insulin concentration correlated positively with body weight: $r = 0.62$, $P < 0.0001$;

**Table 2 Fat cell data in the studied population. Data are presented as means ± S.D.**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Total population $(n = 54)$</th>
<th>Men $(n = 22)$</th>
<th>Postmenopausal women $(n = 21)$</th>
<th>Premenopausal women $(n = 11)$</th>
<th>$P$ (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous Diameter $(\mu$m)</td>
<td>95.1 ± 11.6</td>
<td>98.2 ± 10.7</td>
<td>96.2 ± 13.5</td>
<td>95.5 ± 10.2</td>
<td>0.787</td>
</tr>
<tr>
<td>Weight $(\mu$g)</td>
<td>0.49 ± 0.16</td>
<td>0.46 ± 0.15</td>
<td>0.52 ± 0.18</td>
<td>0.48 ± 0.13</td>
<td>0.521</td>
</tr>
<tr>
<td>Perivisceral Diameter $(\mu$m)</td>
<td>94.9 ± 11.9</td>
<td>98.2 ± 14.1</td>
<td>94.8 ± 13.1</td>
<td>92.9 ± 9.0</td>
<td>0.564</td>
</tr>
<tr>
<td>Weight $(\mu$g)</td>
<td>0.46 ± 0.17</td>
<td>0.52 ± 0.24</td>
<td>0.46 ± 0.17</td>
<td>0.43 ± 0.11</td>
<td>0.458</td>
</tr>
<tr>
<td>Omental Diameter $(\mu$m)</td>
<td>97.4 ± 15.3</td>
<td>96.2 ± 12.7</td>
<td>100.3 ± 8.3</td>
<td>99.5 ± 32.1</td>
<td>0.839</td>
</tr>
<tr>
<td>Weight $(\mu$g)</td>
<td>0.52 ± 0.23</td>
<td>0.49 ± 0.18</td>
<td>0.54 ± 0.13</td>
<td>0.63 ± 0.50</td>
<td>0.552</td>
</tr>
<tr>
<td>Mean fat cell weight $(\mu$g)</td>
<td>0.48 ± 0.15</td>
<td>0.50 ± 0.17</td>
<td>0.49 ± 0.12</td>
<td>0.47 ± 0.16</td>
<td>0.854</td>
</tr>
<tr>
<td>Total fat cell number $(\times 10^{10})$</td>
<td>5.81 ± 2.21</td>
<td>4.89 ± 1.81b</td>
<td>5.42 ± 1.73</td>
<td>7.67 ± 2.57c</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Significant differences between: $^a$ men and premenopausal women; $^b$ men and postmenopausal women; $^c$ postmenopausal and premenopausal women.

**Table 3 Plasma levels of hormones, TNF-α and SHBG. Data are presented as means ± S.D.**

<table>
<thead>
<tr>
<th></th>
<th>Total population $(n = 84)$</th>
<th>Men $(n = 29)$</th>
<th>Postmenopausal women $(n = 33)$</th>
<th>Premenopausal women $(n = 22)$</th>
<th>$P$ (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin $(\mu$IU/ml)</td>
<td>15.6 ± 9.5</td>
<td>13.2 ± 8.7$^b$</td>
<td>14.2 ± 7.6$^a$</td>
<td>20.7 ± 11.3</td>
<td>0.010</td>
</tr>
<tr>
<td>C peptide $(ng/ml)$</td>
<td>3.7 ± 2.0</td>
<td>3.6 ± 2.2</td>
<td>3.3 ± 1.5</td>
<td>4.39 ± 2.4</td>
<td>0.234</td>
</tr>
<tr>
<td>Leptin $(ng/ml)$</td>
<td>23.7 ± 15.1</td>
<td>8.23 ± 3.8$^a,b$</td>
<td>30.0 ± 14.3</td>
<td>25.1 ± 13.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>TNF-α $(pg/ml)$</td>
<td>21.8 ± 8.5</td>
<td>19.3 ± 9.1$^a$</td>
<td>24.7 ± 8.6</td>
<td>20.5 ± 6.3</td>
<td>0.033</td>
</tr>
<tr>
<td>17β-Estradiol $(pg/ml)$</td>
<td>33.3 ± 42.6</td>
<td>22.6 ± 15.6$^a$</td>
<td>14.9 ± 17.9$^c$</td>
<td>76.3 ± 62.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Testosterone $(ng/dl)$</td>
<td>1.4 ± 1.8</td>
<td>3.6 ± 1.4$^a,b$</td>
<td>0.25 ± 0.24</td>
<td>0.26 ± 0.27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DHEA-S $(\mu$g/dl)</td>
<td>112 ± 111</td>
<td>152 ± 154$^a$</td>
<td>69.2 ± 59.3</td>
<td>125 ± 85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SHBG $(nmol/l)$</td>
<td>49.9 ± 34.4</td>
<td>34.5 ± 22.1$^a,b$</td>
<td>55.6 ± 27.4</td>
<td>61.0 ± 48.5</td>
<td>0.010</td>
</tr>
<tr>
<td>Androstenedione $(ng/ml)$</td>
<td>1.47 ± 0.79</td>
<td>1.56 ± 0.86</td>
<td>1.27 ± 0.66</td>
<td>1.65 ± 0.88</td>
<td>0.178</td>
</tr>
</tbody>
</table>

Significant differences between: $^a$ men and postmenopausal women; $^b$ men and premenopausal women; $^c$ postmenopausal and premenopausal women.

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Central obesity, fat cell data and hormones

Figure 1 Correlations between abdominal fat distribution (CT image) and circulating hormones in both genders.

In men, insulin was also significantly correlated with BMI ($r = 0.52$, $P < 0.001$), total body fat ($r = 0.39$, $P < 0.05$) and waist2 ($r = 0.53$, $P < 0.05$). In women, this hormone was positively correlated with the hip circumference and abdominal subcutaneous fat ($r = 0.27$, $P < 0.05$; $r = 0.42$, $P < 0.0001$). Leptin showed a close association with most of the obesity and body fat distribution parameters in the female population: weight ($r = 0.42$, $P < 0.001$); BMI ($r = 0.60$, $P < 0.0001$); % body fat ($r = 0.60$, $P < 0.0001$); waist2 ($r = 0.52$, $P < 0.0001$); waist1 ($r = 0.60$, $P < 0.0001$); hip ($r = 0.55$, $P < 0.0001$), sagittal diameter ($r = 0.63$, $P < 0.0001$) and conicity index ($r = 0.28$, $P < 0.05$). There were no such correlations in the male population. Similarly, TNF-α was positively correlated with the visceral area ($r = 0.27$, $P < 0.05$) and negatively correlated with hip circumference ($r = -0.31$, $P < 0.05$) in the female group, while no significant correlations with any of the obesity and body fat distribution parameters were observed in the male population. Results indicate that most sex hormones were associated with anthropometric and CT measurements. For example, testosterone in men was correlated with the following obesity and abdominal distribution parameters: BMI ($r = -0.45$, $P < 0.05$), % body fat ($r = -0.50$, $P < 0.05$), waist2 ($r = -0.50$, $P < 0.05$), WHR ($r = -0.47$, $P < 0.05$), SA ($r = -0.53$, $P < 0.05$). In women the following associations were positive: BMI ($r = 0.28$, $P < 0.05$), and waist1 ($r = 0.31$, $P < 0.05$). 17β-Estradiol and DHEA-S plasma concentrations showed significant negative correlations with body fat distribution parameters in women: WHR ($r = -0.57$, $P < 0.0001$; $r = -0.37$, $P < 0.001$) and conicity index ($r = -0.43$, $P < 0.0001$; $r = -0.47$, $P < 0.0001$ respectively). Androstenedione showed opposite correlations with the degree of obesity and central obesity in both sexes: VA ($r = -0.38$, $P < 0.05$), and VA/SA ($r = -0.40$, $P < 0.005$) being negative for men, and BMI ($r = 0.38$, $P < 0.05$), sagittal diameter ($r = 0.34$, $P < 0.05$) and coronal diameter ($r = 0.31$, $P < 0.05$) being positive for women. A negative correlation was found between SHBG serum levels and total body fat in men ($r = -0.56$, $P < 0.05$) and with central obesity in the total population: waist1 ($r = -0.35$, $P < 0.05$), WHR ($r = -0.41$, $P < 0.001$), VA ($r = -0.25$, $P < 0.05$), VA/SA ($r = -0.33$, $P < 0.001$).

Evaluating the interrelationships between fat cell data, circulating hormones, SHBG and TNF-α, our results indicate that leptin correlates positively with mean fat cell size in the female population (Fig. 2). A significant positive correlation was observed in the male population between plasma values of insulin, androstenedione and DHEA-S and adipocyte size of the subcutaneous area (Fig. 3). Such correlations were not seen in women, or in any other adipose region. SHBG was the only metabolite which correlated negatively with fat cell size (Fig. 4). Of all the circulating hormones studied, insulin was the only one that significantly correlated with fat cell number, the correlation being positive ($r = 0.25$, $P < 0.05$).

Discussion

Data indicate that body fat distribution, especially visceral fat, differs with gender, as has been described previously (22, 23). Premenopausal women were lowest in most abdominal fat distribution parameters (Table 1).
Based on waist1 circumference (W1) measurements, the studied population can be defined as being of the android type (15). However, it is important to note that premenopausal women showed gynoid type obesity, with a smaller abdominal perimeter, lower visceral area and a larger oblique thigh circumference when waist2 circumferences (W2) were used. The findings underline the importance of clearly defining the type of circumferences and indices used in classifying an obese population according to body fat distribution. Both W1 and W2 mean values exceeded those associated with increased cardiovascular risk (24).

When dividing the population into gynoid and android types, the data showed that gynoid women possessed significantly smaller and more numerous adipocytes than android women, which confirms the findings of other authors (25). Regional differences in fat cell size were found, with visceral fat cells being smaller than subcutaneous fat cells (26).

Serum insulin concentration correlated positively with the grade of obesity and body fat distribution as reflected by waist circumference for men and subcutaneous fat and hip circumference in women (27, 28). It is noteworthy that serum insulin levels correlate positively with subcutaneous fat cell size. These data coincide with previous results highlighting the importance of abdominal adipose tissue and showing that of all the subcutaneous regions studied, only abdominal fat cell size correlates with plasma insulin (29). The lack of correlation between intra-abdominal fat cell size and insulin confirm in vitro results indicating that the antilipolytic effect of insulin is more prominent in subcutaneous than in omental fat (30).

In the present study, serum leptin concentrations were almost four times higher in women than in men, as has been reported previously (13, 31), and were highly correlated with body fat distribution and mean fat cell size only in women (Fig. 2). This is consistent with previous studies showing no significant correlations between leptin and body fat parameters in men (31). The results confirm those obtained in adipocyte cultures that indicate that fat cell size is a major determinant in ob RNA expression (32). The observation that plasma leptin is correlated with the SA but is not related to the VA is consistent with studies demonstrating that leptin expression is lower in omental than in subcutaneous adipose tissue (33, 34).

Plasma levels of TNF-α were higher than those observed in normal-weight populations (Table 3), which is consistent with earlier findings in obese populations (35). The positive relationship with VA in the female group could result from an increased release of TNF-α from this adipose tissue region as a consequence of the higher lipolytic action (36). Contrary to previous studies (35, 37), correlations between TNF-α and VA in men were not significant. The fact that the male population studied was very homogeneous, showing a central type of obesity (VA/SA > 0.4) with a narrow range of values in visceral fat, could partly explain these results. The correlation between serum TNF-α levels and fat cell size in the present study was not significant, perhaps because this interleukin comes from muscle and macrophages, as well as adipose tissue (38). In addition, it is still unclear whether TNF-α emanates from the adipocyte per se or from the associated lymphoid tissue (3).

Contrary to studies showing that estrogen production increases with obesity, these data illustrate that plasma...
levels of 17β-estradiol were normal (Table 3), perhaps because the population did not reach a high degree of obesity. In women, a negative correlation was observed between 17β-estradiol and central obesity, suggesting that this type of obesity is accompanied by an increase in androgenicity. These data are corroborated by the results obtained for the different sex androgens. In the female population, testosterone and androstenedione correlated positively with waist, coronal and sagittal diameters, and also with BMI and the degree of obesity. Various studies in women indicate that abdominal fat is associated with high total and free testosterone levels (39, 40). Even so, not all studies in women confirm these results. Different indices of androgenicity and the very heterogeneity of the studied individuals make comparison between studies difficult (41).

In men, total testosterone and androstenedione increase as BMI and total adiposity decrease. The results might be explained by the fall in SHBG resulting from an increase in body fat in the present study, which has been suggested previously (42). A direct relationship was also found between testosterone levels and SHBG (r = 0.69; P < 0.0001), which confirms that variations in plasma levels of this transporter globulin cause variations, as they do for testosterone.

According to previous studies, an inverse relationship was found between testosterone levels in plasma and the
accumulation of abdominal fat in males (43, 44). Studies on subcutaneous abdominal adipose tissue show that lipolysis increases after treatment with testosterone, stimulating the expression of receptors and inhibiting lipoproteinlipase activity (45). Similarly, in males, androstenedione and central obesity were negatively correlated in the VA and in the relation between areas (VA/SA). In the present cell studies, however, subcutaneous fat cell size in men correlated positively with androstenedione levels in plasma (Fig. 3), while no relationship was observed between androstenedione and omental or perivisceral fat cell size. The findings suggest that the increased androgenicity is associated with a reduction in intra-abdominal fat, which is not caused by a reduction in adipocyte size, and with a relative increase in subcutaneous area which, in this case, is correlated with increased adipocyte size.

Plasma levels of DHEA-S in the obese population studied were low, especially in premenopausal women and in men, and lower than those found in the normal-weight population (46). Different authors have previously found that DHEA and its sulphate have a thermogenic and antiobesity effect (47). Subcutaneous adipocyte size correlated positively with plasma levels of DHEA-S in males (Fig. 3), suggesting that in obese men the higher the DHEA-S production, the larger the abdominal fat cell size. No association was found between abdominal fat distribution in men and DHEA-S, which is consistent with the contradictory data of previous studies (44, 48, 49). In the female population, in spite of the abundance of available data on abdominal obesity and increases in androgenicity, studies on DHEA-S are not numerous, and the relationship with abdominal fat distribution is unclear. Although previous studies found no relationship between these two measures in obese women (46), the present data indicate that DHEA-S correlates inversely with WHR and the conicity index. Furthermore, the correlation with abdominal fat distribution was contrary to that observed with other androgens.

Although body fat percentages were higher in women than in men (Table 1), plasma levels of SHBG were also higher (Table 3), similar to the findings comparing premenopausal and postmenopausal women. These results were in contrast to other studies describing a negative correlation between SHBG and adiposity (50, 51). Abdominal fat was significantly lower in the female population, and in premenopausal women (Table 1), and SHBG in the total population was negatively correlated with abdominal fat, especially with visceral fat. These findings are supported by other authors, suggesting that body fat distribution seems to be a more important factor than obesity itself in plasma levels of SHBG (40). Correlation analysis of plasma levels of SHBG and adipocyte size provided negative correlations for mean fat cell size and perivisceral fat cell size (Fig. 4). Therefore, the reduction of plasma SHBG levels with increased abdominal obesity seems to result from the accumulation of intra-abdominal fat (VA) caused by an increase of abdominal adipose tissue cellular size, especially in the perivisceral area.

In summary, the results of this descriptive study of an obese population suggests differences in abdominal fat distribution between men and women, and in fat cell sizes between subcutaneous and perivisceral fat depots. The specific correlations of insulin, leptin, TNF-α, sex hormones and SHBG with the different adipose tissue regions, differ between genders: in women, central obesity is associated with an increase in insulin, leptin, TNF-α, testosterone and androstenedione levels and a decrease in 17β-estradiol and DHEA-S levels, while in men these correlations are positive with insulin and negative with testosterone and androstenedione. Fat cell size is associated with an increase in serum leptin, insulin, DHEA-S, androstenedione and a decrease in SHBG. In the three abdominal regions studied, fat cell size in the subcutaneous region seems to be more sensitive to hormonal factors than that in other regions.

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References

2 Deprés JP. Abdominal obesity as important component of insulin resistance syndrome. Nutrition 1993 9 452–459.
8 Elbers JM, Asscheman H, Seidell JC & Gooren LJ. Effects of sex steroid hormones on regional fat depots as assessed by magnetic


Central obesity, fat cell data and hormones


