Impact of Obesity on Metabolism in Men and Women

IMPORTANCE OF REGIONAL ADIPOSE TISSUE DISTRIBUTION

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ABSTRACT The distribution of adipose tissue thickness, fat cell weight (FCW), and number (FCN) were studied in four regions in randomly selected middle-aged men and women and in 930 obese individuals. Both the obese and the randomly selected men were found to have the largest adipose tissue thickness in the abdominal region. Women, however, showed a relative preponderance for the gluteal and femoral regions. FCW increased with expanding body fat up to a maximal size of ~0.7–0.8 μg/cell in each region. After this increase in FCW, a more rapid increase in FCN was found.

For the same degree of relative overweight, men had higher triglyceride, fasting glucose, and insulin levels; higher sums of glucose and insulin levels during an oral glucose tolerance test; and higher blood pressure. Furthermore, elevated fasting glucose levels (>7.4 mM) occurred twice as often in the males. These differences between males and females persisted even after body fat matching.

A male risk profile was seen in women characterized by abdominal obesity (high waist/hip circumference ratio) as compared to women with the typical peripheral obesity. Stepwise multiple regression analyses in both women and men showed the obesity complications to be associated in a first step to waist/hip circumference or body fat and in a second to abdominal fat cell size.

It may thus be concluded that: (*a*) In both obese and nonobese subjects, regional differences exist between the sexes with regard to adipose tissue distribution. (*b*) Moderate expansion of body fat is mainly due to FCW enlargement, which is subsequently followed by increased FCN. (*c*) Men and women with a male abdominal type of obesity are more susceptible to the effect of excess body fat on lipid and carbohydrate metabolism.

INTRODUCTION

It is well-recognized that women have more body fat than men even at the same relative body weight index (1). This sex difference is seen already in the first year of life and possibly even prenatally (2). Ultrasound measurements have shown that the larger amount of body fat in women is associated with increased adipose tissue thickness in certain regions (1). It is not clear, however, whether the sex differences in the regional distribution of the fat are maintained in severely obese individuals.

Obesity in both men and women is associated with various aberrations such as hyperinsulinemia, increased propensity for diabetes, and lipid and blood pressure elevations (3–6). There have been no detailed studies, however, analyzing the impact of different amounts of body fat on these parameters in men and women.

The apparent heterogeneity of human obesity has resulted in a number of attempts to identify subgroups. The most recent attempt has been based on the cellular characteristics of the adipose tissue. This subgrouping system has suggested the existence of two types, hypertrophic obesity, which is due to enlarged fat cells or hyperplastic obesity, which is due to an increased number of fat cells (7, 8). Hypertrophic obesity seems to be more closely associated with the various metabolic complications and hypertension than hyperplastic obesity (9, 10).

A scheme for characterizing obesity according to the fat distribution has been suggested by Vague (11). Upper body obesity (android type) was reported to be

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more frequently associated with the various metabolic aberrations of the obese state than lower body obesity (gynoid type).

The development of new techniques for measurement of adipocyte morphology and metabolism has made possible studies that strongly suggest that human adipose tissue is not a homogenous tissue. The size of the abdominal adipocytes is associated with metabolic variables, such as plasma insulin and triglyceride levels; this is not the case with adipocytes from the gluteal and femoral regions (12). On the other hand, the gluteal and femoral adipocytes appear more sensitive to certain steroid hormones such as corticosteroids and estrogen (13, 14). In addition, adipocytes from the abdominal region are more responsive than gluteal adipocytes to stimuli promoting triglyceride storage and release (15).

The present study reports on extensive metabolic and morphologic investigations in 930 obese men and women. The data clearly showed that the men as a group were more susceptible than women to the metabolic aberrations induced by moderate obesity. However, women with a typical male abdominal type of obesity also had a metabolic risk profile resembling that of men. When taken together, the results stressed the importance of the regional distribution of the adipose tissue to the metabolic aberrations that are seen in the obese state.

METHODS

Subjects. The present study comprises 930 obese individuals: 670 women and 260 men. The clinical characteristics of the patients are shown in Table I. The patients were referred to the Obesity Out-patient Clinic during 1970–1976 for weight reduction. Although the patients may have had various clinical manifestations of their obesity which resulted in their referral to the clinic, newly detected diabetes was not one of them. Special Diabetes Out-patient Clinics exist at the hospital and obese subjects with diagnosed diabetes were referred to them. Thus, the present material is likely to underestimate the prevalence of manifest diabetes in obese individuals. Apart from this, the subjects are probably representative of obese adults seeking medical advice for overweight.

The regional adipose tissue distribution was studied in 330 individuals, 215 women and 115 men, and the results were compared with those obtained in a randomly selected sample of 52-yr-old men (n = 39) and women (n = 38) from the population of Gothenburg. These latter subjects were part of ongoing population studies in the city which are aimed at evaluating risk factors for cardiovascular disease (5, 6).

TABLE I
Clinical Characteristics of Obese Men and Women with the Same Relative Overweight

	Mean	Women	p-level
No. of patients	260	670	
Age (*yr*)	42.2±11.4	40.4±12.5	<0.001
Body weight (*kg*)	107.9±26.2	95.9±19.5	<0.001
Length (*cm*)	178.7±7.4	165.4±6.2	<0.001
Percent overweight*	155.1±32.2	155.5±31.0	NS
Body fat (*kg*)	38.8±15.6	46.3±14.1	<0.001
Body cell mass (*kg*)	38.1±6.9	27.7±4.9	<0.001
Average fat cell number ($\times 10^{10}$)	6.7±2.3	7.4±4.2	<0.001
Average fat cell weight (*μg/cell*)	0.59±0.1	0.66±0.3	<0.001
Circumference (*cm*)			
Waist	116.5±14.9	99.6±14.4	<0.01
Hips	118.1±12.9	119.5±13.2	NS
Thigh	60.6±6.2	64.4±8.5	<0.01
Upper arm	36.7±3.8	36.3±4.3	NS
Fasting insulin (*mU/liter*)	23.5±18.7	17.6±10.2	<0.001
OGTT sum of insulin (*mU/liter*)	415.2±180.6	358.6±202.4	<0.001
Fasting glucose (*mM*)	5.1±1.6	4.7±1.5	<0.001
OGTT sum of glucose (*mM*)	38.2±14.2	34.2±14.1	<0.001
Triglycerides (*mM*)	2.2±1.2	1.8±1.2	<0.001
Cholesterol (*mM*)	5.8±1.3	5.6±1.3	NS
Blood pressure (*mmHg*)			
Systolic	147.0±21.0	141.0±25.0	<0.001
Diastolic	94.0±15.0	89.0±14.0	<0.001

Data represent means±SD.
* Calculated according to Natvig et al. (36).

Investigations. At the Obesity Clinic, the subjects were asked to complete a questionnaire giving details about duration of overweight, number of attempts to reduce weight, lowest weight achieved, obesity in family, etc. They were then weighed, in their underclothes, to the nearest 0.1 kg and their height was recorded. Circumferences were measured: in the erect position, around the waist through a point one-third of the distance between the xiphoid process and the umbilicus; in the erect position, around the hips through a point 4 cm below the superior anterior iliac spine; around the thigh at a point one-third of the distance between the superior anterior iliac spine and the patella; and around the upper arm at a point one-third of the distance between the humeroscapular joint and the elbow.

Subcutaneous needle biopsies for fat cell size (FCW)[1] determinations were obtained from the epigastric region at a point one-third of the distance from the xiphoid process to the umbilicus, the hypogastric region at a point one-third of the distance from the superior anterior iliac spine to the umbilicus, the gluteal region in the upper lateral quadrant, and the femoral region at a point one-third of the distance from the superior anterior iliac spine to the patella. FCW was determined on sectioned slices as described by Sjöström et al. (16) and FCW calculated on the assumption that the density of the cells is that of triolein (0.915).

The thickness of the skin and the adipose tissue layer was determined at the same sites by ultrasound measurements using an ultrasonoscope (SmithKline Instruments, Inc., Philadelphia, PA) calibrated for the average velocity of sound in human soft tissue.

An estimation of the local fat cell number (FCN) of these regions was obtained by calculating the number of fat cells in a cylinder with 1-mm^2 bottom surface and the height of the tissue layer measured. The nonfat cell volume of this cylinder was corrected for by using Bjurulf's diagram (17), which gives the relationship between fat cell volume and nonfat cell space. The corrected volume of the cylinder was divided by the mean fat cell volume to obtain the local FCN.

Body potassium was determined in a whole body counter which detects naturally occurring ^{40}K. Lean body mass (LBM) was calculated according to the method of Forbes et al. (18) assuming that LBM had a potassium content of 68.1 mmol/kg. Body fat was then calculated by subtracting LBM from the body weight. Total number of fat cells was calculated by dividing total body fat by the average fat cell weight of the four regions.

Body cell mass (BCM) was calculated from the ^{40}K determinations according to the method of Moore et al. (19) assuming that cells contained 3 mmol potassium/mg nitrogen and had an average protein content of 25%.

Blood pressure measurements were recorded in the recumbent position in the left arm with a mercury manometer after a 10-min rest. Diastolic blood pressure was registered at the disappearance of sound (Korotkow phase 5) to the nearest 2 mm.

After an overnight fast, venous blood samples were drawn for the determination of triglycerides (20) and cholesterol (21). An oral glucose tolerance test (OGTT) was also performed with 100 g glucose dissolved in 200-ml lemon-flavored water. Blood samples were drawn before and at 20-min intervals during 2 h for the determination of glucose (22) and insulin levels (23).

Statistical methods. Conventional *t* test and linear regression analyses were performed. Multivariate regression analyses were carried out using a computer program.

RESULTS

According to the questionnaire, the subjects, on the average, had become obese at ~19 yr of age, and thus had been overweight for more than 20 yr. They had tried various means for weight reduction about 13 times and maintained the lower weights about 10 mo before relapse to or above their initial weights. About 40% of the subjects reported that they had successfully reduced their body weight by 20 kg or more.

Comparison of men and women with the same relative obesity

Regional fat distribution. The fact that there are regional differences in the adipose tissue distribution in both obese as well as randomly selected middle-aged men and women is documented in Fig. 1. For both the obese and the men from the random sample, adipose tissue thickness is the largest in the abdominal region;

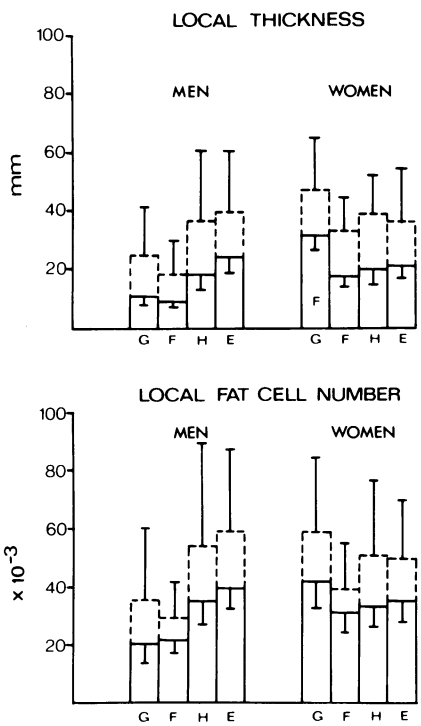

FIGURE 1 Adipose tissue thickness (*top*) and local FCN (*bottom*) in various regions of a randomly selected sample of 52-yr-old men and women (——) and in obese men and women with the same degree of relative obesity (- - -). *G*, gluteal site, *F*, femoral site, *H*, hypogastric site, *E*, epigastric site.

[1] *Abbreviations used in this paper:* BCM, body cell mass; FCN, fat cell number; FCW, fat cell size, fat cell weight; LBM, lean body mass; OGTT, oral glucose tolerance test.

women have a relative preponderance in the gluteal and femoral regions. Thus, women have mainly a peripheral distribution of fat while men have an abdominal adiposity.

This regional distribution is mainly due to differences in local fat cell number between the sexes (Fig. 1). Thus, men have the largest number of fat cells in the abdominal depots while women have a greater number in the gluteal and femoral regions.

FCW was similar in the various regions of obese men; gluteal fat cells were the largest in both the obese women and the women from the random sample, while the epigastric cells were the smallest (Fig. 2).

Clinical characteristics. Table I shows the clinical characteristics of the total sample of obese individuals studied. At the same relative degree of overweight, the men are taller and heavier with a larger BCM but with less body fat than the women. Consonant with the larger amount of body fat in women, adipose cell number and average FCW (means of epigastric, hypogastric, gluteal, and femoral FCW) are greater as compared with men. The largest body circumference for the women was around the hips while for the men, the abdominal diameter was the biggest. The women had larger thighs than the men which may be due to their higher total body fat.

In spite of less body fat, all metabolic variables measured, except for total cholesterol, were higher in the men. Thus, males had higher glucose and insulin levels, both when fasting and after the OGTT. Fasting triglyceride levels were also elevated in the men as was the blood pressure (Table I). Further statistical analyses showed that these differences could not be explained by the small difference in age between the two groups (data not shown).

The differences in glucose and insulin levels between the sexes were further confirmed by analyzing the prevalence of elevated levels. As shown in Table II, the number of obese patients with diabetic fasting glucose levels and impaired glucose tolerance during the OGTT is about twice as high in males. Similarly, hyperinsulinemia is considerably more frequent in men than in women for the same relative overweight.

Comparison of men and women with the same body fat

Regional distribution. As shown in Fig. 3, the regional sex-linked distribution of adipose tissue thick-

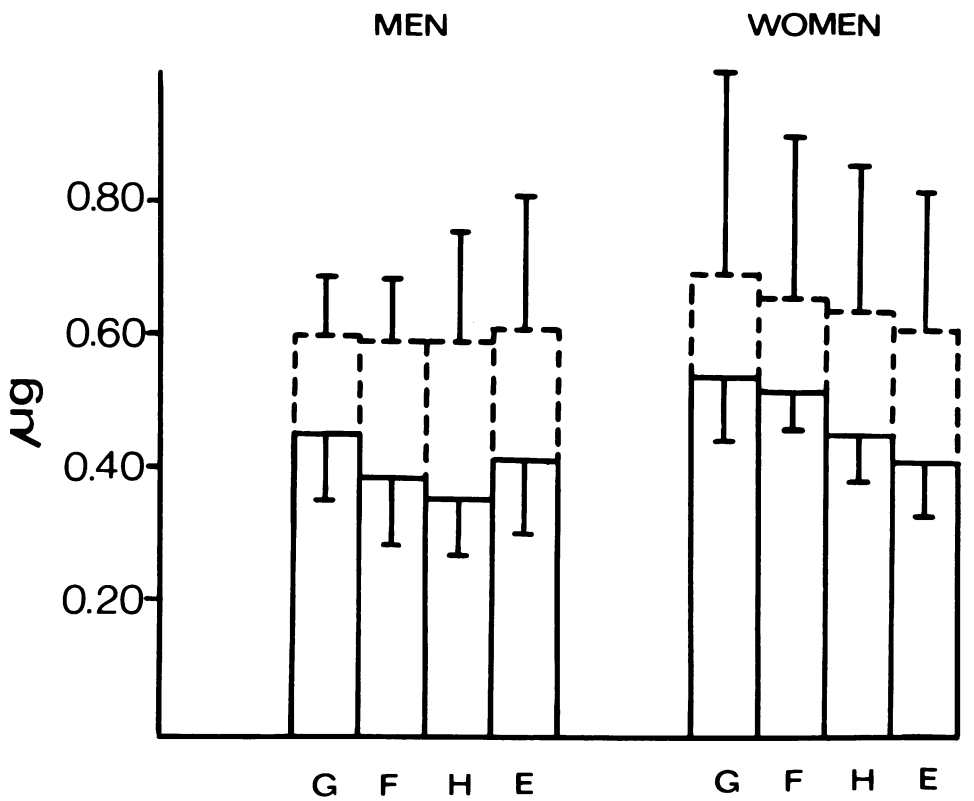

FIGURE 2 FCW in different regions in the same patients. For symbols see Fig. 1.

TABLE II

Effect of Relative Overweight on the Prevalence (Percent) of Elevated Glucose and Insulin Levels in Men and Women During a 100-g OGTT

	Men Percent of relative overweight				Women Percent of relative overweight			
Time during OGTT	100–125	125–150	150–200	Σ	100–125	125–150	150–200	Σ
0 min								
Glucose > 7.4 mM	0.7	1.4	3.4	5.5	0	0.2	2.6	2.8
Insulin > 25 mU/liter	3.6	6.1	26.0	35.7	0.2	2.6	12.8	15.6
30 min								
Glucose > 9.9 mM	0	6.0	12.0	18.0	0.3	1.4	8.2	9.9
Insulin > 95 mU/liter	1.7	7.8	25.2	34.7	0.3	8.0	16.3	24.6
60 min								
Glucose > 12.4 mM	0.8	4.0	10.4	15.2	0	1.4	4.9	6.3
Insulin > 120 mU/liter	1.6	4.1	20.4	26.1	0.6	6.1	12.1	18.8
90 min								
Glucose > 10.4 mM	0.8	6.6	12.3	19.7	0	2.2	10.1	12.3
Insulin > 120 mU/liter	0.8	10.7	18.1	29.6	0.6	4.4	11.7	16.7
120 min								
Glucose > 8.4 mM	0.9	6.0	16.3	23.2	0	2.6	10.8	13.4
Insulin > 110 mU/liter	0.9	11.2	18.1	30.2	0.3	6.7	15.2	22.2

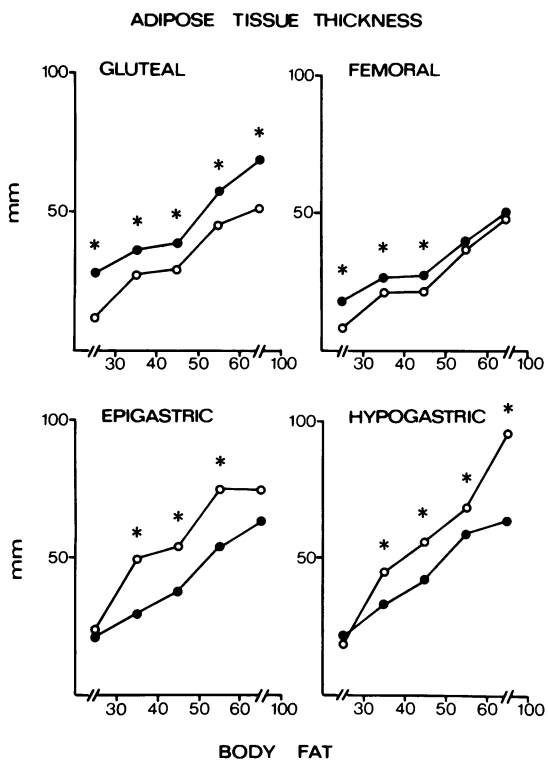

FIGURE 3 Regional adipose tissue thickness in obese men and women matched for amount of body fat (kilograms). *, $P < 0.05$; O, men; ●, women.

ness was maintained throughout the various amounts of body fat. Thus, in the males, the largest adipose tissue thickness was found in the abdominal depots. Females, however, maintained a preponderance of the gluteal and femoral regions.

As an approximation of the intraabdominal fat depots, the thickness of the epigastric layer was subtracted from the waist circumference. Provided that there is no major change in the size of the intestines or increased laxity of the muscles, a clear increase in the intraabdominal fat depots was also seen with increasing adiposity. Furthermore, this increase was more pronounced in the male subjects than in the females (data not shown).

The larger adipose tissue thickness of different regions was due to increases in both FCW (Fig. 4) and FCN (Fig. 5). FCW, however, rapidly increased in both sexes with increased body fat and reached an upper level at ~0.7–0.8 μg/cell when the body fat was ≳40 kg. The females maintained somewhat larger cells in the gluteal and femoral regions while the abdominal cells increased to about the same upper size as in the males.

The males maintained a larger FCN in the abdominal regions and their cellularity rapidly expanded with increasing body fat. The women showed a preponderance in the gluteal region and, at moderate amounts of body fat, in the femoral region.

Clinical characteristics. To better evaluate the im-

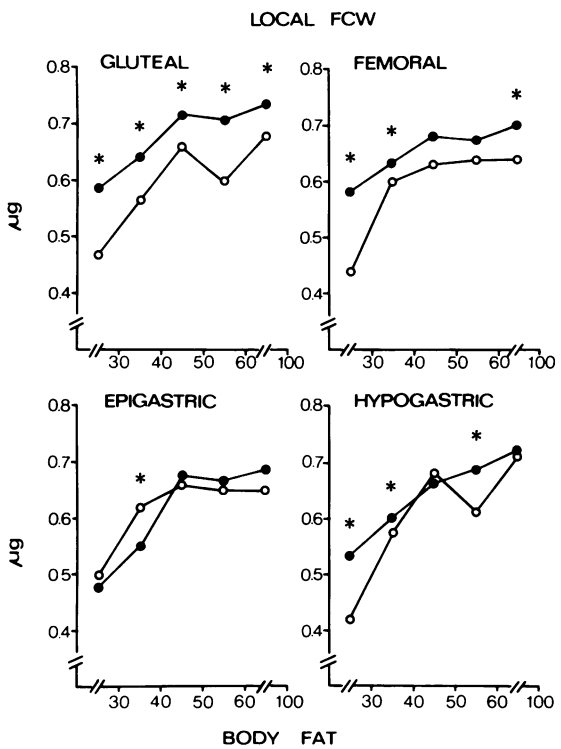

FIGURE 4 FCW in obese men and women matched for amount of body fat (kilograms). *, $P < 0.05$; O, men; ●, women.

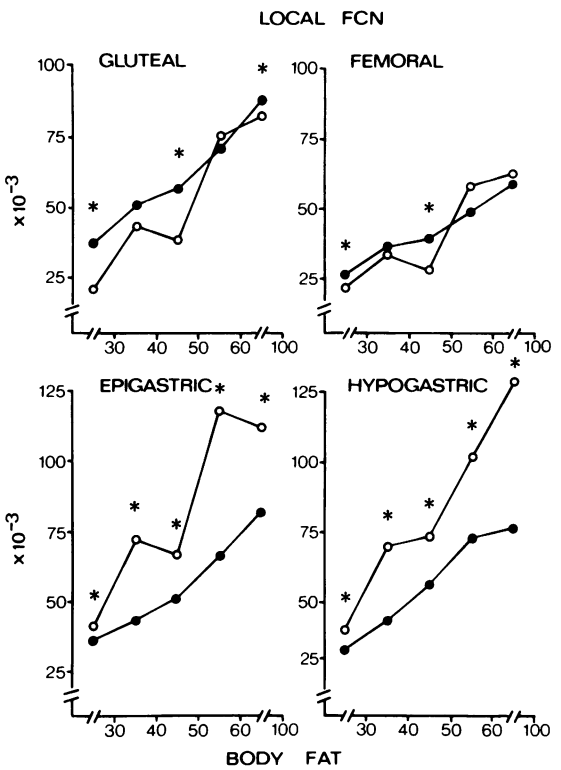

FIGURE 5 Local FCN in obese men and women matched for amount of body fat (kilograms). *, $P < 0.05$; O, men; ●, women.

portance of amount of body fat for the various metabolic aberrations, men and women were compared after body fat matching. As shown in Fig. 6, with increasing amounts of body fat, both sexes exhibited an increase in triglycerides, fasting insulin, and glucose, as well as in the sums of insulin and glucose levels during an OGTT. However, it is also quite clear that there were pronounced differences between the sexes in this respect.

The triglyceride levels increased more rapidly with expanding body fat in the men and reached the upper levels at only a moderate amount of body fat. The women showed a slower and more continuous increase in triglycerides. Similarly, but in contrast to the insulin levels, fasting glucose levels increased rapidly with expanding body fat and reached the upper levels already at a moderate amount. Only in the heaviest women were the same levels reached (Fig. 6). Similar changes were seen with the glucose levels during an OGTT. In marked contrast to this, the insulin levels, both fasting and during an OGTT, showed a continuous increase in both sexes with increasing adiposity. The insulin levels were generally higher in the men as compared with the women, irrespective of amounts of body fat.

Similarly, the men had higher blood pressure than the women and only in the two highest body fat groups was equality between the sexes established (Fig. 7). In fact, only small blood pressure changes were seen in male subjects with increasing body fat; from 145/92 in the least obese group to 152/96 in the heaviest group (i.e., 7 mm-increase in the systolic and 4-mm increase in the diastolic pressure). In contrast, the changes in the same two groups of female subjects were considerably more pronounced; from 131/80 to 155/96 (i.e., 24-mm increase in systolic and 16-mm increase in diastolic pressure).

Importance of the regional distribution of the adipose tissue in men and women

The correlation between the different measurements of the regional adipose tissue distribution (local thickness, FCW, FCN, and circumference measurements), the metabolic variables, and blood pressure was evaluated in both men and women (Table III). More consistently significant associations were found between these variables and the FCW of the epigastric and hypogastric regions than that of the other depots. Fur-

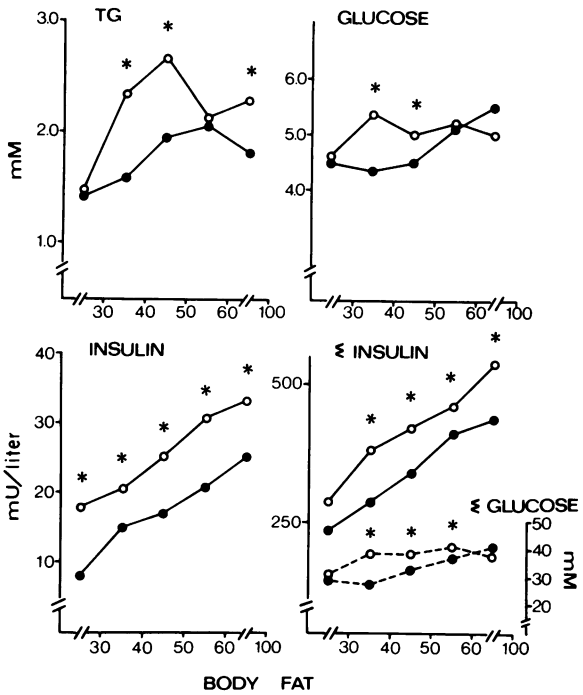

FIGURE 6 Association between body fat amounts (kilograms) and various metabolic parameters in obese men and women. *, $P < 0.05$; O, men; ●, women.

thermore, waist circumference showed strong associations with all these variables in contrast to the other circumference measurements (Table III). Essentially no statistical association was found between the complication variables and FCN (data not shown). Therefore, the following, more detailed analysis of the material concentrates on the importance of the abdominal FCW and the waist circumference.

To overcome intraindividual statistical associations and to specifically examine the importance of the adipocyte size in the abdominal region, these fat cells were analyzed in relation to the adipocyte size of the

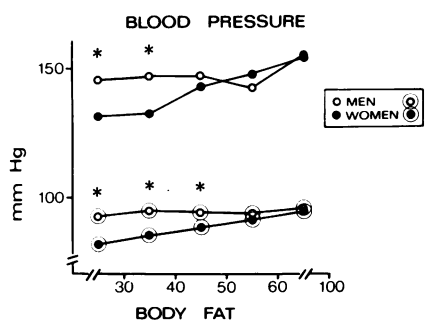

FIGURE 7 Effect of body fat (kilograms) on systolic (*top*) and diastolic (*bottom*) blood pressure in obese men and women. *, $P < 0.05$.

gluteal region for each individual. Therefore, two groups were selected where the epigastric FCW was larger or smaller, respectively, that that of the gluteal region. Similarly, waist circumference, in absolute terms, is highly dependent on the size of the individual examined. Consequently, the ratio of the waist/hip circumferences constituted the basis for further statistical analyses. Only women were included and the results were examined after body fat matching.

As shown in Fig. 8, both the fasting and the sum of the glucose levels during the OGTT were generally higher in the group with larger epigastric fat cells. The prevalence of manifest diabetes mellitus was also increased in these subjects (data not shown). The insulin levels were higher in this group with larger epigastric cells, although this was a less consistent finding than for the glucose levels. No consistent differences were found for either the triglyceride levels or the blood pressure (Fig. 9). Similar analyses based on the hypogastric FCW gave essentially the same results (data not shown).

The importance of the waist/hip circumference was analyzed in a similar way. As seen in Fig. 10, the group with higher waist/hip circumference ratio was found to have a higher level of fasting glucose and sum of glucose levels during the OGTT. Manifest diabetes was also more frequently found in the women with abdominal obesity (data not shown). The insulin and triglyceride levels were higher in this group as was the blood pressure in most of the body fat classes (Fig. 11).

Stepwise regression analyses were also performed in both men and women to evaluate the importance of the different body composition measurements to the metabolic variables and blood pressure (Table IV). In women, fasting insulin was dependent in a first step on body fat and in a second on waist/hip circumference. Additional inclusions did not contribute significantly to the fraction of explained variance. Fasting blood glucose was dependent on the waist/hip circumference and only slightly on body fat. Triglycerides were dependent on body fat in a first step and waist/hip circumference in the next step. Both systolic and diastolic blood pressure were dependent in a first step on body fat and the diastolic pressure in a second step on epigastric FCW.

In men, fasting insulin was dependent in a first step on body fat and in a second on the waist/hip circumference ratio. With blood glucose, the order was waist/hip circumference ratio, as in women, followed by the epigastric FCW (not significant). With triglycerides, waist/hip circumference was the only significant contributor to the fraction of explained variance. Systolic and diastolic blood pressure were dependent on femoral and epigastric FCW, respectively, followed by total FCN (Table IV).

TABLE III

Correlation Coefficients between Regional Obesity Variables and Metabolic Data and Diastolic Blood Pressure in Obese Women and Men

	Women				Men			
	Insulin	Glucose	Triglycerides	Diastolic blood pressure	Insulin	Glucose	Triglycerides	Diastolic blood pressure
Fat cell weight								
Gluteal	0.14*	0.02	0.04	0.05	0.20*	0.02	0.04	0.06
Femoral	0.16*	0.04	0.09	0.06	0.20*	0.00	0.15	0.04
Epigastric	0.26*	0.12*	0.14*	0.10*	0.18*	0.07	0.23*	0.32*
Hypogastric	0.28*	0.20*	0.18*	0.10*	0.14	0.03	0.22*	0.20*
Circumference								
Waist	0.30*	0.23*	0.34*	0.38*	0.61*	0.47*	0.57*	0.36*
Hip	0.21*	0.05	0.22*	0.29*	0.46*	0.24*	0.27*	0.25*
Thigh	0.29*	0.17*	0.02	0.24*	0.03	0.04	0.07	0.04
Arm	0.25*	0.07	0.09	0.37*	0.04	0.05	0.02	0.07

* $P < 0.01$.

DISCUSSION

The present study of subjects whose obesity has been long-standing clearly documents the association between obesity and various metabolic aberrations in both men and women, as also previously reported (3–6). It also shows, however, the differences in propensity for these perturbations between the sexes as well as the importance of the regional distribution of the adipose tissue to the metabolic aberrations of the obese state.

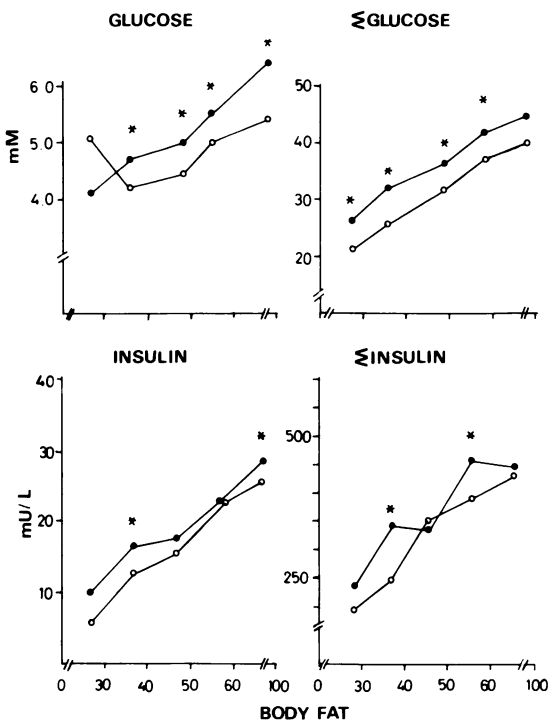

FIGURE 8 Fasting glucose and insulin, and sum of glucose and insulin levels during a 100-g OGTT in obese women subdivided according to the epigastric FCW being larger (●) or smaller than the gluteal fat cells (○). Body fat (kilograms) matching was carried out as shown. *, $P < 0.05$; ●, epi > glut; ○, epi < glut.

Even at a similar degree of relative overweight, men showed higher fasting levels of glucose, insulin, and triglycerides (Table I). Also, during an OGTT, men exhibited on the average ~16% higher insulin levels and ~12% higher glucose levels than women. Both systolic and diastolic blood pressure were also higher in the males.

Expressing the data in terms of relative overweight, however, does not provide a clear estimate of the importance of the amount of body fat for these perturbations since females have in general more body fat than males. Thus, even though the patients in Table I had the same relative overweight, the females had ~20% more body fat. The data were, therefore, also analyzed in terms of absolute amounts of body fat.

The data showed again that men are more vulnerable to the metabolic aberrations of overweight than women. Thus, even at a moderate degree of obesity (30–40 kg body fat), elevations in blood glucose (fasting and sum of glucose during the OGTT) and triglyceride levels were registered. A further increase in body fat did not produce any consistent further elevations in these parameters in the men. The same levels as found in these moderately obese men were only seen in the most obese women (50–100 kg body fat). The insulin levels, however, showed a continuous increase with increasing amounts of body fat in both men and women. The men had consistently higher insulin levels

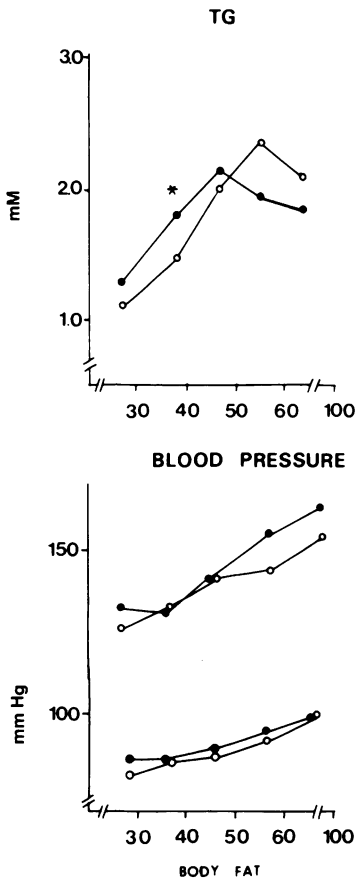

FIGURE 9 Same obese women subdivided as shown in Fig. 8. TG, fasting plasma triglycerides. Systolic (*top*) and diastolic (*bottom*) blood pressure. Body fat given in kilograms. *, $P < 0.05$; ●, epi > glut; ○ epi < glut.

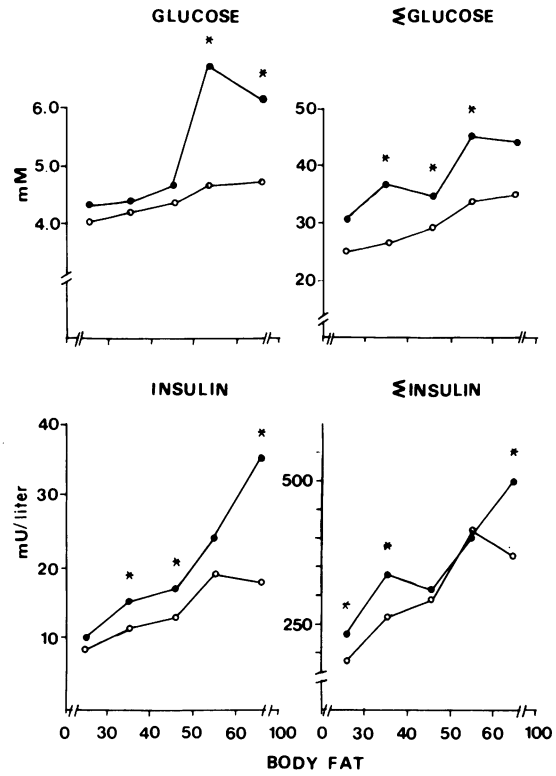

FIGURE 10 Fasting glucose and insulin, and sum of glucose and insulin levels after a 100-g OGTT in obese women subdivided according to the waist/hip circumference ratio being above (●) or below average (○). Body fat (kilograms) matching was performed as indicated. *, $P < 0.05$; ●, W/H↑; ○, W/H↓.

than the women at similar body fat amounts. This was not simply due to the higher glucose levels in the males. Calculations of the insulin/glucose ratio during the OGTT, as an index of the peripheral insulin sensitivity, also showed higher levels in the males which suggests a greater cellular resistance to the action of insulin. In keeping with this conclusion is the finding that arbitrarily set definitions of hyperinsulinemia were present about twice as often in males as in females at all degrees of obesity (Table II). Frank diabetes, defined by fasting glucose levels > 7.4 mM, was also considerably more prevalent in the males as was the occurrence of a reduced glucose tolerance.

As with the metabolic variables, moderately obese men had higher blood pressure than the women. Only in the most obese women was blood pressure similar to that seen in the men. Surprisingly, however, there was no clear correlation between systolic and diastolic blood pressure and amounts of body fat in the males, whereas this was clearly found in the females. Other investigators have also reported on such associations in males (3, 5). The reason for this discrepancy is probably that no normal-weight individuals were included in our study; if they had been included, such a statistical association may well have been substantiated.

Thus, the present data show that overweight men exhibited more pronounced changes in established cardiovascular risk factors. In fact, it seems that women can accumulate ~20–30 kg more body fat than the men before equality is established between the sexes for the various risk factors. This finding is partly at variance with other published studies (24). However, the extent of the present investigations and the size of the cohort of obese subjects exceeded those of any previous report. Even though these subjects were not randomly selected, they were probably, with one exception, representative of the obese individuals seeking medical advice for their condition as discussed above. The prevalence of diabetes, however, was probably underestimated in this sample. Diabetes, defined as fasting glucose levels > 7.4 mM, was present in ~2.8% of the women and ~5.5% of the men, which is less

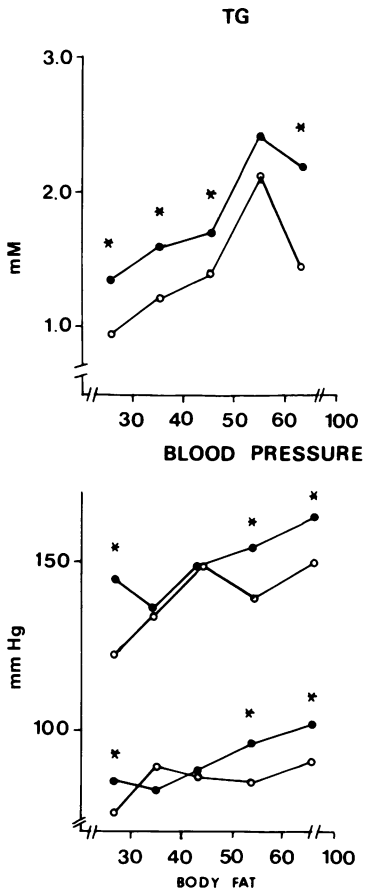

FIGURE 11 Same obese individuals as in Fig. 10. TG, triglycerides. Body fat given in kilograms. *, $P < 0.05$; ●, W/H↑; ○, W/H↓.

than reported in obese individuals by other investigators (~8–10% at similar age) (25).

The randomly selected, nonobese population showed a regional distribution of the adipose tissue which was typical for males and females. Women accumulated fat in the gluteal and femoral regions while men have preferential abdominal accumulation. This distribution pattern was maintained throughout the various degrees of overweight. Thus, the accumulation of fat in various regions is not only influenced by nutritional factors, but also by other sex-linked factors. It would seem reasonable to assume that sex hormones are involved in this regulation. It has also been shown previously that the administration of sex steroids leads to preferential accumulation of fat in specific regions (14). Corticosteroids also have well-known specific effects on the regional distribution of the fat (13).

The increase in adipose tissue thickness followed the same general pattern in the various regions, i.e., for moderate increases in body fat, FCW was rapidly increased to a maximal size of ~0.7–0.8 μg/cell. No further increase in FCW was then seen in the larger body fat groups. Some increase in FCN was also seen in the moderately obese groups. A clearly more rapid increase in FCN was seen in the groups after the "maximal" FCW had been attained. These findings, then, are in agreement with the hypothesis that recruitment of preadipocytes, either preformed or newly formed cells, is associated with enlargement of the mature fat cells. The present results suggest that a critical level is reached at a FCW of ~0.7 μg/cell. The typical male abdominal type of obesity is preferentially achieved by the recruitment or enlargement of cells in this region, while the typical peripheral obesity of the female is achieved by both more and larger fat cells in the gluteal and femoral regions.

As previously shown, the FCW of different regions are correlated with each other (1). The absolute value of the abdominal FCW is, therefore, to some extent a parallel measure of the degree of obesity. Thus, in order to more specifically analyze the association between regional FCW and the different obesity complications, the epigastric cells were analyzed in relation to the gluteal cells. Similarly, the waist/hip circumference rather than the absolute waist circumference was used to correct for subjects with larger or smaller skeletal frames or BCM.

Although it is quite clear that the amount of body fat plays a major role in the metabolic aberrations seen, the analyses also show that for a given degree of obesity, the regional distribution of the fat is important. Thus, the different measures of abdominal obesity (waist/hip circumference or abdominal FCW) are good predictors of the obesity complications. For the obese women, a subgrouping system based on the waist/hip ratio discriminated more precisely the obesity complications than the abdominal FCW. Furthermore, in the stepwise regression analyses, the waist/hip circumference ratio was a better predictor in both women and men than epigastric FCW for insulin, glucose, and triglyceride levels. When considered together, these data show that the waist/hip ratio is a better predictor of the measured obesity complications than the abdominal FCW.

The reason for the increased metabolic aberrations associated with the abdominal type of obesity is unknown. It may be that as yet undefined factors (sex hormones?) influence both the regional deposition of the fat and the metabolic aberrations associated with obesity. However, it is equally possible that the regional accumulation of the fat is influenced by hormonal factors and that the abdominal accumulation of the adipose tissue leads to more pronounced metabolic aberrations than the peripheral type. We have previously postulated that this could be the case (26).

TABLE IV

Stepwise Multiple Regression Analysis of Variables Associated with Complications in Obese Women and Men

Dependent variable	Women		Men	
Fasting insulin				
Step 1: Body fat	R: 0.42		Body fat	R: 0.38
	FEV: 17%			FEV: 15%
	t: 4.31‡			t: 1.99*
Step 2: Waist/hip circumference	R: 0.47		Waist/hip circumference	R: 0.58
	FEV: 23%			FEV: 23%
	t: 2.39‡			t: 1.54
Fasting blood glucose				
Step 1: Waist/hip circumference	R: 0.32		Waist/hip circumference	R: 0.33
	FEV: 11%			FEV: 11%
	t: 3.23‡			t: 1.65
Step 2: Body fat	R: 0.38		Epigastric fat cell size	R: 0.38
	FEV: 14%			FEV: 15%
	t: 1.92*			t: 1.04
Triglyceride				
Step 1: Body fat	R: 0.43		Waist/hip circumference	R: 0.39
	FEV: 19%			FEV: 15%
	t: 4.40‡			t: 2.45‡
Step 2: Waist/hip circumference	R: 0.46		Epigastric fat cell size	R: 0.43
	FEV: 21%			FEV: 18%
	t: 2.50‡			t: 0.50
Systolic blood pressure				
Step 1: Body fat	R: 0.40		Femoral fat cell size	R: 0.40
	FEV: 16%			FEV: 16%
	t: 4.06‡			t: 2.12‡
Step 2: Epigastric fat cell size	R: 0.43		Total fat cell number	R: 0.55
	FEV: 18%			FEV: 30%
	t: 1.58			t: 2.05‡
Diastolic blood pressure				
Step 1: Body fat	R: 0.46		Epigastric fat cell size	R: 0.37
	FEV: 21%			FEV: 14%
	t: 4.83‡			t: 1.92
Step 2: Epigastric fat cell size	R: 0.52		Total fat cell number	R: 0.41
	FEV: 27%			FEV: 17%
	t: 2.69			t: 0.90

Independent variables included were: body weight, body fat, total fat cell number, regional fat cell sizes and number, and circumferences of waist, hip, thigh, upper arm, and waist/hip.

* $P < 0.10$.

‡ $P < 0.05$.

Thus, the various metabolic aberrations usually seen in obesity were found in a patient with a regional abdominal obesity in spite of a reduced total amount of body fat. FCW of the abdominal region was extremely large (1.2 μg/cell) and lipolysis of these fat cells in vitro was highly elevated (26). A similar association has recently been confirmed in other patients with a partial lipoatrophy (27).

The visceral fat cells, which are included in the waist/hip circumference measurement, may be of particular importance for the metabolic aberrations because of their unique position and relationship to the portal circulation. The liver is, consequently, directly exposed to the lipolytic products of the visceral adipocytes. It is known that exposure of the liver to excessive levels of free fatty acids under appropriate conditions may cause hypertriglyceridemia (28). However, the associations between abdominal obesity and the other complication variables, such as hyperinsulinemia and hyperglycemia, are currently unclear and

deserve further study. The recent findings that fat cells from different subcutaneous regions exhibit differences in hormonal sensitivity, responsiveness, and metabolic rates are likely to be of importance (15, 29–32).

The results of the present study should be integrated into previous attempts to use adipocyte morphology as the basis for subdividing human obesity. It has previously been suggested that hypertrophic obesity is associated with metabolic complications such as hyperinsulinemia (33), hypertriglyceridemia (9, 34), and the onset of diabetes mellitus in adulthood (10, 35). This can now be more clearly defined as valid for abdominal obesity associated with abdominal adipocyte hypertrophy. This is a typical male type of obesity and clearly overlaps extensively with the android obesity described by Vague (11). The previous work of Vague (11), however, focused its attention mainly on the obesity of the upper part of the body rather than the abdominal obesity, or more specifically, the intraabdominal fat which may be the more important. In its pure form, hyperplastic obesity has not been found to be associated with metabolic derangements or hypertension in previous studies. It, then, is an obesity located, perhaps mainly, outside the abdominal region and includes the large subcutaneous gluteal-femoral depots. Typically, with hyperplastic obesity, fat cell enlargement is absent or moderate and the total number of fat cells is increased. This is also an obesity typical in women. The findings reported in the present study substantiate the validity of subdividing human obesity according to the adipocyte morphology as discussed above, but they focus more clearly on the importance of the regional distribution in this regard.

While this work was in progress, Kissebah et al. (29) reported findings of associations between elevated glucose, insulin, and triglyceride levels and abdominal FCW in a rather limited number of female subjects with "upper body obesity." Their findings are in excellent agreement with the present work on this point. However, the obesity complications and the abdominal fat mass is better correlated than the association with abdominal FCW.

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