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### Research Article

Insulin resistance and insulin hypersecretion are established features of obesity. Their prevalence, however, has only been inferred from plasma insulin concentrations. We measured insulin sensitivity (as the whole-body insulin-mediated glucose uptake) and fasting posthepatic insulin delivery rate (IDR) with the use of the euglycemic insulin clamp technique in a large group of obese subjects in the database of the European Group for the Study of Insulin Resistance (1,146 nondiabetic, normotensive Caucasian men and women aged 18-85 yr, with a body mass index (BMI) ranging from 15 to 55 kg.m<sup>-2</sup>). Insulin resistance, defined as the lowest decile of insulin sensitivity in the lean subgroup (608 subjects with a mean BMI of 29 kg.m<sup>-2</sup>). Insulin sensitivity declined linearly with BMI at an age- and sex-adjusted rate of 1.2 micromol.min<sup>-1</sup>.kg FFM<sup>-1</sup> per BMI unit (95% confidence intervals = 1.0-1.4). Insulin hypersecretion, defined as the upper decile of IDR, was significantly (P<0.0001) more prevalent (38%) than insulin resistance in the obese group. In the whole dataset, IDR rose as a function of both BMI and insulin resistance in a nonlinear fashion. Neither the waist circumference nor the waist-to-hip ratio, indices of body fat distribution, was related to insulin sensitivity after adjustment for age, gender, and BMI; both, however, were positively associated (P<0.001) with insulin hypersecretion, particularly in women. In nondiabetic, normotensive obese subjects, the [...]

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# Insulin Resistance and Hypersecretion in Obesity

Ele Ferrannini, Andrea Natali, Patrick Bell, Paolo Cavallo-Perin, Nebojsa Lalic, and Gertrude Mingrone, on behalf of the European Group for the Study of Insulin Resistance (EGIR)

## Abstract

Insulin resistance and insulin hypersecretion are established features of obesity. Their prevalence, however, has only been inferred from plasma insulin concentrations. We measured insulin sensitivity (as the whole-body insulin-mediated glucose uptake) and fasting posthepatic insulin delivery rate (IDR) with the use of the euglycemic insulin clamp technique in a large group of obese subjects in the database of the European Group for the Study of Insulin Resistance (1,146 nondiabetic, normotensive Caucasian men and women aged 18–85 yr, with a body mass index (BMI) ranging from 15 to 55 kg·m<sup>-2</sup>). Insulin resistance, defined as the lowest decile of insulin sensitivity in the lean subgroup (608 subjects with BMI ≤ 25 kg·m<sup>-2</sup>), was present in 26% of the obese subgroup (538 subjects with a mean BMI of 29 kg·m<sup>-2</sup>). Insulin sensitivity declined linearly with BMI at an age- and sex-adjusted rate of 1.2 μmol·min<sup>-1</sup>·kg FFM<sup>-1</sup> per BMI unit (95% confidence intervals = 1.0–1.4). Insulin hypersecretion, defined as the upper decile of IDR, was significantly ( $P < 0.0001$ ) more prevalent (38%) than insulin resistance in the obese group. In the whole dataset, IDR rose as a function of both BMI and insulin resistance in a nonlinear fashion. Neither the waist circumference nor the waist-to-hip ratio, indices of body fat distribution, was related to insulin sensitivity after adjustment for age, gender, and BMI; both, however, were positively associated ( $P < 0.001$ ) with insulin hypersecretion, particularly in women.

In nondiabetic, normotensive obese subjects, the prevalence of insulin resistance is relatively low, and is exceeded by the prevalence of insulin hypersecretion, particularly in women with central obesity. In the obese with preserved insulin sensitivity, risk for diabetes, cardiovascular risk, and response to treatment may be different than in insulin resistant obesity. (*J. Clin. Invest.* 1997. 100:1166–1173.) Key words: insulin resistance • obesity • insulin action • insulin secretion • body fat distribution

## Introduction

Obesity is the insulin resistant state par excellence. The first demonstration, by Rabinowitz and Zierler (1), of resistance to insulin stimulation of glucose uptake was obtained in the forearm of obese subjects. In obese as well as in nonobese subjects,

the presence of insulin resistance signals the concomitance of other metabolic and hemodynamic abnormalities, a cluster known as the insulin resistance syndrome (2). Cardiovascular morbidity and mortality are increased in obese individuals independently of other risk factors (3). Mounting (4–7), though not fully consistent (8) evidence indicates that hyperinsulinemia, a surrogate of insulin resistance, is an independent predictor of cardiovascular disease. A logical corollary of these findings is that insulin resistance is responsible for the heightened cardiovascular risk of the obese.

The prevalence of insulin resistance in obesity is not known. In Pima Indians (9), insulin sensitivity, measured by the euglycemic clamp technique, has been shown to decline with increasing body mass index (BMI).<sup>1</sup> The function was, however, nonlinear, with most of the decrement in insulin sensitivity occurring for small increments in BMI. In other studies of insulin resistance in obesity, the groups were generally too small to assess its prevalence (10–12). Furthermore, the obese groups often included subjects with impaired glucose tolerance, a condition itself associated with insulin resistance. In the present work, we have estimated the prevalence of insulin resistance in obesity from the database of the European Group for the Study of Insulin Resistance (EGIR). This database, including data from 1,146 healthy Caucasian men and women aged 18–85 yr, is the largest so far in which insulin action has been measured by the euglycemic insulin clamp technique.

Insulin hypersecretion is another key feature of obesity (13). Much research, in experimental animals as well as in humans, has been devoted to the loss of appetite regulation that leads to chronic overfeeding (14, 15). The rising incidence of obesity (16) has focused attention on its etiology in societies with westernized lifestyle. The prevalence of insulin hypersecretion in obesity, however, is likewise not known. Therefore, another aim of this study was to derive, from the EGIR database, estimates of insulin hypersecretion and its correlates.

## Methods

**Subjects.** Twenty clinical research centers in Europe (three in Finland, one in Sweden, one in United Kingdom, one in Denmark, four in Germany, one in Switzerland, seven in Italy, one in Yugoslavia and one in Greece) contributed between 21 and 122 cases each. These centers agreed to provide their available clamp studies (whatever the original purpose of these studies) on the condition that the study subjects met the following criteria: (a) no clinical or laboratory evidence of cardiac, renal, liver, or endocrine disease; (b) a fasting plasma glucose concentration < 6.7 mmol/liter and normal glucose tolerance by WHO criteria (17), (c) normal blood pressure (< 160/95 mmHg), (d) no recent change (≥ 10%) in body weight, and (e) no current medication. Of the 1,146 subjects in the present series (766 men and 380 women), 425 were recruited in northern Europe (Sweden, Finland, and the United Kingdom), 289 in central Europe (Denmark, Ger-

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1. Abbreviations used in this paper: BMI, body mass index; CI, confidence intervals; IDR, insulin delivery rate; WHR, waist-to-hip circumference ratio.

Table I. Population Characteristics

	Lean		Obese		P*
	Men	Women	Men	Women	
n	388	220	376	162	
Age (yr)	39±17	38±16	47±15	45±15	a
Height (cm)	177±8	166±8	174±8	165±9	a,b
Weight (kg)	71±8	61±7	87±13	84±16	a,b,c
BMI (kg·m <sup>-2</sup> )	22.8±1.6	22.2±1.8	28.8±3.9	30.6±5.7	a,b,c
Fat-free mass (kg)	53±5	42±5	58±5	50±7	a,b,c
Waist (cm)	86±7	81±9	100±11	100±14	a,c
Hip (cm)	97±8	96±6	107±10	110±11	a
WHR (cm/cm)	0.88±0.06	0.80±0.08	0.93±0.09	0.89±0.09	a,b,c

\*Values are mean±1 SD; P values for the effect of obesity and gender by two-way analysis of variance: a = P < 0.01 or less for the effect of obesity; b = P < 0.05 or less for the effect of gender; c = P < 0.05 or less for the interaction obesity x gender.

many, and Switzerland), and 432 in southern Europe (Italy, Yugoslavia, and Greece). At each center, the protocol was reviewed and approved by the local Ethics Committee, and informed consent was obtained from all subjects before their participation. The analysis by age of the present data has been reported previously (18).

**Protocol.** The minimum of information required for each case included the following variables: age, anthropometric variables, fasting and steady-state (final 40 min of a 2-h clamp, see below), and plasma glucose and insulin measurements. Height was measured to the nearest centimeter, weight to the nearest kilogram. BMI was calculated as the weight divided by the square of height. The waist-to-hip circumference ratio (WHR) was determined (in a subset of 529 subjects, 372 men and 157 women) by measuring the waist circumference at the narrowest part of the torso, and the hip circumference in a horizontal plane at the level of the maximal extension of the buttocks.

Insulin action was measured in all subjects by the euglycemic insulin clamp technique (19) using an insulin infusion rate of 1 mU·min<sup>-1</sup> per kg of body weight (7 pmol·min<sup>-1</sup>·kg<sup>-1</sup>). In brief, polyethylene cannulas were inserted into an antecubital vein (for the infusion of glucose and insulin) and retrogradely into a wrist vein heated at 60°C in a hot box or a heating pad (for intermittent blood sampling of arterialized venous blood). At time zero, a primed-con-

stant infusion of regular insulin was begun, and continued for 120 min. 4 min into the insulin infusion, an exogenous glucose infusion was started, and adjusted every 5–10 min to maintain plasma glucose within ~ 10% of its baseline value. Blood samples were obtained at timed intervals in the fasting state and during the clamp, for the measurement of plasma glucose and insulin levels.

**Analytical procedures.** Plasma glucose was measured by the glucose oxidase method. Plasma insulin concentrations were measured by radioimmunoassay.

**Data analysis.** Insulin action was expressed as the whole-body glucose disposal rate during steady-state euglycemic hyperinsulinemia. With the insulin dose used in the current study, hepatic glucose output has been previously shown to be fully suppressed in old as well as young subjects (20, 21). Therefore, glucose disposal (M value) was calculated from the exogenous glucose infusion rate during the last 40 min of the 2-h clamp after correction for changes in glucose concentration in a total distribution volume of 250 ml·kg<sup>-1</sup>. Whole-body glucose disposal was normalized per kg of body weight (M<sub>bw</sub>) or per kg of fat-free mass (M<sub>ffm</sub>), as calculated by Hume's formula (22). In 542 subjects, a direct measurement of fat-free mass had been made with the use of electrical bioimpedance or the labeled water technique (which are largely equivalent methods [23]). In this subgroup, ob-

Table II. Metabolic Characteristics

	Lean		Obese		P*
	Men	Women	Men	Women	
FPG (mmol/liter)	4.99±0.49	4.93±0.42	5.20±0.53	5.04±0.52	a,b
FPI (μU/ml)	7 (17)	7 (18)	10 (47)	11 (44)	a
SSPI (μU/ml)	63 (89)	62 (75)	74 (135)	74 (150)	a
M <sub>bw</sub> (μmol·min <sup>-1</sup> ·kg <sup>-1</sup> )	39.5±12.0	36.6±11.6	30.7±12.5	27.0±12.9	a,b
M <sub>ffm</sub> (μmol·min <sup>-1</sup> ·kg <sup>-1</sup> )	52.6±16.0	53.2±16.7	45.5±17.6	43.9±19.6	a
M <sub>bw</sub> /I	9.6±3.0	8.9±2.8	7.3±3.0	6.4±3.3	a,b
M <sub>ffm</sub> /I	12.8±4.0	12.8±4.0	10.8±4.2	10.5±5.0	a
CR <sub>i</sub> (liter·min <sup>-1</sup> )	1.11 (1.59)	0.96 (1.3)	1.16 (2.40)	1.10 (2.44)	a,b,c
IDR (mU·min <sup>-1</sup> )	7.6 (25)	6.8 (26)	11.9 (70)	12.0 (50)	a

FPG, fasting plasma glucose concentration; FPI, fasting plasma insulin concentration; SSPI, steady-state plasma insulin concentration; M<sub>bw</sub>, M value normalized by body weight; M<sub>ffm</sub>, M value normalized by fat-free mass; M<sub>bw</sub>/I, M<sub>bw</sub> divided by the natural logarithm of SSPI (in μmol·min<sup>-1</sup>·kg<sup>-1</sup> per μU/ml); M<sub>ffm</sub>/I, M<sub>ffm</sub> divided by the natural logarithm of SSPI (in μmol·min<sup>-1</sup>·kg<sup>-1</sup> per μU/ml); CR<sub>i</sub>, metabolic clearance rate of insulin; IDR, fasting posthepatic insulin delivery rate. \*Values are mean±1 SD; for FPI, SSPI, MCR<sub>i</sub>, and IDR, values are the geometric mean (range in parenthesis); P values for the effect of obesity and gender by two-way analysis of variance: a = P < 0.01 or less for the effect of obesity; b = P < 0.05 or less for the effect of gender; c = P < 0.05 or less for the interaction obesity x gender.

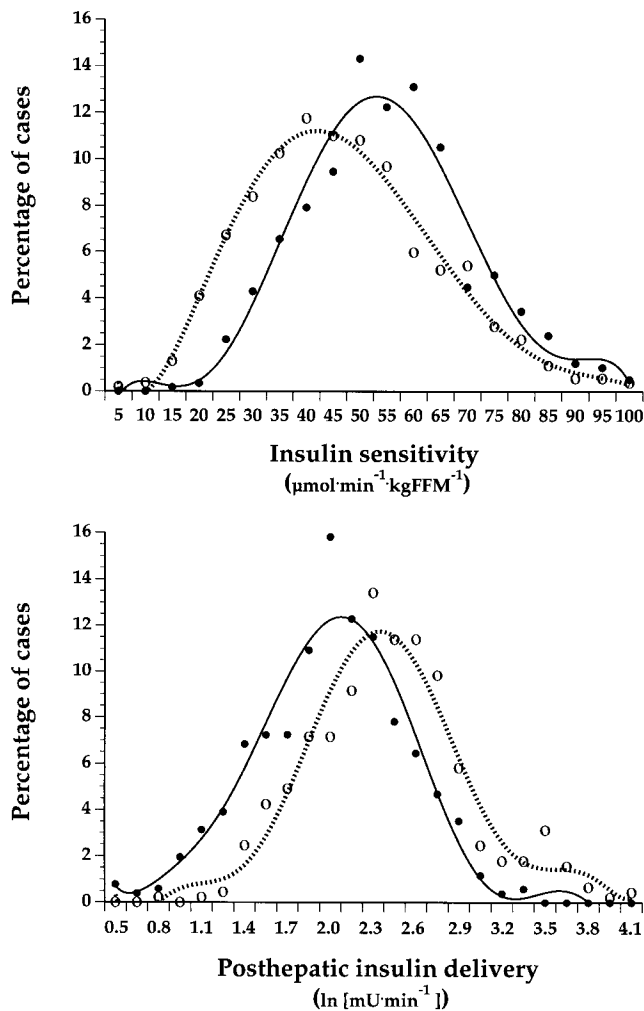


Figure 1. Frequency distribution plots of insulin sensitivity (as the  $M_{\text{fim}}$ , top) and fasting posthepatic insulin delivery rate (as the natural logarithm of IDR, bottom) in lean and obese subjects. Lines are polynomial functions only used for the purpose of outlining the two distributions. By the Shapiro-Wilk W test, the distribution function of insulin sensitivity deviates from normality in both obese and lean subjects, whereas the corresponding functions for log-transformed IDR do not. Filled circles, lean; open circles, obese.

served and expected values of fat-free mass were highly correlated ( $r = 0.82$ ,  $P < 0.0001$ ). Additionally, insulin action was expressed as the M/I ratio, i.e., the ratio of M to the steady-state plasma insulin concentration (19).

The posthepatic clearance rate of plasma insulin ( $CR_i$ ) was computed as the ratio of the insulin infusion rate by the steady-state plasma insulin concentration (24). Fasting posthepatic insulin delivery rate (IDR) was then obtained as the product of posthepatic insulin clearance by fasting plasma insulin concentration (25).

For statistical analysis, insulin concentration, clearance rate, and posthepatic delivery rate values were transformed into their natural logarithms to normalize their distribution. Normality of frequency distribution functions was tested by the Shapiro-Wilk W test. Data are given as mean  $\pm$  SD. A dummy variable was introduced to account for between-center differences, and was included in all regression models. Proportions were compared by the  $\chi^2$  test. Two-way ANOVA, simple and multiple regression analyses were carried out by standard techniques. 95% confidence intervals (CI) were calculated for regression coefficients.

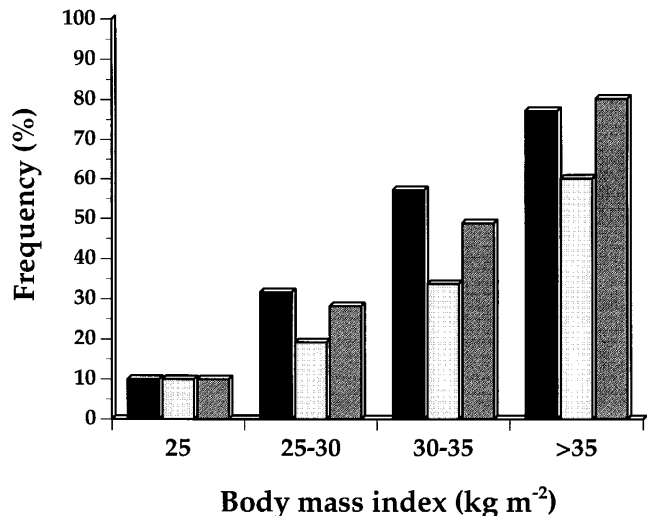


Figure 2. Prevalence rates of insulin resistance, hyperinsulinemia, and insulin hypersecretion (all defined as the top decile of the respective distributions in lean subjects) as a function of the BMI. Black bars, hyperinsulinemia; light gray bars, insulin resistance; dark gray bars, hypersecretion.

## Results

By defining obesity as a BMI  $\leq 25$  kg·m<sup>-2</sup>, 47% of the subjects (42% of women and 49% of men) in the present series were obese (Table I). As compared to the lean group, both obese women and obese men were older. In addition, the obese subjects had higher waist and hip circumferences, waist-to-hip ratios, fasting plasma glucose, fasting and steady-state plasma insulin concentrations, and posthepatic plasma insulin clearance rates (Table II). By all indices of insulin sensitivity, the obese were insulin-resistant as a group. Of note, the average difference in insulin sensitivity between the obese and the lean group was 24–34% by the indices based on body weight ( $M_{\text{bw}}$  and  $M_{\text{bw}}/I$ , respectively), but was only 15–25% according to the indices based on fat-free mass ( $M_{\text{fim}}$  and  $M_{\text{fim}}/I$ ). By the latter, the gender difference in insulin resistance was canceled. The distribution of  $M_{\text{fim}}$  deviated from a normal distribution in both lean and obese subjects ( $P < 0.01$  for both) due to an excess of low values; in the obese group, the distribution was shifted to the left as compared to the lean group (Fig. 1). Posthepatic insulin delivery (IDR) was 80% larger in obese than in lean subjects, with little gender difference. The distribution of log-transformed IDR values in obese individuals was shifted to the right of that of the lean subjects (Fig. 1).

When insulin resistance was defined as the bottom 10% of  $M_{\text{fim}}$  values in the lean group, 26% of all obese subjects were insulin resistant. In particular, the frequency of insulin resistance was 19% in subjects with a BMI  $< 30$  kg·m<sup>-2</sup> and 34% in subjects with a BMI  $< 35$  kg·m<sup>-2</sup>, reaching 60% only in subjects with a BMI  $> 35$  kg·m<sup>-2</sup> (Fig. 2). Different definitions of obesity (lower quartile of BMI distribution) or insulin resistance (lower quartile of  $M_{\text{fim}}$  distribution) resulted in prevalence ratios of insulin resistance in obese vs. lean subjects in the range 2.3–3.3. Using the upper 10% of fasting plasma insulin concentrations in the lean group, the frequency of hyperinsulinemia in the obese group was 41% (32, 57, and 77%, respectively, in the three BMI groups) (Fig. 2).

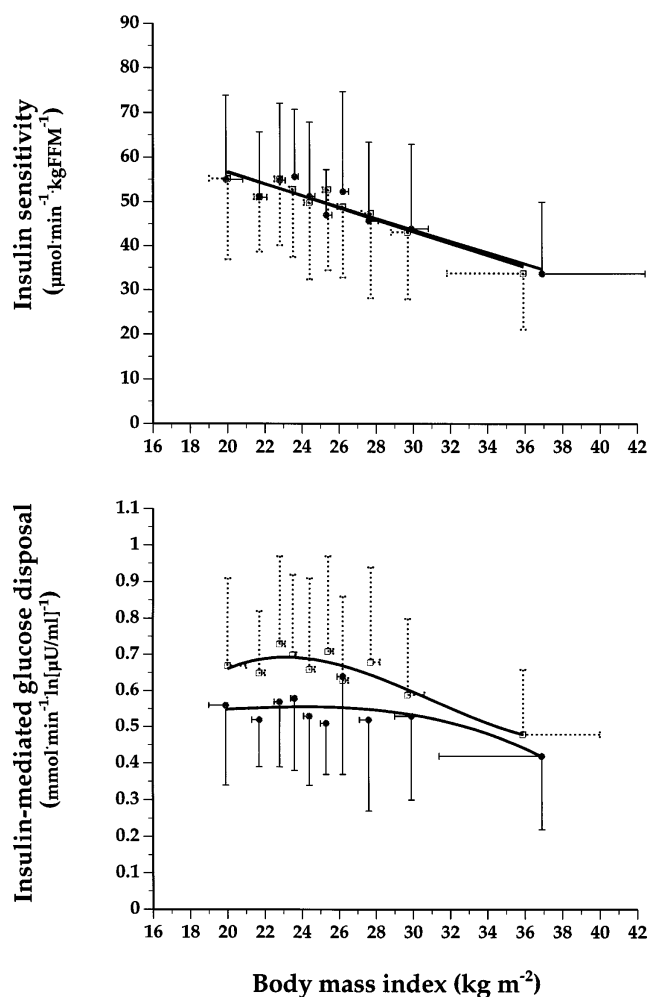


Figure 3. Insulin sensitivity (as the insulin-mediated glucose disposal rate normalized by kg of fat-free mass) and total insulin-mediated glucose disposal (normalized by the steady-state plasma insulin concentration) by decile of BMI and by sex (women, filled circles; men, empty squares). The thick lines are sex-specific linear (for insulin sensitivity) or polynomial (for total glucose disposal) interpolating functions.

In the whole group, insulin sensitivity (as the  $M_{\text{ffm}}$ ) declined linearly with increasing BMI, at an age-adjusted rate of  $1.2 \mu\text{mol}\cdot\text{min}^{-1}\cdot\text{kgFFM}^{-1}$  per BMI unit (CI = 1.0–1.4,  $P < 0.0001$ ), with no sex difference (Fig. 3). Thus, a body weight difference of 10 BMI units (= 30 kg for a height of 173 cm) translated into a 25% decrement in insulin sensitivity (from a mean group value of  $49 \mu\text{mol}\cdot\text{min}^{-1}\cdot\text{kgFFM}^{-1}$ ). Of note is that insulin-mediated glucose disposal, when expressed as the whole-body rate (mmol per min) normalized only by the steady-state plasma insulin concentration, was weakly related to BMI, a decline being evident for BMI over  $28 \text{ kg}\cdot\text{m}^{-2}$  in men and  $30 \text{ kg}\cdot\text{m}^{-2}$  in women (Fig. 3).

By defining the lean subjects in the top 10% of the distribution of posthepatic insulin delivery rate as hypersecretors, there were significantly more hypersecretors (38%,  $\chi^2 = 22.1$ ,  $P < 0.0001$ ) than insulin-resistant subjects in the obese group. In particular, the frequency of insulin hypersecretion was 28% in subjects with a BMI  $< 30 \text{ kg}\cdot\text{m}^{-2}$ , 49% in subjects with a

BMI  $< 35 \text{ kg}\cdot\text{m}^{-2}$ , and 80% in subjects with a BMI  $> 35 \text{ kg}\cdot\text{m}^{-2}$  (Fig. 2).

The simultaneous dependence of fasting posthepatic insulin delivery rate on BMI and insulin sensitivity was analyzed by multiple regression. In a model adjusting by age and gender, BMI and  $M_{\text{ffm}}$  were independently related to insulin delivery rate ( $P < 0.0001$  for both, total explained variance = 36%). The model-predicted changes in insulin delivery as a function of  $M_{\text{ffm}}$  in a subject with a BMI of  $22.5 \text{ kg}\cdot\text{m}^{-2}$  (i.e., the mean value of the lean subgroup), in a subject with a BMI of  $29.3 \text{ kg}\cdot\text{m}^{-2}$  (i.e., the mean value of the obese subgroup), and in a very obese person (BMI =  $36.0 \text{ kg}\cdot\text{m}^{-2}$ ) are plotted in Fig. 4 to illustrate the highly nonlinear nature of this dependence.

In men as well as in women, the waist-to-hip ratio increased with increasing BMI; the relationship, however, flattened for BMI values greater than  $\sim 28 \text{ kg}\cdot\text{m}^{-2}$ , whereas the waist circumference was quasi-linearly related to BMI over the entire range (Fig. 5). Neither the waist circumference nor WHR was related to any index of insulin sensitivity ( $M_{\text{ffm}}$  or  $M_{\text{bw}}$  or their ratios to insulin) after adjustment for age, sex, and BMI (Table III). The same result was obtained when this model was run on the lean or the obese dataset separately. In contrast, insulin delivery rate increased significantly ( $P < 0.0001$ ) as a function of WHR, considerably more in women than in men (Fig. 6). Finally, in a multivariate model with age, sex, BMI, WHR (or waist circumference), and insulin sensitivity (explaining 45% of the total variance of insulin delivery), high values of BMI and of WHR (or waist circumference) were both significant predictors of higher values of insulin delivery rate (Table III). With this model, 0.1 U of WHR had an equivalent effect on insulin delivery as one BMI U or 20 U of  $M_{\text{ffm}}$ .

In the whole dataset, insulin sensitivity (as  $M_{\text{ffm}}$ ) was inversely related to fasting plasma insulin concentration (with a regression coefficient of  $11 \mu\text{mol}\cdot\text{min}^{-1}\cdot\text{kgFFM}^{-1}$  per  $\ln[\mu\text{U/ml}]$ , CI = 9–13,  $P < 0.0001$ ) (Fig. 7). This relationship was independent of age and sex. As shown in Fig. 7 for six centers

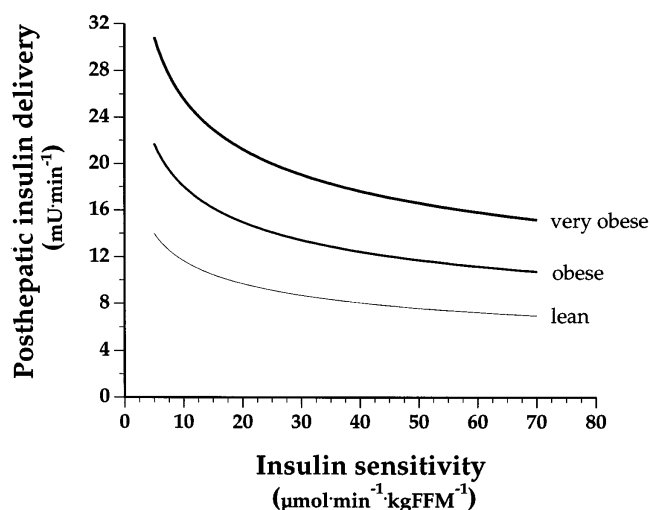


Figure 4. Posthepatic insulin delivery rates as a function of insulin sensitivity in a lean population (BMI =  $23 \text{ kg}\cdot\text{m}^{-2}$ ), in an obese population (BMI =  $29 \text{ kg}\cdot\text{m}^{-2}$ ), and in a very obese population (BMI =  $36 \text{ kg}\cdot\text{m}^{-2}$ ). Data calculated from the whole dataset by a multiple regression model adjusting for age, gender, and body mass index.

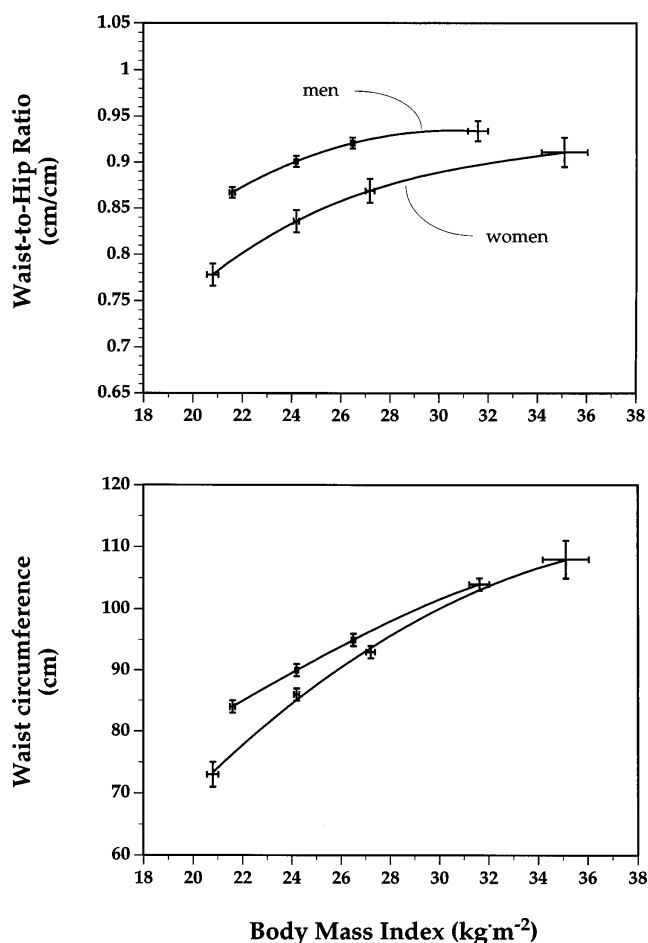


Figure 5. Relationship between the waist-to-hip ratio (top) or the waist circumference (bottom), and the BMI (quartiles) in men and women.

(for a total of 499 subjects), the relation between  $M_{\text{fifm}}$  and fasting insulin was remarkably similar across centers. Thus, between-center variability of insulin measurements did not affect the pattern of relationship of the variables based on plasma insulin concentration (similar results for  $CR_i$  and IDR not shown).

Table III. Multiple Regression Analysis

	$M_{\text{fifm}}$		Insulin delivery rate	
	Stdz RC	P	Stdz RC	P
Age	-0.29	0.51	-0.165	0.0001
Sex	0.047	0.28	0.056	0.14
BMI	-1.17	0.0001	0.579	0.0001
WHR	0.007	0.88	0.117	0.0001
$M_{\text{fifm}}$			-0.099	0.01
Explained variance	14%		45%	

Models were run in the subgroup of 529 subjects in whom WHR measurements were available. Stdz RC, standardized regression coefficient, adjusted by center.

## Discussion

This large series of Caucasian subjects of all ages living in Europe were selected for having normal glucose tolerance and arterial blood pressure levels. Though not a random sample of the European population, this group still resembles a general population in many respects, particularly the age-dependence of metabolic parameters (18).

Even in the lean segment of our cohort, insulin sensitivity was found to vary over a very wide range. For the purpose of this analysis, overweight, obesity, and massive obesity, which are commonly regarded as weight disturbances of increasing severity, were lumped together by the cut-off of a BMI  $> 25 \text{ kg}\cdot\text{m}^{-2}$ . Having thus defined normal body weight as a BMI  $\leq 25 \text{ kg}\cdot\text{m}^{-2}$ , obesity was found to be associated with a statistically highly significant reduction in insulin sensitivity, as expected. Three novel aspects, however, emerge from the data. First, the severity of insulin resistance in obesity was overestimated when insulin-mediated glucose uptake was normalized by body weight (as is often done). Under euglycemic clamp conditions, over 70% of total glucose uptake occurs in skeletal muscle (26); fat tissue, being  $> 95\%$  triglyceride mass, contributes much to body weight but little to total glucose disposal. When insulin-mediated glucose use was normalized by the metabolically active (lean) mass, the obese group was only 15–25%, on average, less sensitive to insulin than the lean group, with no difference between men and women (Table II). Second, the prevalence of insulin resistance among the obese subjects was surprisingly low: only one in four subjects was as resistant as the bottom decile of the lean group. Even in the presence of definite obesity (BMIs of  $28\text{--}50 \text{ kg}\cdot\text{m}^{-2}$ ), only one in two individuals was insulin-resistant. Regression analysis showed that a rather large difference in body weight (30 kg) was associated with only a modest (25%) decrement in insulin sensitivity. Thus, we conclude that the quantitative impact of obesity on insulin action in otherwise healthy subjects is not as large as previously thought. In some studies, the inclusion of obese subjects with glucose intolerance or high blood pressure, which themselves carry a quota of insulin resistance (11, 27), may have led to overestimating the influence of obesity per se

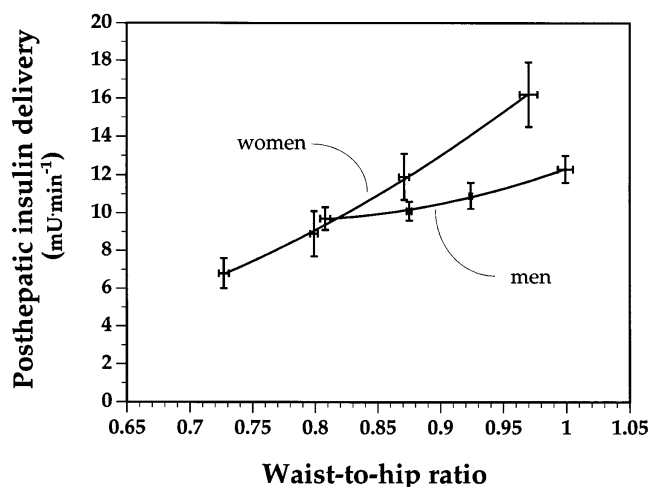


Figure 6. Relationship between posthepatic insulin delivery rate and the waist-to-hip ratio (quartiles) in men and women.

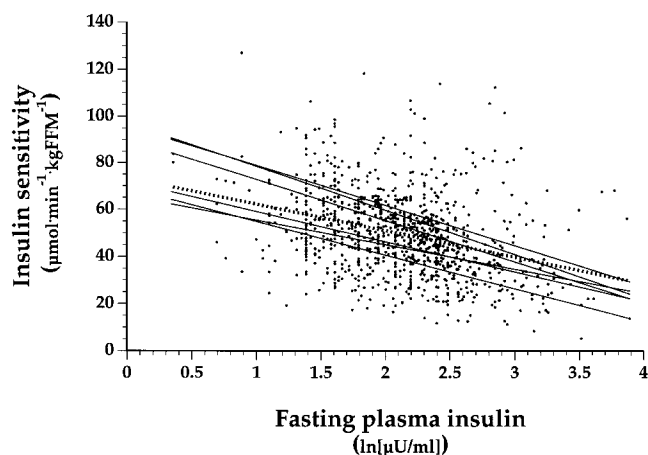


Figure 7. Relationship between insulin sensitivity and fasting plasma insulin concentration in the whole dataset. The dotted line is the interpolating function for the whole population; the other thin lines are the corresponding functions for six different participating centers.

on insulin sensitivity. Normalizing insulin-mediated glucose uptake by body weight rather than lean mass and/or using plasma insulin concentrations as a surrogate measure of insulin sensitivity (Fig. 1) may have contributed to this overestimate. Third, when whole-body glucose uptake was expressed in absolute terms, the impact of BMI was marginal (Fig. 3). This finding reflects the fact that fat-free mass is expanded in the obese (Table I); though relatively resistant to the action of insulin, this excess fat-free tissue is metabolically active and contributes to glucose tolerance. Conversely, to the extent that weight reduction includes loss of fat-free tissue, this compensatory adjustment is lost.

A relevant question is why a high proportion of obese subjects are not insulin resistant. One possibility is that the high rate of conversion of insulin resistance into impaired glucose tolerance and overt diabetes (28) may have removed many obese individuals from a cohort selected on the basis of normal glucose tolerance. The size of such a bias cannot be estimated from our data. Another possibility is that in some individuals weight gain occurs in ways or at sites that do not interfere with insulin action on glucose uptake. A strong candidate mechanism for this is fat distribution (29). In the present series, however, there was little effect of fat distribution, as measured by the WHR or the waist circumference, on insulin sensitivity when simultaneously accounting for BMI. Numerous studies have found a separate influence of fat mass and fat distribution (particularly visceral) on insulin sensitivity (30, 31). Study groups, however, have generally been small (30, 32), have only included women (30, 33, 34), have used computerized tomography to estimate abdominal fat (30), or have inferred insulin sensitivity from plasma insulin measurements (35). Furthermore, in population-based surveys (such as the San Antonio Heart Study), a high WHR segregated strongly with arterial blood pressure, particularly in men (36). Thus, the inclusion of borderline or mild hypertensives into obese groups may bias the association of insulin resistance with fat distribution. To the extent that the WHR and waist circumference are markers for abdominal adipose mass (37), the present data do not indicate that in obese men and women (selected for having normal glucose tolerance and blood pres-

sure) gross fat distribution impairs insulin action over and above the effect of BMI itself.

A final explanation for the normal insulin sensitivity of many obese subjects is that their level of insulin sensitivity was even higher before they gained weight. In accord with this possibility, it is known from longitudinal studies (38) that the risk of weight gain is higher in insulin-sensitive as compared to insulin-resistant individuals, presumably because of better metabolic efficiency. Thus, the obese subject with preserved insulin sensitivity may have been supersensitive to the hormone before gaining weight. In this view, the obese segment of the population would be originally enriched with very insulin-sensitive subjects, in whom the decrease in insulin sensitivity with weight gain may have developed as a compensatory adaptation to limit further weight gain (39). In these subjects, weight reduction would still be expected to improve insulin resistance (40).

Another finding of this study is that, contrary to prevalent opinion (36, 41) the metabolic clearance rate of plasma insulin is higher in the obese than in the lean, particularly in women (Table II). Once again, expressing plasma insulin clearance by kilogram of body weight artificially lowers the values of overweight subjects. As the vast majority ( $\sim 80\%$ ) of plasma insulin is eventually cleared by the liver (42), clearance rates should be normalized by liver weight. Indeed, the slightly higher absolute values in our obese group could reflect a larger liver size, in line with the general organomegaly of obesity (14). It follows that the fasting hyperinsulinemia of obese individuals can hardly be attributed to overflow of pancreatic insulin into the systemic circulation caused by inefficient hepatic degradation. On the other hand, because of the threefold porto-systemic gradient for plasma insulin and the saturation threshold (100–200  $\mu\text{U/ml}$ ) for hepatic insulin metabolism (42, 43), overflow of pancreatic insulin must be more common in obese than in lean subjects during the absorptive state, when insulin secretion is stimulated.

The values of fasting posthepatic insulin delivery rate calculated from the clamp in our lean subjects are similar to those previously obtained in lean, healthy volunteers by direct measurement of plasma insulin clearance with radioiodinated insulin (44). Assuming 50% liver extraction (42), the calculated mean value of insulin secretion rate in our lean group (18  $\text{mU}\cdot\text{min}^{-1}$  [= 128  $\text{pmol}\cdot\text{min}^{-1}$ ]) falls well within the range measured by Polonsky et al. (13) with the use of C-peptide kinetics and deconvolution analysis. Insulin hypersecretion, defined by the same statistical criterion as used for insulin resistance, was significantly more prevalent than insulin resistance in the obese group as a whole as well as in the three BMI subgroups (Fig. 2). Furthermore, combined insulin resistance and insulin hypersecretion was present in 14% of the obese subjects, a 10-fold enrichment as compared to the prevalence of this combination in the lean group (1.6%). A nonlinear (hyperbolic) relationship between indices of insulin action and insulin secretion has been reported previously (45); the confounding effect of obesity, however, has not been considered. We show that insulin release is simultaneously affected by insulin resistance and obesity. Quantitatively (Fig. 4), insulin delivery rose hyperbolically as insulin resistance increased, and the more so the higher the BMI. These results prove that insulin resistance is not the only mechanism through which obesity enhances insulin secretion; other, stronger signals, originating in the central nervous system (46), must be involved.

By considering that 24-h pancreatic insulin release is approximately twice the fasting secretory rate (47), and that fasting and stimulated insulin release are strongly correlated with one another in nondiabetic subjects (13, 25), the current data extrapolate to 24-h insulin outputs ranging from 10 to over 400 U of insulin. This impressive 40-fold range indicates that in healthy subjects glucose tolerance is maintained at the expense of a very ample modulation of  $\beta$ -cell function. Therefore, it is plausible that long-standing obesity, especially if associated with insulin resistance, may eventually lead to stress failure of the  $\beta$ -cell in predisposed individuals. Indeed, the conversion rate to NIDDM has been found to be more than double in obese than in lean normoglycemic men (48–50).

The relationship between BMI and the WHR (Fig. 5) suggests that, in men as well as in women, moderate excess of adipose tissue is deposited preferentially in the upper part of the body, but further accumulation is equally distributed above and below the waist. In contrast to insulin sensitivity, the relative distribution of body fat did bear an independent relation to insulin delivery rate. Especially in women, central fat accumulation was associated with higher rates of insulin delivery for the same degree of obesity and insulin sensitivity (Fig. 6). The physiological mechanism(s) underlying this association is not entirely understood. Multiple evidence suggests that preferential deposition of adipose tissue in the abdominal region is under hormonal control (29). In particular, the pattern of changes in activity of the hypothalamic-pituitary-adrenal axis observed in association with visceral obesity is consistent with a centrally mediated stress reaction (50). An interplay between insulin, an appetite suppressant, and other neurohormones (notably neuropeptide Y, an appetite stimulant) at the level of selected areas of the midbrain (15) might conceivably result in the combination of insulin hypersecretion and centripetal fat routing.

In summary, in simple obesity insulin resistance is not as prevalent as previously thought, and is less frequent than insulin hypersecretion. The hyperinsulinemia of obesity is the result of both compensatory (to insulin resistance) and primary (central) hypersecretion of insulin. The clinical implication of these findings is that the risk, for NIDDM and/or cardiovascular disease, associated with the predominantly insulin-resistant or insulin-hypersecreting obese phenotype may be different. Also, sensitivity to caloric restriction (by diet or pharmacological treatment), and metabolic and cardiovascular adaptation to weight loss may be sufficiently different in these obese phenotypes to require differential strategies of followup and management.

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## References

- Rabinowitz, D., and K.L. Zierler. 1962. Forearm metabolism in obesity and its response to intraarterial insulin. Characterization of insulin resistance and evidence for adaptive hyperinsulinism. *J. Clin. Invest.* 12:2173–2181.
- Reaven, G.M. 1988. Role of insulin resistance in human disease. *Diabetes.* 37:1595–1607.
- Manson, J., G. Colditz, M. Stampfer, W.C. Willet, B. Rosner, R.R. Monson, F.E. Speizer, and C.H. Hennekens. 1990. A prospective study of obesity and risk of coronary heart disease in women. *N. Engl. J. Med.* 322:882–889.
- Welborn, T., and K. Wearne. 1979. Coronary artery disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diabetes Care.* 2:154–160.
- Fontbonne, A., G. Tchobrousky, E. Eschwege, J. Richards, J. Claude, and G. Rosselin. 1988. Coronary heart disease mortality risk: plasma insulin level is a more sensitive marker than hypertension or abnormal glucose tolerance in overweight males. The Paris prospective study. *Int. J. Epidemiol.* 12: 557–565.
- Pyorala, K. 1991. Hyperinsulinemia as predictor of cardiovascular disease: epidemiological evidence. *Diabetes Metab. Rev.* 17:87–92.
- Després, J., B. Lamarche, P. Mauriege, B. Cantin, G.R. Dagenais, S. Moorjani, and P.J. Lupien. 1996. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N. Engl. J. Med.* 334:952–957.
- Wingard, D., E. Barrett-Connor, and A. Ferrara. 1995. Is insulin really a heart disease risk factor? *Diabetes Care.* 18:1299–1304.
- Bogardus, C., S. Lillioja, D. Mott, G. Reaven, A. Kashiwagi, and J. Foley. 1984. Relationship between obesity and maximal insulin stimulated glucose uptake in vivo and in vitro in Pima Indians. *J. Clin. Invest.* 73:800–805.
- Kolterman, O., J. Insel, M. Saekow, and J. Olefsky. 1980. Mechanism of insulin resistance in obesity. Evidence for receptor and post-receptor defect. *J. Clin. Invest.* 65:1272–1284.
- Hollenbeck, C., Y.-D. Chen, and G. Reaven. 1984. A comparison of the relative effect of obesity and non-insulin dependent diabetes mellitus on in vivo insulin-stimulated glucose utilization. *Diabetes.* 33:622–626.
- Bonadonna, R., L. Groop, N. Kraemer, E. Ferrannini, S. Del Prato, and R. DeFronzo. 1990. Obesity and insulin resistance in humans: a dose response study. *Metabolism.* 39:452–459.
- Polonski, K., B. Given, and E. Van Cauter. 1988. Twenty-four hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J. Clin. Invest.* 81:442–448.
- Bray, G. 1995. The syndromes of obesity: an endocrine approach. *In Endocrinology.* Vol. 3. L. DeGroot, editor. W.B. Saunders Company, Philadelphia. 2624–2662.
- Schwartz, M., D. Figlewitz, D. Baskin, S. Woods, and D. Porte, Jr. 1992. Insulin in the brain: a hormonal regulator of energy balance. *Endocr. Rev.* 13: 387–414.
- Kuczmarski, R., K. Flegal, S. Campbell, and C. Johnson. 1994. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. *JAMA (J. Am. Med. Assoc.)* 272:205–211.
- WHO expert committee on Diabetes Mellitus. Second report. Geneva: World Health Organization, 1980.
- Ferrannini, E., S. Vichi, H. Beck-Nielsen, M. Laakso, G. Paolisso, and U. Smith. 1996. Insulin action and age. *Diabetes.* 45:947–953.
- DeFronzo, R.A., J.D. Tobin, and R. Andres. 1979. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am. J. Physiol.* 237:E214–E223.
- DeFronzo, R. 1979. Glucose intolerance and aging: evidence for tissue insensitivity to insulin. *Diabetes.* 28:1095–1101.
- Robert, J.J., J.C. Cummins, R.R. Wolfe, M. Durkot, D.E. Matthews, X.H. Zhao, D.M. Bier, and V.R. Young. 1982. Quantitative aspects of glucose production and metabolism in healthy elderly subjects. *Diabetes.* 31:203–211.
- Hume, R. 1966. Prediction of lean body mass from height and weight. *J. Clin. Pathol.* 19:389–391.
- Fulcher, G.R., M. Farrer, M. Walker, D. Rodham, B. Clayton, and K.G.M.M. Alberti. 1991. A comparison of measurements of lean body mass derived by bioelectrical impedance, skinfold thickness and total body potassium. A study in obese and non-obese normal subjects. *Scand. J. Lab. Invest.* 51:245–253.
- Ferrannini, E., and C. Cobelli. 1987. The kinetics of insulin in man. I. General aspects. *Diabetes Metab. Rev.* 3:335–363.
- Ferrannini, E., and A. Pilo. 1979. Pattern of insulin delivery after intravenous glucose injection in man and its relation to plasma glucose disappearance. *J. Clin. Invest.* 64:243–254.



26. Shulman, G.I., P.W. Landenson, M.H. Wolfe, E.C. Ridgway, and R.R. Wolfe. 1990. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by  $^{13}\text{C}$  nuclear magnetic resonance spectroscopy. *N. Engl. J. Med.* 322:223–228.
27. Ferrannini, E., G. Buzzigoli, R. Bonadonna, M.A. Giorico, M. Oleggini, L. Graziadei, R. Pedrinelli, L. Brandi, and S. Bevilacqua. 1987. Insulin resistance in essential hypertension. *N. Engl. J. Med.* 317:350–357.
28. Lillioja, S., D.M. Mott, B.V. Howard, P.H. Bennett, H. Yki-Järvinen, D. Freymond, B.L. Nyomba, F. Zurlo, B. Swinburn, and C. Bogardus. 1988. Impaired glucose tolerance as a disorder of insulin action. *N. Engl. J. Med.* 318:1217–1225.
29. Björntorp, P. 1988. Abdominal obesity and the development of non-insulin dependent diabetes mellitus. *Diabetes Metab. Rev.* 4:615–622.
30. Bonora, E., S. Del Prato, R. Bonadonna, G. Gulli, A. Solini, M.L. Shank, A.A. Ghiatas, J.L. Lancaster, R.F. Kilcoyne, A.M. Alyassin, and R.A. DeFronzo. 1992. Total body fat content and fat topography are associated differently with in vivo glucose metabolism in nonobese and obese nondiabetic women. *Diabetes.* 41:1151–1159.
31. Krotkiewski, M., P. Björntorp, L. Sjöström, and U. Smith. 1983. Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. *J. Clin. Invest.* 72:1150–1162.
32. Pedersen, S., J. Børghlum, O. Schmitz, J. Bak, N. Sørensen, and B. Richelsen. 1993. Abdominal obesity is associated with insulin resistance and reduced glycogen synthase activity in skeletal muscle. *Metabolism.* 52:998–1005.
33. Evans, D., R. Hoffmann, R. Kalkhoff, and A. Kissebah. 1984. Relationship of body fat topography to insulin sensitivity and metabolic profiles in premenopausal women. *Metabolism.* 33:68–75.
34. Peiris, A., R. Mueller, G. Smith, M. Struve, and A. Kissebah. 1986. Splanchnic insulin metabolism in obesity: influence of body fat distribution. *J. Clin. Invest.* 78:1648–1657.
35. Pasquali, R., F. Casimirri, S. Cantobelli, N. Melchionda, A.M.M. Labbate, R. Fabbri, M. Capelli, and L. Bortozoli. 1991. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism.* 40:101–104.
36. Ferrannini, E., S.M. Haffner, M.P. Stern, B.D. Mitchel, A. Natali, H.P. Hazuda, and J.K. Patterson. 1991. High blood pressure and insulin resistance: influence of ethnic background. *Eur. J. Clin. Invest.* 21:280–287.
37. Kissebah, A., and G. Krakower. 1994. Regional adiposity and morbidity. *Physiol. Rev.* 74:761–811.
38. Swinburn, B., B. Nyomba, M. Saad, F. Zurlo, I. Raz, W.C. Knowler, S. Lillioja, C. Bogardus, and E. Ravussin. 1991. Insulin resistance associated with lower rates of weight gain in Pima Indians. *J. Clin. Invest.* 88:168–173.
39. Flatt, J. 1988. Importance of nutrient balance in body weight regulation. *Diabetes Metab. Rev.* 4:571–581.
40. Webber, J., M. Donaldson, S. Allison, N. Fukagawa, and I. Macdonald. 1994. The effects of weight loss in obese subjects on the thermogenic, metabolic and haemodynamic responses to the glucose clamp. *Int. J. Obes.* 18:725–730.
41. Castillo, M., A. Scheen, M. Letiexhe, and P. Lefebvre. 1994. How to measure insulin clearances. *Diabetes Metab. Rev.* 10:119–150.
42. Ferrannini, E., and C. Cobelli. 1987. The kinetics of insulin in man. II. Role of the liver. *Diabetes Metab. Rev.* 3:365–397.
43. Ferrannini, E., J. Wahren, O.K. Faber, P. Felig, C. Binder, and R.A. DeFronzo. 1983. Splanchnic and renal metabolism of insulin in human subjects: a dose-response study. *Am. J. Physiol.* 244:E517–E527.
44. Navalesi, R., A. Pilo, and E. Ferrannini. 1978. Kinetic analysis of plasma insulin disappearance in nonketotic diabetic patients and in normal subjects. A tracer study with  $^{125}\text{I}$ -insulin. *J. Clin. Invest.* 61:197–208.
45. Kahn, S., R. Prigeon, D. McCulloch, E.J. Boyko, R.N. Bergman, M.W. Schwartz, J.L. Neifing, W.K. Ward, J.C. Beard, J.P. Palmer, and D. Porte, Jr. 1993. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes.* 42:1663–1672.
46. Jeanrenaud, B. 1988. Neuroendocrine and metabolic basis of type II diabetes as studied in animal models. *Diabetes Metab. Rev.* 4:603–614.
47. Polonsky, K.S., B.D. Given, L.J. Hirsch, H. Tillil, E.T. Shapiro, C. Beebe, B.H. Frank, J.A. Galloway, and E. Van Cauter. 1988. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 318:1231–1239.
48. Modan, M., A. Karasik, H. Halkin, Z. Fuchus, A. Lusky, A. Shitrit, and B. Modan. 1986. Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non insulin dependent) diabetes and on insulin response: the Israeli study of glucose intolerance, obesity and hypertension. *Diabetologia.* 29:82–89.
49. Ohlson, L., B. Larsson, K. Svärdsudd, L. Welin, H. Eriksson, L. Wilhelmsen, B. Björntorp, and G. Tibblin. 1985. The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes.* 34:1055–1058.
50. Brindley, D., and Y. Rolland. 1989. Possible connections between stress, diabetes, obesity, hypertension and altered lipid metabolism that may result in atherosclerosis. *Clin. Sci. (Lond.).* 77:453–461.