

β -Cell Function in Morbidly Obese Subjects During Free Living

Long-Term Effects of Weight Loss

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Insulin hypersecretion and insulin resistance are physiologically linked features of obesity. We tested whether extreme hypersecretion impairs β -cell function under free-living conditions and whether major weight loss modifies insulin hypersecretion, insulin sensitivity, and β -cell function. Plasma glucose, C-peptide, and free fatty acid concentrations were measured at hourly intervals during 24 h of normal life (including calorie-standardized meals) in 20 morbidly obese nondiabetic patients (BMI 48.4 ± 1.7 kg/m²) and 7 nonobese age- and sex-matched control subjects; 8 of the obese patients were restudied 6 months and 2 years following biliopancreatic diversion. Insulin secretion was reconstructed from C-peptide levels by deconvolution and related to concurrent glucose levels through a mathematical model incorporating key features of β -cell function: rate sensitivity, β -cell glucose sensitivity, and potentiation. Insulin sensitivity (by the euglycemic insulin clamp technique) was reduced by 50% in obese subjects (23.1 ± 2.5 of obese subjects vs. 52.9 ± 4.9 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1}$ of control subjects, means \pm SE, $P = 0.0004$) as was mean 24-h insulin clearance (median 809 [interquartile range 451] vs. 1,553 [520] ml \cdot min⁻¹ \cdot m⁻², $P < 0.001$) due to a 50% reduction in hepatic insulin extraction ($P < 0.01$). Over 24 h, insulin secretion was doubled in obese subjects (468 nmol [202] in obese subjects vs. 235 [85] of control subjects, $P = 0.0002$). Despite the hypersecretion, β -cell glucose sensitivity, rate sensitivity, and potentiation were similar in obese and control subjects. Six months postoperatively (weight loss = 33 ± 3 kg), both insulin hypersecretion (282 nmol [213]) and insulin sensitivity (51.6 ± 3.7 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1}$) were normalized. At 2 years (weight loss = 50 ± 8 kg), insulin sensitivity was supernormal (68.7 ± 3.3 $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1}$) and

insulin secretion was lower than normal (167 nmol [37]) (both $P < 0.05$ vs. control subjects). In conclusion, severe uncomplicated obesity is characterized by gross insulin hypersecretion and insulin resistance, but the dynamic aspects of β -cell function are intact. Malabsorptive bariatric surgery corrects both the insulin hypersecretion and the insulin resistance at a time when BMI is still high. With continued weight loss over a 2-year period, moderately obese subjects become supersensitive to insulin and, correspondingly, insulin hyposecretors. *Diabetes* 54:2382–2389, 2005

Hyperinsulinemia is a characteristic feature of obesity (1,2). Several studies have shown that insulin hypersecretion (2,3) and impaired insulin clearance are main mechanisms for the increased plasma insulin levels found in obese patients (4). In a study of 14 lean subjects and 15 moderately obese patients, Polonsky et al. (3) used the C-peptide deconvolution method (5) and intravenous glucose infusions to quantitate the contribution of insulin secretion and insulin clearance to plasma insulin levels. They found that under basal fasting conditions, hypersecretion contributes more than reduced insulin clearance to the genesis of hyperinsulinemia. In the same group of subjects, these authors also evaluated the 24-h profile of insulin secretion (6). They found that whereas insulin secretion was higher than in lean subjects throughout 24 h, the temporal pattern of secretion was unaltered in obese subjects, suggesting that the functional β -cell mass was expanded but regulatory mechanisms were still operative. Detailed analyses of the relationship between insulin hypersecretion and the concomitant plasma glucose concentrations under free-living conditions and between insulin hypersecretion and insulin resistance, however, have not been carried out.

Morbid obesity, such as is seen in relatively young subjects, may be a partially different condition from the overweight and moderate obesity more often developing after the 4th decade of life (7). For example, in morbidly obese subjects, the cardiovascular risk factor profile is frequently quite favorable despite the accumulation of >40 kg of excess fat (8). Although it can be presumed that severe obesity poses an extreme burden on the endocrine pancreas, little is known about β -cell function in morbid

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FFA, free fatty acid; FFM, fat-free mass; TBW, total body water.

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TABLE 1
Anthropometric and metabolic characteristics

| | Obese subjects | Control subjects | <i>P</i> |
|----------------------------|----------------|------------------|----------|
| Sex (M/F) | 6/14 | 3/4 | NS |
| Age (years) | 40 ± 3 | 35 ± 4 | NS |
| Body weight (kg) | 130 ± 7 | 74 ± 3 | <0.0001 |
| BMI (kg/m ²) | 49.5 ± 1.7 | 26.5 ± 0.4 | <0.0001 |
| FFM (kg) | 71 ± 4 | 52 ± 4 | 0.01 |
| Fat mass (kg) | 60 ± 3 | 22 ± 2 | <0.0001 |
| Fat mass (%) | 46 ± 1 | 30 ± 3 | <0.0001 |
| Waist (cm) | 134 ± 5 | 76 ± 1 | <0.0001 |
| Mean 24-h glucose (mmol/l) | 5.08 ± 0.19 | 5.65 ± 0.21 | NS |
| Mean 24-h FFAs (mmol/l) | 0.53 ± 0.04 | 0.33 ± 0.05 | 0.004 |

Data are means ± SE.

obesity. In a study of eight such patients, Jimenez et al. (9) reported the presence of fasting hyperinsulinemia and a higher C-peptide secretory response to intravenous glucose (using the hyperglycemic clamp), which was fully corrected by a weight loss amounting to ~60% of the weight excess obtained by gastroplasty. More recently, Guldstrand, Ahren, and Adamson (10) described a progressive fall in insulin secretion, as measured by the glucose-dependent arginine stimulation test, in morbidly obese subjects with 15 and 25% weight reductions following bariatric surgery. No information is available on the long-term metabolic outcome of major weight loss induced by surgery.

C-peptide-based methods make it possible to reconstruct insulin secretion rate under most circumstances, including meals and free living (5,6). Assessing β -cell function, however, requires some model of the dependence of insulin secretion on plasma glucose concentrations (11–13). For example, potentiation of insulin secretion by repeated glucose stimulation is known to be of physiological importance and has been considered with great attention in early mathematical models of insulin secretion (14,15). We have developed a physiological model of the glucose control of insulin secretion that incorporates three main features of β -cell function emerging from studies in the isolated perfused pancreas: proportional response to glucose, response to glucose rate of change, and potentiation (16). The purpose of the present study was to apply this model to quantitatively assess multiple aspects of β -cell function in morbidly obese patients under free-living conditions who represent the far end of the distribution of spontaneous overstimulation of the endocrine pancreas. More specifically, we set forth to test how the β -cell adapts to chronic overstimulation and insulin resistance and which features of β -cell function are changed by major weight loss maintained over the long run.

RESEARCH DESIGN AND METHODS

Twenty morbidly obese (BMI >40 kg/m²) nondiabetic patients and seven sex- and age-matched nonobese (BMI <28 kg/m²) healthy volunteers were studied (Table 1). None of the obese patients had the metabolic syndrome by either the National Cholesterol Education Program Adult Treatment Panel III (17) or the World Health Organization (18) definition. At the time of the baseline study, all subjects were on a diet with the following average composition: 60% carbohydrate, 30% fat, and 10% protein (at least 1 g/kg body wt). This dietary

regimen was maintained for 1 week before the study. The study protocol was approved by the institutional ethics committee of the Catholic University of Rome. The nature and purpose of the study were carefully explained to all subjects before they provided their written consent to participate. The baseline and 6-month follow-up insulin sensitivity data alone have been used in a previous publication (19).

All subjects underwent the metabolic study at baseline, after which 10 obese patients underwent biliopancreatic diversion consisting of a partial gastrectomy with a distal Roux-en-Y reconstruction (20). Eight of these obese subjects, sex- and age-matched to control subjects, were restudied 6 months and 2 years postoperatively.

For the basal study, each subject spent 24 h (starting at 8:00 A.M.) on the metabolic ward. During this period, four meals were administered for a total caloric intake of 30 kcal (126 kJ) per kg of fat-free mass (FFM; 20% breakfast, 40% lunch, 10% afternoon snack, and 30% dinner). Diet composition was 17% protein, 35% fat, and 48% carbohydrate. Hourly blood samples were drawn from a central venous catheter for the measurement of glucose, insulin, C-peptide, and free fatty acid (FFA) concentrations. Body composition was evaluated, on a separate day, by the determination of total body water (TBW) using 0.19 Bq ³H₂O in 5 ml saline administered as an intravenous bolus injection (21). Blood samples were drawn before and 3 h after the injection. Radioactivity was determined in duplicate on 0.5 ml plasma in a β -scintillation counter (Model 1600TR; Canberra-Packard, Meriden, CT). Corrections were made for nonaqueous hydrogen exchange (22). Water density at body temperature was assumed to be 0.99371 kg/l. TBW (kg) was computed as ³H₂O dilution space (liters) \times 0.95 \times 0.99371. FFM was obtained by dividing TBW by 0.732 (23). Fat mass was obtained as the difference between body weight and FFM. On another day, a 2-h euglycemic-hyperinsulinemic clamp (240 pmol \cdot min⁻¹ \cdot m⁻²) was performed in each subject for the measurement of insulin sensitivity (24). All procedures and measures described for the basal study were repeated in the eight obese subjects participating in the two follow-up studies.

Analytical procedures. Plasma glucose was measured by the glucose oxidase technique on a Beckman Glucose Analyser (Beckman, Fullerton, CA). Plasma insulin and adiponectin (Linco Research, St. Charles, MO) were assayed by a specific radioimmunoassay. C-peptide was assayed by radioimmunoassay (MYRIA; Technogenetics, Milan, Italy). Serum FFAs, triglycerides, and total and HDL cholesterol were measured spectrophotometrically.

Modeling. The model used to reconstruct 24-h insulin secretion and its control by glucose has been previously described (16). In brief, the model consists of three blocks: *A*) a model for fitting the glucose concentration profile, the purpose of which is to smooth and interpolate plasma glucose concentrations; *B*) a model describing the dependence of insulin (or C-peptide) secretion on glucose concentration; and *C*) a model of C-peptide kinetics, i.e., the two-exponential model proposed by Van Cauter et al. (25) in which the model parameters are individually adjusted to the subject's anthropometric data.

In particular, with regard to the insulin secretion block (*B*), the relationship between insulin release and plasma glucose concentrations is modeled as the sum of two components. The first component is the relationship between insulin secretion and glucose concentration, i.e., a dose-response function. The dose-response function is modulated by a time-varying factor, expressing a potentiation effect on insulin secretion (26). The dose-response function is a parameterized function of glucose concentration that can be either quasi-linear or convex, depending on the parameters (16). The mean slope of the dose-response function is taken to represent β -cell glucose sensitivity. The potentiation factor encompasses glucose-induced potentiation, incretin potentiation, and circadian rhythms and pulsatility of insulin secretion and was expressed here as the ratio of the daytime (fed state) to the nighttime (fasting state) values during the 24 h of observation. The second insulin secretion component represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration, i.e., rate sensitivity. Total insulin secretion is the sum of the two components described above and is calculated every 10 min for the whole 24-h period.

Data analysis. Twenty-four-hour insulin output was calculated as the integral of total insulin secretion. Nocturnal insulin output was computed as the mean insulin secretion between 12:00 P.M. and 7:00 A.M. Insulin clearance (MCR_I) was calculated as the ratio of the mean 24-h insulin secretion rate to the mean 24-h plasma insulin concentration. Hepatic extraction ratio was calculated as the ratio ($MCR_I - MCR_{ph}$) to MCR_p , where MCR_{ph} is the posthepatic clearance of insulin calculated from the clamp as the ratio of the exogenous insulin infusion rate to the steady-state peripheral plasma insulin concentrations (27).

All data are given as means ± SE. Insulin parameters are generally nonnormally distributed and are therefore presented as the median and (interquartile range). Mann-Whitney *U* test was used to compare group values,

TABLE 2
Insulin parameters at baseline

| | Obese subjects | Control subjects | P |
|--|----------------|------------------|--------|
| Insulin sensitivity ($\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}_{\text{FFM}}^{-1}$) | 23.1 \pm 2.5 | 52.9 \pm 4.9 | 0.0004 |
| Mean 24-h insulin level (pmol/l) | 244 (193) | 88 (11) | 0.0001 |
| Mean 24-h insulin clearance ($\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) | 809 (451) | 1,553 (520) | <0.001 |
| Hepatic fractional insulin extraction | 0.33 (0.39) | 0.60 (0.20) | <0.01 |
| 24-h insulin output (nmol) | 468 (202) | 235 (85) | 0.0002 |
| Nocturnal insulin output (nmol) | 219 (67) | 80 (54) | <0.001 |
| β -Cell glucose sensitivity ($\text{pmol} \cdot \text{min}^{-1} \cdot \text{mmol}^{-1} \cdot \text{l}^{-1}$) | 186 (174) | 129 (103) | NS |
| Rate sensitivity ($\text{nmol} \cdot \text{mmol}^{-1} \cdot \text{l}^{-1}$) | 0.8 (2.9) | 1.3 (2.1) | NS |
| Potential factor (day-to-night ratio) | 1.8 (0.8) | 1.5 (0.3) | NS |

Data are means \pm SE or median (interquartile range).

whereas treatment-induced changes in the obese group were tested by the Wilcoxon's signed-rank test. Simple associations were tested by calculating the Spearman rank correlation coefficient (ρ) and power functions were calculated by nonlinear regression techniques. Bivariate regression was carried out by standard techniques, and the results were expressed as partial correlation coefficients (r) and their statistical significance.

RESULTS

Baseline studies. Obese and control subjects were matched for sex, age, and glucose tolerance, while differing widely in body size and composition (Tables 1 and 2). Plasma insulin, C-peptide, and FFA levels were higher in obese than control subjects throughout the day (Fig. 1). In

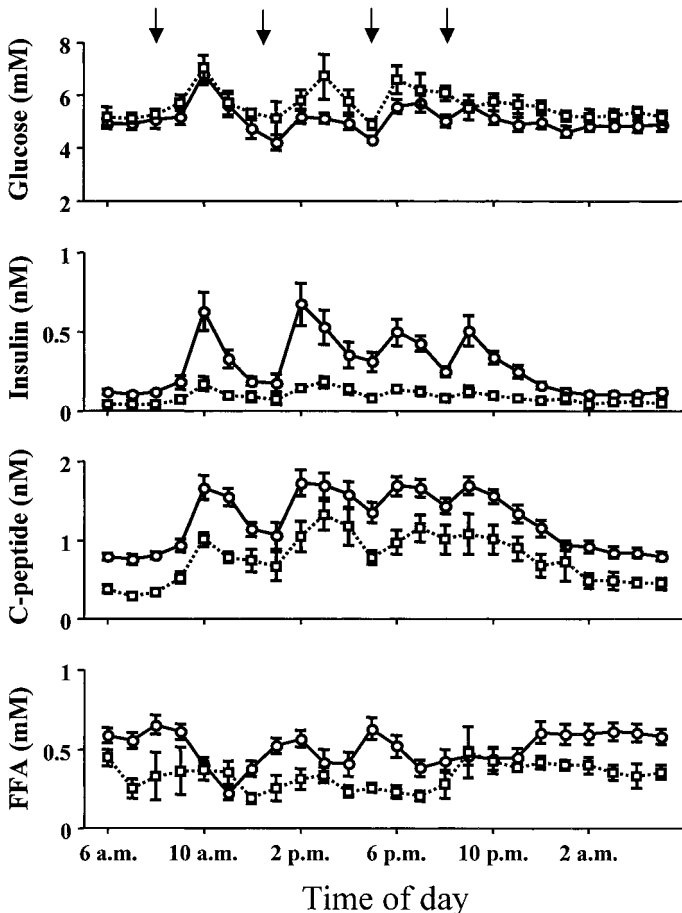


FIG. 1. Twenty-four-hour profile of plasma glucose, insulin, C-peptide, and FFA concentrations in morbidly obese (○) and control (□) subjects. Data are means \pm SE. Arrows point to meal times.

obese subjects, insulin sensitivity, insulin clearance, and hepatic insulin extraction were all decreased by \sim 50% compared with control subjects. The temporal pattern of insulin secretion was similar in obese and control subjects, but the former had much higher rates of insulin secretion throughout the 24-h period (Fig. 2). Over 24 h, insulin secretion was twice as large in the obese (78 units/day [34], range 50–225) as in the control group (39 units/day [14], range 32–58). Nocturnal insulin secretion was enhanced to an even greater extent (approximately threefold) than total secretion. On the other hand, β -cell glucose sensitivity was similar in the two groups (Fig. 3). Over 24 h, rate sensitivity accounted for a small fraction (\sim 5%) of total insulin output and was similar in the two groups. The secretory pattern of the control subjects showed evidence of potentiation, whereby the first meal of the day enhanced the secretory response to the subsequent meal. Over the 24 h of the study, this phenomenon had a mean time of \sim 6 h and resulted, on average, in a 60% stronger response to glucose during the daytime compared with the nocturnal period. This phenomenon was unaltered in the obese group.

In univariate analysis of the pooled baseline data from all study subjects ($n = 27$), 24-h insulin secretion was directly related to all indexes of fatness (body weight, BMI, fat mass, and waist circumference, with ρ values 0.61–0.74, all $P < 0.001$) but was unrelated to sex, age, or the waist-to-hip ratio.

Effects of weight loss. In the patients who underwent surgery, weight loss at 6 months averaged 33 ± 3 kg, of which about one-half was fat tissue. Glucose tolerance was unchanged and similar to control subjects, whereas mean 24-h plasma FFA levels were still significantly higher than in control subjects. Insulin sensitivity and insulin clearance both increased to reach control levels, while mean 24-h insulin levels, 24-h insulin output, and nocturnal insulin output decreased to reach control levels. None of the dynamic parameters of β -cell function (β -cell glucose sensitivity, rate sensitivity, and potentiation) changed significantly (Tables 3 and 4).

Two years following surgery, the obese patients had lost a total of 50 ± 8 kg, of which approximately two-thirds was fat mass. Mean 24-h plasma glucose concentrations were now significantly lower than in control subjects, while 24-h plasma FFAs had decreased significantly to reach control levels. Blood pressure and serum lipids were significantly improved and plasma adiponectin had dou-

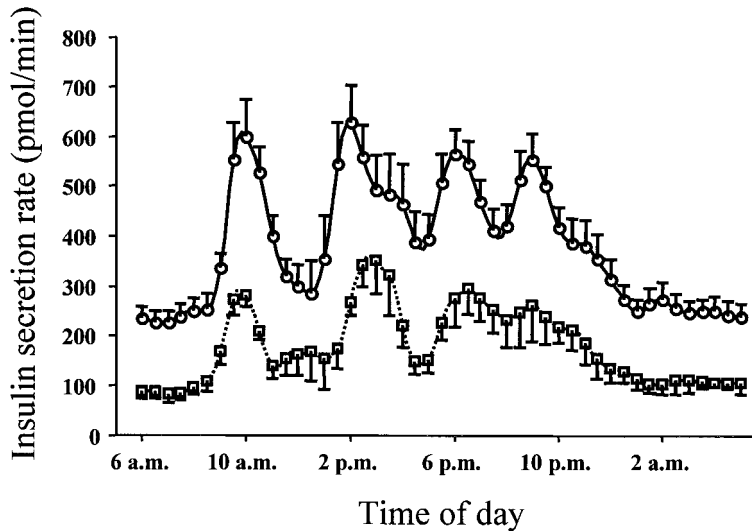


FIG. 2. Twenty-four-hour profile of insulin secretion rates in morbidly obese (○) and lean (□) subjects.

bled. Insulin sensitivity had risen to supernormal values, whereas mean 24-h insulin concentrations, 24-h insulin output, and nocturnal insulin output were significantly lower than in control subjects (Fig. 4). None of the dynamic parameters of β -cell function changed significantly (Fig. 5). The 2-year changes in adiponectin were related to the corresponding changes in BMI ($\rho = 0.83$, $P = 0.01$) and nocturnal insulin secretion ($\rho = 0.73$, $P = 0.04$). In multiple regression, 2-year changes in BMI, nocturnal insulin secretion, and insulin sensitivity explained 80% of adiponectin changes.

In the whole dataset, both 24-h insulin output ($r = 0.66$, $P < 0.0001$) and nocturnal insulin output ($r = 0.64$, $P < 0.0001$, Fig. 6) were reciprocally related to insulin sensitivity in a nonlinear fashion. In bivariate analysis, both insulin sensitivity (partial $r = -0.36$, $P < 0.03$) and BMI (partial $r = +0.43$, $P < 0.01$) were independent correlates of 24-h insulin output. Insulin sensitivity and hepatic insulin extraction were directly related to one another ($\rho = 0.48$, $P < 0.01$).

DISCUSSION

The main findings of our study were the following. First, we found that the extreme hyperinsulinemia of our severely obese subjects was the combined result of a 50% reduction in plasma insulin clearance and a 50% increase in 24-h insulin output. The reduced plasma insulin clearance was mainly due to a decreased hepatic extraction, the main determinant of plasma insulin clearance (28), which in turn was quantitatively related to insulin resistance of glucose uptake (in line with previous evidence [2]). With regard to 24-h insulin output, in the obese group it was found to vary from a value (50 units/day) similar to the highest value of the control group (58 units/day) to one that was 4.5-fold greater despite a BMI range of only 41–70 kg/m². This discrepancy between severity of obesity and degree of insulin hypersecretion is explained by the finding that total insulin output was also dependent on insulin sensitivity. From the bivariate model of the data, we can calculate that with a normal degree of insulin sensitivity

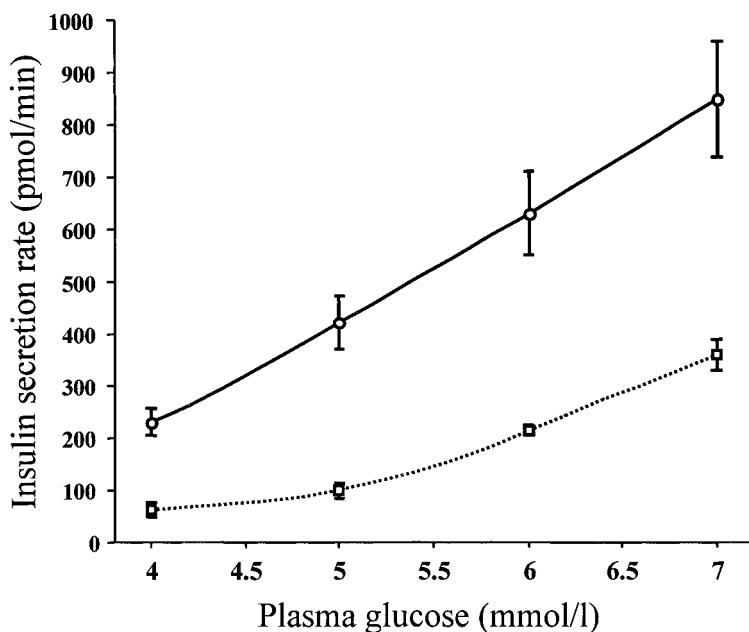


FIG. 3. Dose response of glucose-induced insulin secretion in morbidly obese (○) and lean (□) subjects. The mean slope of the curve is β -cell glucose sensitivity.

TABLE 3
Effect of weight loss on anthropometric and metabolic parameters

| | Baseline | 6 months | 2 years | P_1 | P_2 | P_3 |
|-------------------------------|----------------|--------------|----------------|-------|-----------|-------|
| Body weight (kg) | 137 ± 9* | 104 ± 7* | 87 ± 4* | 0.01 | 0.01 | 0.01 |
| BMI (kg/m ²) | 51.1 ± 2.8* | 39.0 ± 3.0* | 33.1 ± 2.8* | 0.01 | 0.01 | 0.01 |
| FFM (kg) | 75 ± 5* | 59 ± 5 | 57 ± 5 | 0.01 | 0.01 | NS |
| Fat mass (kg) | 62 ± 5* | 45 ± 5* | 30 ± 5 | 0.01 | 0.01 | 0.01 |
| Fat mass (%) | 45 ± 2* | 44 ± 3* | 34 ± 5 | NS | 0.02 | 0.04 |
| Waist (cm) | 143 ± 5* | 119 ± 5* | 108 ± 3* | 0.01 | 0.01 | 0.04 |
| Mean 24-h glucose (mmol/l) | 5.04 ± 0.27 | 5.72 ± 0.38 | 4.63 ± 0.43* | NS | NS | NS |
| Mean 24-h FFAs (mmol/l) | 0.51 ± 0.02* | 0.66 ± 0.06* | 0.42 ± 0.04 | NS | NS | 0.01 |
| Blood pressure (mmHg) | 129 ± 2/83 ± 2 | — | 116 ± 2/77 ± 2 | — | 0.03/0.04 | — |
| Plasma triglycerides (mmol/l) | 1.53 ± 0.08 | — | 1.02 ± 0.02 | — | 0.02 | — |
| Total cholesterol (mmol/l) | 5.53 ± 0.34 | — | 3.26 ± 0.08 | — | 0.02 | — |
| HDL cholesterol (mmol/l) | 1.03 ± 0.08 | — | 1.19 ± 0.08 | — | NS | — |
| Plasma adiponectin (µg/ml) | 7.9 ± 0.6 | — | 16.2 ± 0.9 | — | 0.01 | — |

Data are means ± SE. P_1 = 6 months vs. baseline, P_2 = 2 years vs. baseline, and P_3 = 2 years vs. 6 months. * P ≤ 0.05 vs. control subjects.

(e.g., 50 µmol · min⁻¹ · kg_{FFM}⁻¹), a doubling of BMI (from 25 to 50 kg/m²) is associated with an increase in 24-h insulin output of 13 units/day, whereas a halving of normal insulin sensitivity at a BMI of 20 kg/m² translates into an increase in 24-h insulin output of 8 units/day. These estimates highlight the concept that the insulin hypersecretion of obesity is in part primary (i.e., independent of insulin resistance). The notion that primary insulin hypersecretion is an inherent feature of obesity has been put forward in previous studies (29,30); however, none of them have simultaneously accounted for the impact of insulin resistance in a quantitative fashion as done in the present study. Which feature of obesity signals to the β-cell to chronically increase its secretory activity is uncertain. Among substrates, FFAs acutely enhance insulin release in humans. Chronic (48-h) experimental elevations in FFAs have been reported to stimulate (31) or downregulate (32) glucose-induced insulin release. Signals originating in the central nervous system, be they humoral or neural, may be responsible for a sustained upregulation of β-cell function (33,34).

Second, the dynamic aspects of β-cell response to glucose were unaltered in the morbidly obese subjects. Thus, the ability of the β-cell to anticipate a phase of rising secretion (or rate sensitivity), to adequately respond to the glucose stimulus itself (or glucose sensitivity), and to memorize the glucose stimulus as well as reading incretin signals (collectively, potentiation) was similar in obese

and control subjects. In terms of glucose dose response, in obese subjects, the secretory curve was shifted upwards of that of control subjects but had a similar slope (Fig. 3), indicating that the tone or set point was upregulated, whereas phasic responses occurred normally. It should be stressed that the obese subjects all had normal glucose tolerance (Fig. 1 and Table 1). In subjects with glucose intolerance, β-cell glucose sensitivity would have likely been depressed (35). Conversely, our results demonstrate that glucose tolerance is maintained even in severely obese insulin-resistant subjects as long as β-cell glucose sensitivity is preserved regardless of the secretory stress imposed on the endocrine pancreas. Whether the ability of an essentially normal β-cell to cope with extreme demands would be eventually compromised with long duration of obesity (i.e., whether bona fide exhaustion would ever occur) remains an untested possibility.

Third, biliopancreatic diversion, a predominantly malabsorptive type of surgery, caused profound and sustained weight loss over a 2-year period (by reducing fat mass by 50% and FFM by 25%). By this time, subjects were only moderately obese, a therapeutic result that other interventions rarely achieve (36). Strikingly, at 6 months postoperatively, all insulin parameters—clearance, action, and secretion—were already normalized despite an average BMI of 39 kg/m². Even more dramatically, at 2 years postsurgery, insulin sensitivity was better than normal, while insulin output was even lower than in the control

TABLE 4
Effect of weight loss on parameters of insulin secretion

| | Baseline | 6 months | 2 years | P_1 | P_2 | P_3 |
|---|--------------|-------------|-------------|-------|-------|-------|
| Insulin sensitivity (µmol · min ⁻¹ · kg _{FFM} ⁻¹) | 23.0 ± 0.9* | 51.6 ± 3.7 | 68.7 ± 3.3° | 0.01 | 0.01 | 0.04 |
| Mean 24-h insulin (pmol/l) | 347 (153)* | 77 (58) | 58 (19)* | 0.02 | 0.02 | 0.04 |
| Insulin clearance (ml · min ⁻¹ · m ⁻²) | 669 (356)* | 1,554 (620) | 1,794 (667) | 0.02 | 0.03 | NS |
| Hepatic fractional insulin extraction | 0.08 (0.38)* | 0.65 (0.15) | 0.62 (0.23) | 0.02 | 0.02 | NS |
| 24-h insulin output (nmol) | 427 (324)* | 282 (213) | 167 (37)* | 0.02 | 0.01 | 0.05 |
| Nocturnal insulin output (nmol) | 209 (92)* | 129 (49) | 61 (24)* | 0.01 | 0.01 | 0.03 |
| β-Cell glucose sensitivity (pmol · min ⁻¹ · mmol ⁻¹ · l ⁻¹) | 192 (231) | 66 (183) | 208 (279) | NS | NS | NS |
| Rate sensitivity (nmol · mmol ⁻¹ · l ⁻¹) | 0.8 (1.7) | 0.6 (1.4) | 1.2 (2.3) | NS | NS | NS |
| Potentiation factor (day-to-night ratio) | 1.7 (0.7) | 1.5 (0.3) | 1.3 (0.3) | NS | NS | NS |

Data are means ± SE or median (interquartile range). P_1 = 6 months vs. baseline, P_2 = 2 years vs. baseline, and P_3 = 2 years vs. 6 months. * P ≤ 0.05 vs. control subjects.

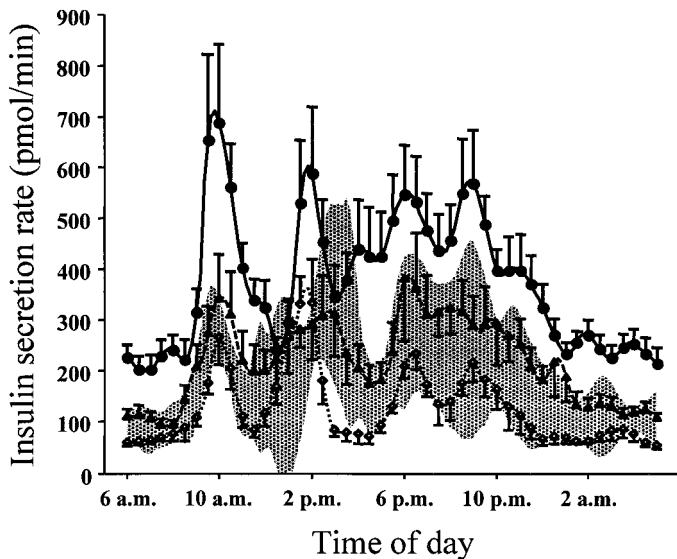


FIG. 4. Twenty-four-hour profile of insulin secretion rates in eight morbidly obese patients undergoing biliopancreatic diversion at baseline (●) and 6 months (▲) and 2 years postoperatively (◇). The shaded area reproduces the means \pm SD of the control subjects.

group. This new clinical phenotype, anthropometrically obese but metabolically supernormal, has been ascribed to the selective depletion of intramyocellular fat induced by lipid malabsorption (19). In contrast, with diet-induced weight loss (37) or following predominantly restrictive surgery (38), insulin sensitivity has been shown to improve in rather precise proportion to the weight loss. Insulin sensitivity, rather than insulin resistance, is a predictor of incident obesity (39–41). In Pima Indians with normal glucose tolerance, reduced insulin secretion is an additional independent predictor of weight gain (42).

Whatever the mechanism involved in insulin supersensitivity, in our subjects insulin output consistently matched the degree of insulin sensitivity. In fact, when plotting nocturnal insulin output against insulin action, all study groups fell on the same regression line (Fig. 6). We

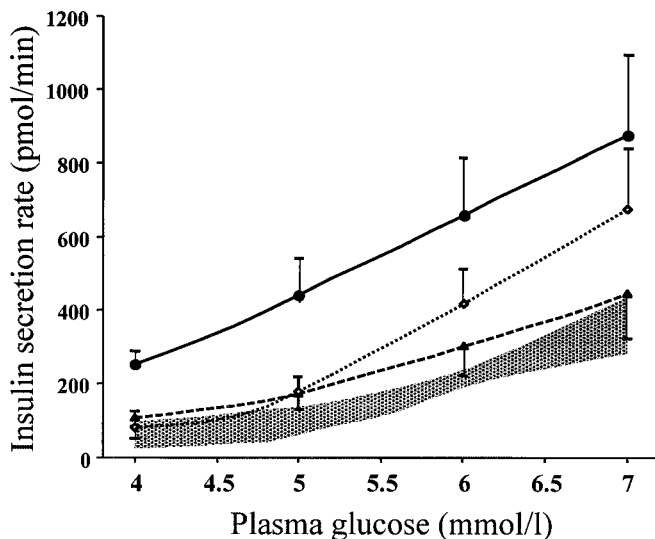


FIG. 5. Dose response of glucose-induced insulin secretion in eight morbidly obese patients undergoing biliopancreatic diversion at baseline (○) and 6 months (▲) and 2 years postoperatively (◇). The shaded area reproduces the means \pm SD of the control subjects.

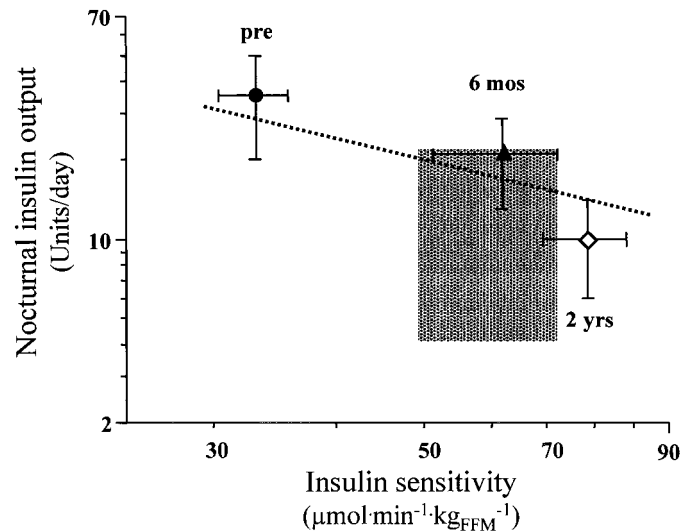


FIG. 6. Relationship between 24-h insulin output (median and interquartile range) and insulin sensitivity (means \pm SD) in the obese patients at baseline and 6 months and 2 years postoperatively. The shaded area plots the corresponding data for the control group, and the dotted line is the fitting function ($y = 241/x^{0.66}$, $r = -0.60$, $P < 0.0001$) of the entire dataset ($n = 43$).

interpret this result as evidence that insulin resistance primarily controls nocturnal (i.e., basal) insulin secretion, which can be viewed as the closest index of the β -cell secretory set point. In contrast, β -cell glucose sensitivity was unrelated to insulin sensitivity across the different physiological states. In other words, the set point represents the compensatory adaptation of the β -cell to extant insulin resistance and adiposity. β -Cell glucose sensitivity, on the other hand, is an inherent property of the secretory machinery that is responsible for maintaining tolerance to acute glucose stimulation. In our study, β -cell glucose sensitivity was normal and basal insulin secretion was appropriate for insulin action under all circumstances explored (i.e., severe obesity and the postobese state that follows malabsorptive surgery).

Finally, at baseline, we found elevated plasma FFA concentrations in obese subjects throughout the 24-h test, despite their marked hyperinsulinemia. This finding was expected on the basis of previous evidence that the insulin resistance of obesity extends to lipolysis, resulting in unrestrained FFA release (43). At 6 months postsurgery, mean 24-h FFA concentrations were still higher than in control subjects, despite mean 24-h plasma insulin levels that were no longer different from control subjects. Two years after surgery, mean FFA concentrations were similar to those of control subjects in the face of significantly lower mean plasma insulin levels (Fig. 7A). This apparently paradoxical result can be explained by taking into account the size of the largest pool from which circulating FFAs originate (i.e., fat mass). Thus, when mean 24-h plasma FFA concentrations were normalized to the fat mass, all available measurements, basal and postsurgery together, fell on the same regression line (Fig. 7B). This relationship suggests that, under the circumstances of our protocol in each unit of body fat mass, FFA release is markedly restrained by the prevailing plasma insulin concentration; however, the presence of insulin resistance of lipolysis prevents maintaining normal FFA concentrations.



FIG. 7. A: Plot of mean 24-h plasma insulin concentration (median and interquartile range) and mean 24-h plasma FFA concentrations (means \pm SD) in the obese patients at baseline and 6 months and 2 years postoperatively. The shaded area plots the corresponding data for the control group. **B:** Relationship ($y = 43/x^{0.26}$, $r = -0.48$, $P = 0.002$) between mean 24-h plasma insulin concentration and mean 24-h plasma FFA levels normalized to the fat mass.

In summary, severe uncomplicated obesity is characterized by gross insulin hypersecretion, which is partly adaptive to insulin resistance and partly primary (i.e., inherent) in obesity itself. The dynamic properties of β -cell function are, however, intact, thereby preserving glucose tolerance. Malabsorptive bariatric surgery corrects both the insulin hypersecretion and the insulin resistance at a time when BMI is still high. With continued weight loss over a 2-year period, moderately obese subjects become supersensitive to insulin and, correspondingly, insulin hyposecretors.

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