β-Cell Function in Obesity
Effects of Weight Loss

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In nondiabetic subjects, obesity is associated with a modest expansion of β-cell mass, possibly amounting—according to the best available estimates—to 10–30% for each 10 kg of weight excess. Whether age of onset and duration of obesity, recent changes in body weight, and body fat distribution have any effect on β-cell mass in humans is unknown. Both fasting insulin secretion and the total insulin response to oral glucose have the following characteristics: *1*) they increase with BMI in an approximately linear fashion, *2*) both fat-free and fat mass are significant positive correlates, and *3*) BMI exerts a positive effect separate from that of insulin resistance (i.e., obesity may be a state of primary insulin hypersecretion). The mechanisms are currently unknown, though chronic small increments in plasma glucose may play a role. In contrast, dynamic properties of β-cell function, such as glucose sensitivity (i.e., dose-response function), rate sensitivity, and potentiation, do not appear to be substantially altered by the presence of obesity, body fat distribution, or insulin resistance as long as glucose tolerance is maintained. Weight loss, by diet or restrictive bariatric surgery, is associated with consensual decrements in insulin resistance and insulin hypersecretion. The latter, however, seems to be more persistent, suggesting that the postobese state may reproduce the primary insulin hypersecretion of the obese state. Malabsorptive bariatric surgery, in contrast, normalizes insulin sensitivity and abolishes insulin hypersecretion even before achievement of ideal body weight. Lipid-triggered messages from the gastrointestinal tract to the insulin target tissues and endocrine pancreas are the subject of intense investigation. *Diabetes* 53 (Suppl. 3):S26–S33, 2004

Obesity is the hyperinsulinemic state par excellence. Indeed, the very first human study simultaneously showing the presence of hyperinsulinemia and insulin resistance was conducted by Rabinovitz and Zierler (1) in the forearm of obese subjects. Since then, countless studies have documented the extent and circumstances of the hyperinsulinemia of obesity using a variety of experimental techniques. There are, nevertheless, still areas of significant uncertainty and gaps of knowledge that limit a full understanding of β-cell function in obesity. This review, while concisely summarizing what is well known, will try to focus on the less well known and the open questions.

β-CELL MASS IN HUMAN OBESITY

In rats, β-cell mass increases throughout the postweaning lifespan, closely matching the increment in body weight; both β-cell hypertrophy and hyperplasia contribute to the expansion of β-cell mass, although in different proportions in young and older animals (2). In humans, determining β-cell mass is methodologically difficult, particularly in postmortem material, and in vivo imaging and quantification of β-cell mass is not yet possible. A recent article reported careful histochemistry in postmortem specimens from subjects with or without diabetes (3). Among the nondiabetic subjects, 31 were obese (mean BMI = 37 kg/m^2) and 17 were lean (mean BMI = 23 kg/m^2), a difference equivalent to ~40 kg of body weight. In the obese, the relative (to the exocrine tissue) β-cell volume (which averaged 2% of whole pancreatic volume) was increased by ~50% in comparison with the lean. These latter subjects, however, had died at an older age than the obese ones (11 years on average). As a consequence of the loss of β-cells believed to occur with aging in both animals and humans (4,5), the excess β-cell mass of the obese may have been overestimated. In another study in Korean subjects, relative β-cell mass was directly related to BMI, increasing twofold between BMI 18 and 29 kg/m^2 (6).

With the proviso that data in humans are limited and not always of optimal quality, it may be concluded that in nondiabetic subjects obesity is associated with a modest expansion of β-cell mass, possibly amounting—according to the best available estimates—to 10–30% for each 10 kg of weight increment. Whether age of onset and duration of obesity, recent changes in body weight, and body fat distribution have any effect on β-cell mass in humans is

unknown. While single β-cell and whole islet volume appear to be rather constant across obesity and diabetes (3), whether β-cell mass expansion takes place by replication or neogenesis is uncertain; no data are available on the extent and time course of β-cell mass reduction after weight loss.

INSULIN SECRETION IN HUMAN OBESITY

In reviewing the available information on in vivo β-cell function in human obesity, a preliminary issue relates to the use of peripheral plasma insulin concentrations as indicators of insulin secretion. The vast majority of the published data pertaining to β-cell function are expressed as plasma insulin concentrations (7). Beside the problems posed by the variability and specificity (versus proinsulin and its split products) of insulin assays (8), circulating insulin concentrations are dependent on β-cell insulin release through insulin distribution into body fluids and clearance from plasma (9). In general, the total-body volume of distribution of the hormone does not appear to vary with the insulin secretion rate, whereas plasma insulin clearance (mostly via hepatic and renal degradation) can be regulated by the insulin concentration itself (i.e., it is a saturable process) and by insulin sensitivity of glucose uptake. With regard to the latter factor, it is well established that insulin-resistant subjects usually show a decrease in insulin clearance (10).

The fasting state. The rate of posthepatic insulin delivery in the fasting state (IDR) can be estimated as the product of fasting plasma insulin concentration and posthepatic insulin clearance; the latter can be calculated as the ratio of the exogenous insulin infusion rate and steady-state plasma insulin concentrations achieved during a euglycemic hyperinsulinemic clamp experiment (11). In the European Group for the study of Insulin Resistance (EGIR) database, in 1,233 subjects aged 18–80 years with a fasting plasma glucose <6.1 mmol/l and normal oral glucose tolerance (10), posthepatic insulin clearance decreases from lean subjects (body mass index [BMI] ≤25 kg/m², n = 613) to overweight subjects (BMI <30 kg/m², n = 428) to obese subjects (BMI <40 kg/m², n = 152) to morbidly obese subjects (BMI >40 kg/m², n = 40) (Fig. 1). This reciprocal relationship is not appreciably changed when data are adjusted for insulin resistance, itself a significant correlate of decreased insulin clearance. In the same groups of subjects, fasting plasma insulin concentrations and IDR rise quasilinearly with BMI (Fig. 1). Thus, peripheral hyperinsulinemia in obese subjects is the combined result of insulin hypersecretion and reduced insulin clearance. The latter may in part relate to hepatic insulin resistance (11) and in part be linked with the fatty liver that is prevalent in obese subjects (12,13).

From these data, it is interesting to calculate [by assuming a hepatic insulin extraction ratio of ~0.6 (11)] that, at the lower end of the distribution of IDR values in this cohort, there are lean subjects whose basal IDR extrapolated to 24 h is <10 units of insulin; at the other extreme, there are obese subjects who require at least 240 units of basal insulin to maintain glucose homeostasis. Over the BMI range 23–37 kg/m², basal IDR increases by 300%, a much larger change than that which can be accounted for by the 50–100% increase in β-cell mass found in obese
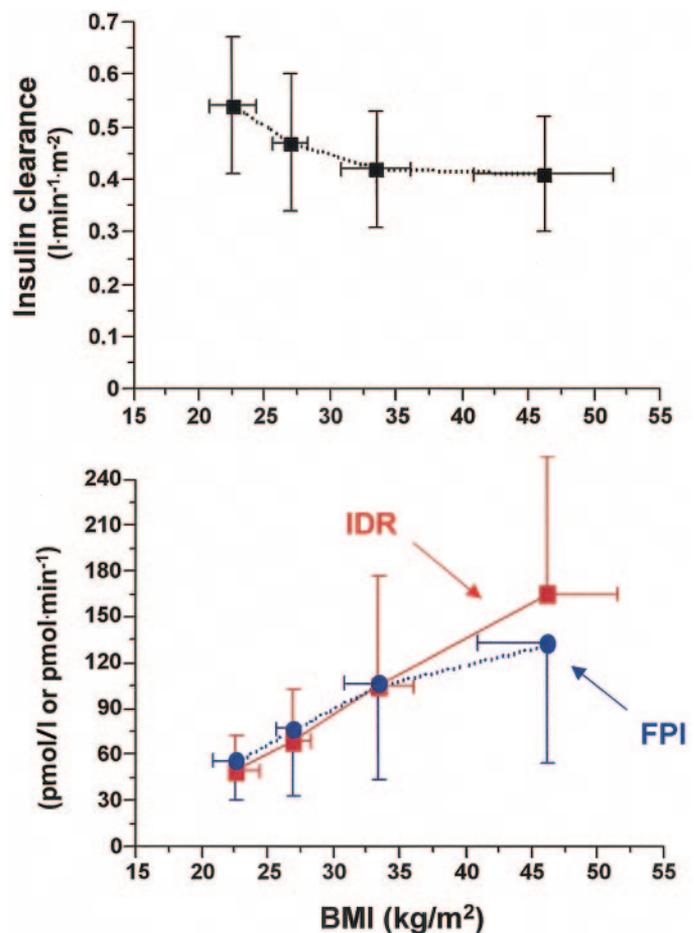

FIG. 1. Relationship between BMI and posthepatic insulin clearance rate (*top panel*) and fasting plasma insulin (FPI) concentrations and posthepatic IDR (*bottom panel*). Symbols plot the mean and standard deviation for lean subjects (BMI ≤25 kg/m², n = 613), overweight subjects (BMI <30 kg/m², n = 428), obese subjects (BMI <40 kg/m², n = 152), and morbidly obese subjects (BMI >40 kg/m², n = 40). Data from the EGIR database (5).

nondiabetic subjects at autopsy (3,6). This contrast clearly suggests that β-cell function, rather than β-cell mass, is the major physiological mechanism of adaptation of insulin secretion in humans.

Also of physiological interest is to determine which body mass compartment, fat mass (FM) or fat-free mass (FFM), is associated with fasting insulin release. As plotted in Fig. 2, both FM and FFM are significant correlates of IDR over the range of BMI (15–64 kg/m²) covered by the EGIR cohort. In a multiple regression model, IDR was independently related to both FFM and FM, increasing by 7 and 23 pmol/min for each 10 kg of FFM and FM, respectively. These relationships can also be viewed as the in vivo dose-response of the anabolic action of insulin on adipose and lean tissues.

A point of great interest is the extent to which the insulin hypersecretion of obesity is related to the insulin resistance present in this condition (14). In the EGIR subjects as a whole, IDR is reciprocally related to insulin sensitivity (as the M value from the clamp) in a curvilinear fashion (the best fit being the power function: IDR = 359 · $M^{-0.5}$, $P < 0.0001$) (Fig. 3). However, when the same relationship is explored in the four BMI groups separately, the curves have somewhat different shapes and, more
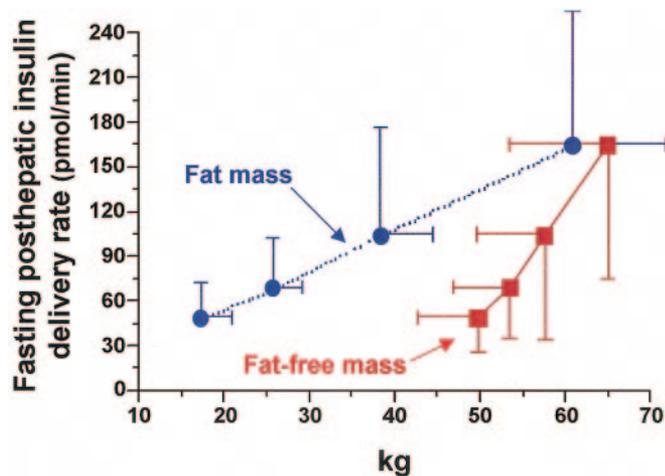
FIG. 2. Relationship between fasting posthepatic insulin delivery and FM and FFM in the groups of subjects of Fig. 1.

important, they shift upward and to left ($P < 0.0001$) in the transition from leanness to severe obesity (Fig. 4). Thus, for equivalent degrees of insulin resistance, subjects with different BMIs deliver different amounts of insulin to the systemic circulation in the fasting state. Applying multivariate analysis to these data, one calculates that IDR is independently related to both insulin sensitivity (reciprocally) and BMI (directly); the model predicts an increase in IDR of ~4 pmol/min for each unit of BMI increase or for each 10 μmol · min^{-1} · kg FFM^{-1} decrease in insulin sensitivity. This dual dependence is not modified by sex, age, or fasting plasma glucose concentrations in this nondiabetic cohort.

The application of decovolution analysis (initially used with insulin (15) to plasma C-peptide concentrations (16) and the validation of a standard plasma C-peptide disappearance function (17) has made it possible to reconstruct insulin secretory rates from peripheral C-peptide concentrations independently of insulin clearance. In a group of adult subjects with normal oral glucose tolerance and BMI values ranging from 21 to 39 kg/m^2 (personal data), fasting rates of pancreatic insulin secretion (ISR) averaged 157

FIG. 4. The relationship of Fig. 3 is here drawn separately for lean, overweight, obese, and morbidly obese subjects to show its progressive leftward shift with increasing BMI. Each line is the best fit (a power function) of the experimental data.

pmol/min (range 51–392); if maintained for 24 h, this rate would amount to a total insulin output ranging from 12 to 94 units (Fig. 5). As in the case of IDR, ISR was independently related to FFM and FM, increasing by 20 and 52 pmol/min for each 10 kg of FFM and FM, respectively. Moreover, fasting ISR was simultaneously related to BMI (directly) and insulin sensitivity (reciprocally) even after adjusting for fasting plasma glucose concentrations. The statistical model predicts an increase in fasting ISR of 12 pmol/min for each unit of BMI increase and of 20 pmol/min for each 10 μmol · min^{-1} · kg FFM^{-1} decrease in insulin sensitivity.

In summary, whether measuring posthepatic delivery or total release, insulin secretory activity in nondiabetic subjects in the fasting (postabsorptive) state has the following characteristics: *1*) it increases with BMI in an approximately linear fashion, *2*) both FFM and FM are significant positive correlates, and *3*) insulin resistance
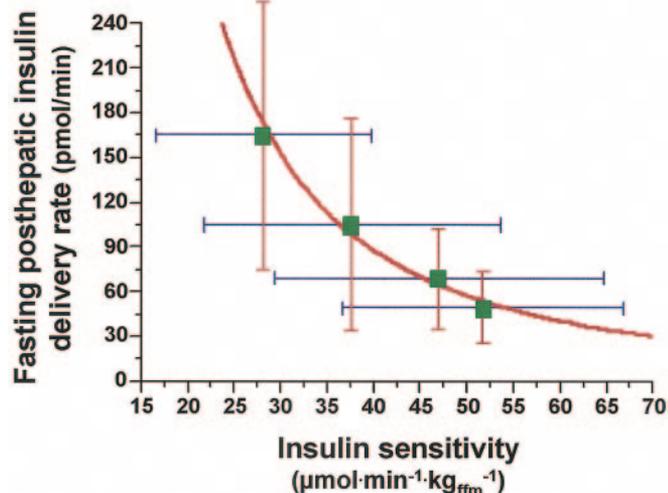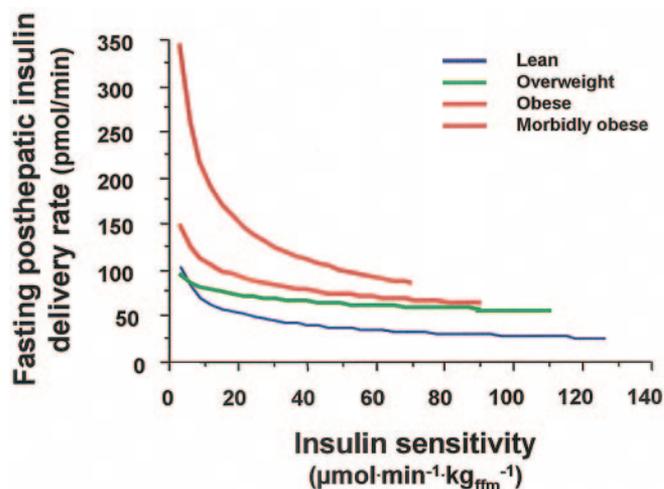

FIG. 3. Curvilinear reciprocal relationship between fasting posthepatic insulin delivery and insulin resistance (as measured by the euglycemic clamp technique) in the groups of subjects of Fig. 1.
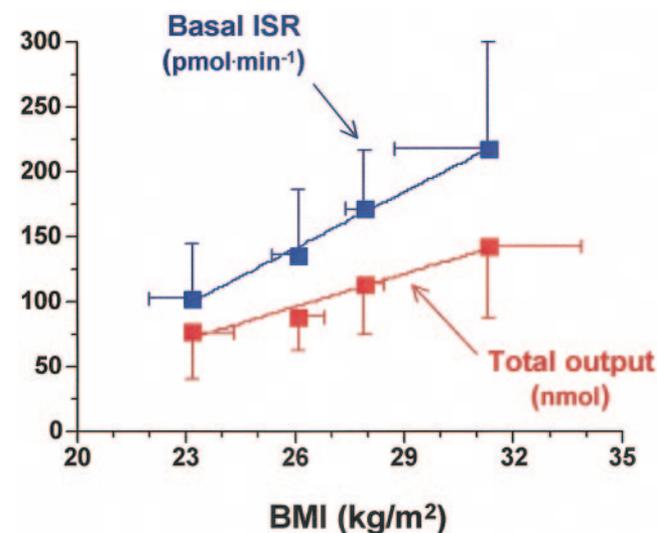

FIG. 5. Parallel relationship of fasting ISR (basal ISR) and total insulin output during the 2 h following an oral glucose load in nondiabetic subjects grouped in quartiles of BMI (personal data).
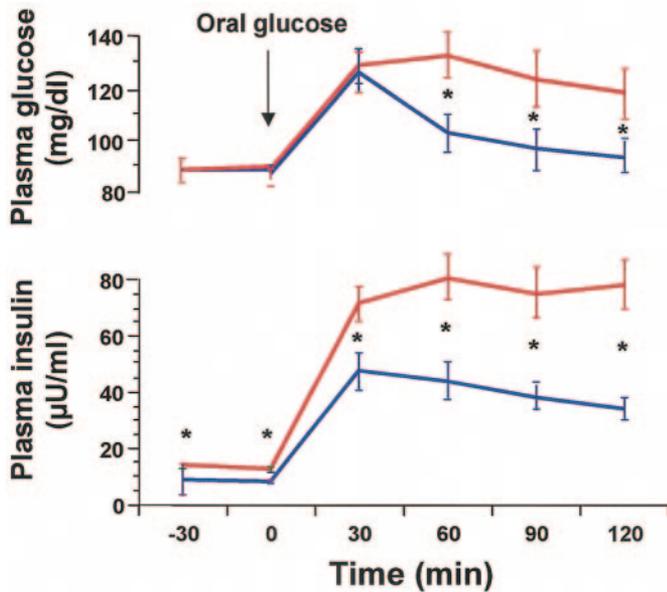
FIG. 6. Plasma glucose and insulin response to a 75-g oral glucose load in normotolerant lean (blue lines) and obese (red lines) subjects matched by age and sex (redrawn from ref. 18).

FIG. 7. Fasting and postinsulin plasma concentrations of FFAs in the subjects in Fig. 1 stratified by insulin sensitivity (redrawn from ref. 19).

exerts a positive effect separate from that of body mass and composition.

The messengers that signal to the β-cell the presence and extent of adiposity and/or insulin resistance remain unclear. Slight elevations in plasma glucose or free fatty acid (FFA) concentrations are plausible candidates, as both substrates have a stimulatory influence on β-cell function. In the EGIR subjects plotted in Figs. 1–4 (who, by selection, had fasting plasma glucose levels <6.1 mmol/l and oral glucose tolerance within the normal limits), fasting glucose did not differ between lean and obese subjects. One cannot, however, dismiss the possibility of minor hyperglycemia occurring repeatedly in the postprandial phase. Indeed, plasma glucose levels during the second hour following glucose ingestion usually are significantly, if slightly, raised in obese in comparison with lean individuals even when subjects are selected for having normal glucose tolerance by standard diagnostic criteria (e.g., Fig. 6) (18).

With regard to circulating FFAs, in the EGIR cohort plasma FFAs, either fasting or postinsulin (i.e., averaged over the last 40 min of a 2-h clamp), were raised in association with insulin resistance but not obesity per se (Fig. 7) (19). Thus, the mechanisms by which an expanding FM feeds back to the endocrine pancreas to increase β-cell mass and/or function remain elusive. Adipocytokines (leptin, adiponectin, tumor necrosis factor [TNF]-α, resistin, and others) are obvious candidates.

The fed state. By using the C-peptide deconvolution technique, the total amount of insulin released in response to a challenge (intravenous or oral glucose, mixed meal) can be measured. In nondiabetic lean subjects studied with hourly blood sampling during 24 h of free living (including three meals and a snack for a total of 30 kcal/kg body wt), 24-h insulin output averaged 136 nmol/m², corresponding to 40 units of insulin, of which 16 units were released during the 8-h nocturnal period (20). After an oral load of 75 g of glucose, total insulin output over the
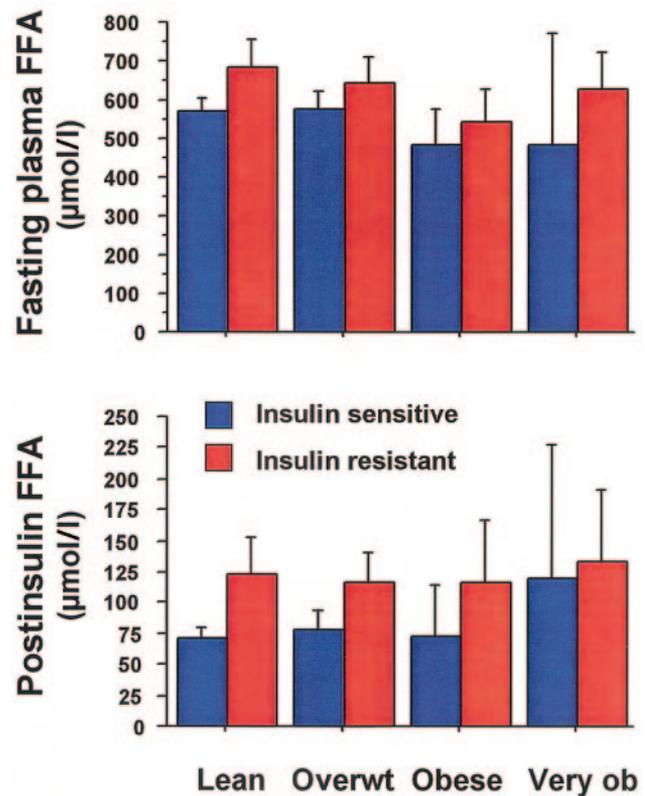
2 h following ingestion increases in linear proportion to BMI (Fig. 5), ranging 5–45 units (over the BMI range 21–39 kg/m²) and averaging six times the basal ISR. Again, total postglucose insulin output was independently related to both obesity and insulin resistance, the statistical model predicting an increase of 6 nmol for each unit of BMI increase and an increase of 16 nmol for each 10 μmol · min^{-1} · kg FFM^{-1} decrease in insulin sensitivity.

Thus, in nondiabetic subjects stimulated insulin output is proportional to basal insulin release (Fig. 8), suggesting that obesity and insulin resistance raise the set-point, or static control, of β-cell response to glucose.
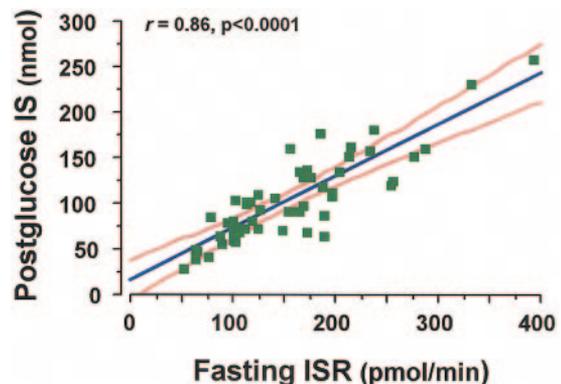

FIG. 8. Linear relationship between basal insulin secretion rate and total insulin output during the 2 h following oral glucose in normotolerant subjects with a BMI range of 21–39 kg/m² (personal data).
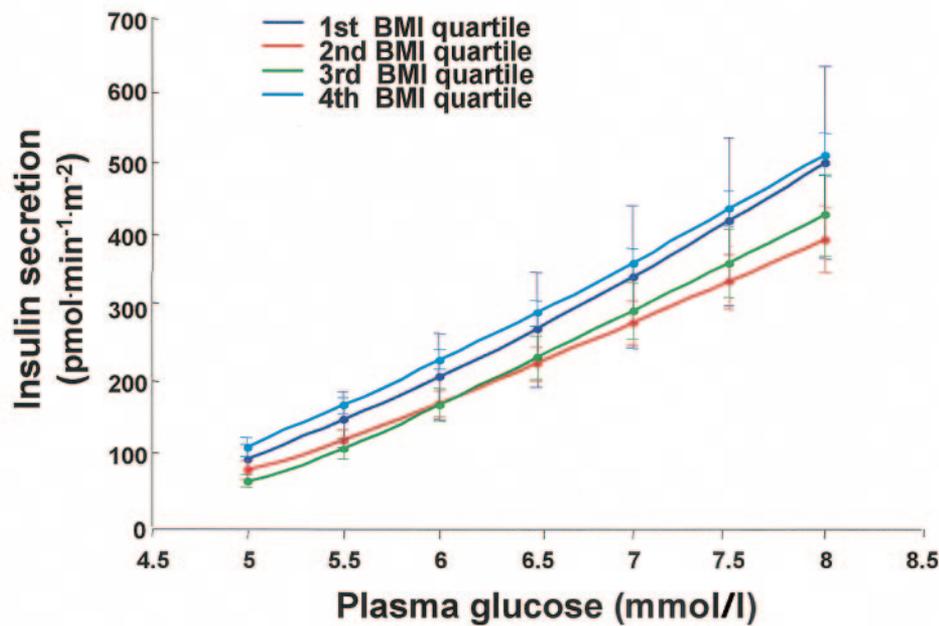
FIG. 9. Dose-response curves (derived by mathematical modeling [30]) in the subjects in Fig. 8 divided in quartiles of BMI.

β-CELL FUNCTION IN OBESITY

The preceding paragraphs have dealt with the impact of obesity on insulin secretion in absolute terms (i.e., the amount of hormone released in the fasting state or its total response to a stimulus). An important aspect of β-cell function is the ability to increase insulin release in appropriate amount and time course to cope with acute changes in plasma glucose concentration. This dynamic property of β-cell activity is controlled by several factors (mostly identified in perfused rat pancreas experiments [21,22]), among which three appear to have the closest in vivo equivalent: *1*) glucose sensitivity, or the dose-response function linking insulin release to plasma glucose levels; *2*) rate sensitivity, or the additional response to the rate of rise in glucose levels; and *3*) potentiation, i.e., the fact that the secretory response to any given plasma glucose level depends on previous glucose exposure as well as the potentiation of glucose-stimulated insulin secretion by incretins. These factors have been variably described and estimated with the use of mathematical models of β-cell function (23–29).

When a mathematical model developed from multiple meal studies (30,31) is used to estimate glucose sensitivity on the oral glucose tolerance test in the nondiabetic subjects shown in Fig. 5, no significant change in the slope of the dose-response (i.e., glucose sensitivity) is seen between subjects in quartiles of BMI (Fig. 9). This result is not changed when simultaneously adjusting for insulin sensitivity and glucose tolerance by multiple regression analysis. Likewise, rate sensitivity and the parameter accounting for the potentiation phenomenon do not differ between lean and obese subjects. Thus, the dynamic properties of β-cell function are not substantially altered by the presence of obesity or insulin resistance as long as glucose tolerance is normal.

It is of interest that, when the subjects in Fig. 9 are stratified by the median amount of visceral fat (as measured by multiscan magnetic resonance imaging) at the abdomen, those with visceral fat accumulation (1.4 kg on average) had lower insulin sensitivity and, consequently,

greater total insulin output in response to oral glucose than those with less visceral fat (0.6 kg on average). Nevertheless, glucose sensitivity was similar in the two groups (Fig. 10). Thus, abdominal visceral obesity is associated with an increase in absolute insulin response that is proportional to the degree of insulin resistance but not with an impairment in the dynamic properties of the β-cell.

EFFECTS OF WEIGHT LOSS

Weight loss is generally associated with an improvement in whole-body insulin sensitivity. In Pima Indians with normal glucose tolerance, spontaneous long-term (~2.5 years) changes in body weight have been found to be linearly associated with changes in insulin action (as measured by the euglycemic clamp technique) in a reciprocal manner (32). In that study, the observed changes in the acute insulin response (AIR) to intravenous glucose paralleled the changes in insulin sensitivity: weight loss led to a reduction in AIR, whereas weight gain was associated with an increased AIR. As mentioned in previous paragraphs, differences in insulin secretion are related to, among other factors, differences in insulin action in a quantitative fashion. However, whether the decrease in insulin secretion seen with weight loss is exactly matched to the improvement in insulin action is not clear from the available evidence. In a study in obese women with the polycystic ovary syndrome, Holte et al. (33) found that an average 15% weight loss achieved by diet over 15 months was associated with the expected increase in insulin sensitivity but little change in AIR. Likewise, in morbidly obese patients undergoing gastroplasty, Jimenez et al. (34) reported that the plasma C-peptide response to a hyperglycemic clamp was unchanged at a time after surgery when insulin sensitivity was normalized and insulin clearance was improved. A common paradigm to interpret changes in AIR in the light of changes in insulin action is to calculate their product, termed disposition index (35). Using this approach, Guldstrand et al. (36) recently re-
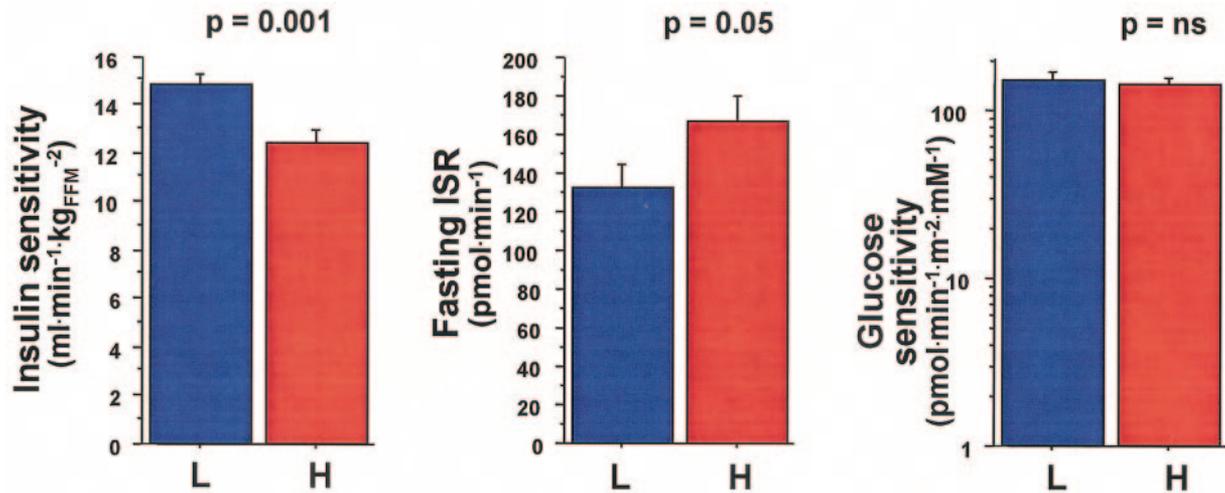
FIG. 10. Insulin sensitivity, fasting insulin secretion rate, and glucose sensitivity in subjects with low (L) or high (H) abdominal visceral fat mass (personal data).

ported that the disposition index increases over time as morbidly obese patients treated by gastroplasty lose up to 25% of their initial weight (Fig. 11).

These findings invite the following considerations. First, the fact that insulin secretion may not fall in proportion to the rise in insulin sensitivity with weight loss could be viewed as another manifestation of the primary insulin hypersecretion of obesity. In other words, the postobese state may, at least in some subjects, reproduce features of the preobese state, in which an innate hyperactivity of the β-cell response to feeding is the cause of weight gain rather then the consequence of achieved weight excess. In support of this possibility, findings of longitudinal studies, such as those in Pima Indians (37) and in the bi-ethnic population of the San Antonio Heart Study (38), show that weight gain is predicted by low fasting insulin concentrations and good insulin sensitivity rather than fasting hyperinsulinemia or insulin resistance. Of interest in this respect is the observation that pharmacological inhibition of β-cell activity in obese rodents dose-dependently reduces insulin secretion, food intake, and weight gain (39).

Second, the effects of weight reduction described in this article only apply to subjects with normal glucose tolerance. In obese patients with type 2 diabetes, weight loss is followed by an increase in insulin sensitivity and an increase, rather than a decrease, in β-cell activity (40). Because weight loss is invariably associated with improved glycemic control, the paradoxical rise in insulin secretion is commonly viewed as the result of removing the toxic effect of chronic hyperglycemia on β-cell function (41–43).

Third, caloric restriction may impact on β-cell function independently of weight loss. Thus, short-term (3–6 days) fasting in normotolerant subjects induces insulin resistance and a compensatory increase in the insulin response to oral glucose while in diabetic patients it reduces glucose levels and increases β-cell secretion (44). Likewise, in diabetic patients, 7 days of calorie restriction (800 kcal/day) produces approximately half of the increase in insulin sensitivity and insulin secretion that is obtained after a weight loss of ~13 kg by very low calorie diet (40).
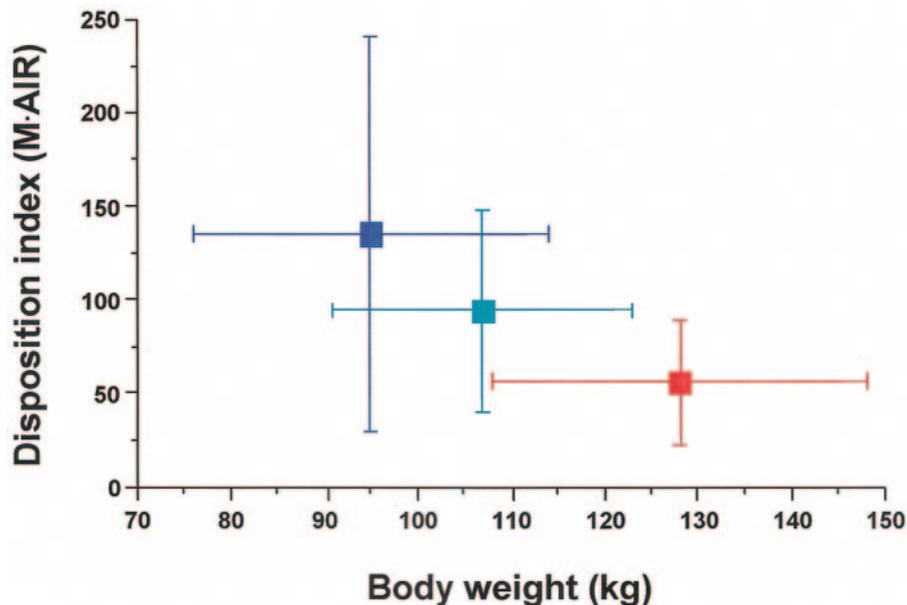

FIG. 11. Changes in the disposition index (acute insulin response × insulin sensitivity) in morbidly obese patients undergoing gastroplasty. Symbols plot the mean ± SD of values obtained at baseline, 6 months, and 12 months postsurgery. Redrawn from ref. 36.
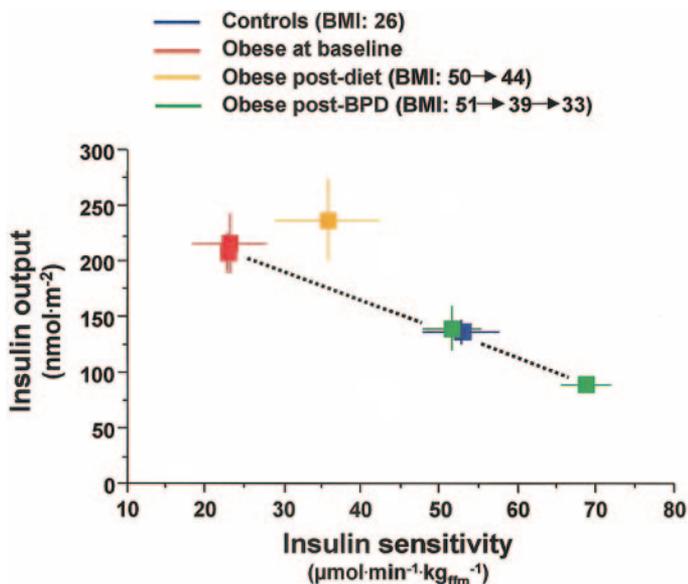
FIG. 12. Insulin secretion (as the total output in response to oral glucose) and insulin action (as the insulin-mediated glucose uptake during a euglycemic insulin clamp protocol) in severely obese patients at baseline (red squares), following weight loss by diet (orange square) or by biliopancreatic diversion (green squares). Data are means ± SEM. Redrawn from ref. 20.

Whether such a regulatory role of calorie restriction is also evident in obese nondiabetic subjects is not known.

Finally, the modality of weight loss may play a role of its own in the coordinated changes in insulin sensitivity and β-cell function. In fact, in severely obese patients (BMI ≥50 kg/m²) undergoing biliopancreatic diversion—a surgical technique that results in major lipid malabsorption—we observed (20) that insulin sensitivity was already normalized at a time when BMI was still elevated (39 kg/m²) and was actually higher than normal at a BMI of 33 kg/m². In contrast, patients losing weight by diet gained insulin sensitivity in predicted proportion to the weight lost. When plotting insulin secretion (as the total insulin output in response to oral glucose) against insulin sensitivity, once again the diet-treated patients showed evidence of insulin hypersecretion (i.e., insulin release out of proportion to the decrement in insulin sensitivity). In contrast, in surgically treated patients, insulin secretion declined exactly as predicted by the concomitant increase in insulin action (Fig. 12). Selective depletion of intramyocellular lipid depots has been documented in the skeletal muscle tissue of the patients treated with malabsorptive bariatric surgery (20). The signals traveling from the gastrointestinal tract to the insulin target tissues and, possibly, to the pancreatic islets under these circumstances are not known. It is intriguing to hypothesize that the secretion of incretin hormones may be differentially affected by manipulation of dietary lipids or restrictive/malabsorptive surgery and may impact on dietary lipid traffic and on the endocrine activity of adipose tissue. This remains an area of intensive investigation.

In conclusion, obesity is a condition of predominantly β-cell functional upregulation rather than β-cell expansion. This upregulation involves the static responses (i.e., basal and total secretion) much more than the dynamic responses (i.e., glucose sensitivity and potentiation), at

least as long as glucose-tolerant subjects are concerned. The insulin hypersecretion of obesity has a primary component, which cannot be explained by adaptation to insulin resistance and can be tracked through the period of weight loss (induced by calorie reduction or restrictive bariatric surgery). The residual insulin hypersecretion of the postobese (or weight-reduced) state may be the equivalent of an inherent insulin hypersecretion of the preobese condition. The intriguing observation that marked lipid malabsorption results in an obese phenotype with normal insulin sensitivity and insulin secretion points to complex cross-talking between the gut, the insulin target tissues, and the β-cell.

ACKNOWLEDGMENTS

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