β-Cell Function in Severely Obese Type 2 Diabetic Patients

Long-term effects of bariatric surgery

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Bariatric surgery in severely obese diabetic patients can restore glucose tolerance (1). Malabsorptive bariatric surgery (e.g., bilio-pancreatic diversion [BPD]) in nondiabetic subjects induces an improvement in insulin sensitivity that is greater than predicted by weight loss (2,3); such an effect can be demonstrated early after surgery (4). Impaired β-cell function is the main determinant of glucose intolerance, and modeling of C-peptide responses to graded glucose infusions (5) or oral glucose administration (6) makes it possible to estimate key dynamic parameters of β-cell function such as β-cell glucose sensitivity. The impact of bariatric surgery on β-cell function in diabetic subjects has been investigated using the intravenous glucose tolerance test (7). This test, however, can misjudge β-cell function as compared with more physiological challenges (such as the oral glucose tolerance test or mixed meals) because it explores only one specific aspect of islet function, namely the acute insulin discharge in response to a sudden maximal increment in plasma glucose concentrations (8). Recently, we have applied C-peptide–based modeling to reconstruct insulin secretion and β-cell function during a 24-h multiple-meal test (9). Here, we adopted this approach to analyze the long-term effects of BPD on glucose metabolism in morbidly obese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— We studied 10 morbidly obese (mean ± SE BMI 49.5 ± 2.9 kg/m^2), non–insulin-treated type 2 diabetic patients (3 men and 7 women) (age 50 ± 2 years) whose weight had been stable (±2 kg) for the preceding 6 months. Oral antidiabetic drugs were discontinued 1 week before the baseline studies. The study protocol was approved by the local ethics committee, and all subjects provided informed written consent to participate.

Following the baseline studies, patients underwent BPD, consisting of a partial gastrectomy with a distal Roux-en-Y reconstruction (2), and were restudied 24 ± 2 months postsurgery.

For the basal study, subjects spent 24 h (starting at 8:00 A.M.) in the metabolic ward. During this period, four meals were administered for a total caloric intake of 30 kcal/kg fat-free mass (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, and C-peptide concentrations. Body composition was evaluated by measuring total body water with the ^3H_2O technique (10). On another day, a 2-h euglycemic-hyperinsulinemic clamp (240 pmol/min per m^2) was performed (2). All procedures and measures were repeated in the follow-up study. Eight morbidly obese nondiabetic subjects (BMI 51.1 ± 2.8 kg/m^2), who were studied with the same protocol before surgery and 24 months after BPD, served as the control group; the complete data on these subjects have been reported (9).

Analytical procedures

Plasma glucose was measured by the glucose oxidase technique on a Beckman Glucose Analyzer (Beckman, Fullerton, CA). Plasma insulin was assayed by a specific radioimmunoassay (Linco Research, St. Charles, MO). C-peptide was assayed by radioimmunoassay (MYRIA; Technogenetics, Milan, Italy).

Modeling

The model used to reconstruct 24-h insulin secretion and its control by glucose has been previously described (11). In brief, it consists of a model for fitting the glucose concentration profile, a model describing the dependence of insulin secretion on glucose concentration, and a model of C-peptide kinetics, in which the model parameters are individually adjusted to the subject's anthropometric data (12). The dependence of insulin release on plasma glucose concentrations is modeled as the sum of two components. The first is the relationship between insulin secretion and glucose concentration, i.e., a dose-response function, whose mean slope (calculated over the individual-observed glycemic range) represents β-cell glucose sensitivity. The dose-response function is modulated by a time-varying factor, the potentiation factor, which encompasses glucose-induced potentiation, incretin potentiation, circadian rhythms, and pulsatility of insulin secretion, and was expressed here as the ratio of the daytime (fed state) to the nighttime (fasting state) value. The second component represents the dependence of insulin secretion on

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Abbreviations: BPD, bilio-pancreatic diversion.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Anthropometrics, glucose metabolism, and β-cell–function parameters in severely obese patients with type 2 diabetes pre- and postsurgery and in nondiabetic subjects postsurgery*

	Diabetic			Nondiabetic	
	Presurgery	*P**	Postsurgery	*P*†	Postsurgery
Body weight (kg)	136 ± 10	0.01	89 ± 4	NS	87 ± 4
BMI (kg/m^2)	49.5 ± 2.9	0.01	33.1 ± 2.2	NS	33.1 ± 2.8
Fat-free mass (kg)	80 ± 5	0.01	64 ± 3	NS	57 ± 5
Fat mass (kg)	56 ± 5	0.01	26 ± 3	NS	30 ± 5
Fasting glucose (mmol/l)	7.7 ± 0.9	0.03	5.1 ± 0.3	0.01	4.0 ± 0.4
A1C (%)	8.2 ± 0.6	0.01	4.1 ± 0.1	—	—
Mean 24-h glucose (mmol/l)	7.6 ± 0.8	0.03	5.3 ± 0.2	0.01	4.7 ± 0.4
M (μmol · min^{-1} · kg$_{FFM}^{-1}$)	26.4 ± 2.7	0.01	55.2 ± 2.1	0.01	68.7 ± 3.3
Fasting insulin (pmol/l)	154 (114)	NS	79 (65)	0.01	20 (20)
Mean 24-h insulin (pmol/l)	233 (182)	NS	136 (125)	0.001	58 (19)
24-h insulin output					
nmol/m^2	228 (83)	0.04	158 (76)	0.01	89 (11)
nmol	608 (214)	0.01	330 (159)	0.01	167 (37)
β-cell glucose sensitivity					
pmol/min per m^2/mmol/l	44 (32)	0.037	76 (89)	NS	65 (47)
pmol · min^{-1} · mmol/l^{-1}	99 (78)	0.1	160 (208)	NS	122 (98)
Rate sensitivity					
nmol/m^2 per mmol/l	0.45 (1.61)	NS	0.01 (0.17)	NS	0.59 (1.20)
nmol/mmol/l	1.3 (3.9)	NS	0.01 (0.4)	NS	1.2 (2.3)
Potentiation factor (day/night)	1.19 (0.40)	NS	0.85 (0.53)	0.02	1.37 (0.57)

Data are means ± SE or median (interquartile range) unless otherwise indicated. NS, not significant. *Presurgery versus postsurgery by Wilcoxon signed-rank test; †diabetic versus nondiabetic by the Mann-Whitney *U* test.

the rate of change of glucose concentration (rate sensitivity).

Data analysis

Data are given as means ± SE. Insulin parameters, which have a skewed distribution, are presented as median (interquartile range). Wilcoxon's signed-rank test was used to test treatment-induced changes, and the Mann-Whitney *U* test was used to compare groups. Bivariate regression was carried out by standard techniques, and the results were expressed as partial correlation coefficients.

RESULTS — Two years after BPD, patients had lost 47 ± 9 kg, of which ~2/3 was fat (Table 1). Fasting glycemia, A1C, and day-long glycemia were essentially normalized in all patients (Fig. 1 [available in an online appendix at http://dx.doi.org/10.2337/dc06-1845]), and none needed antidiabetic treatment. On the clamp, insulin sensitivity doubled, while fasting and mean 24-h plasma insulin and C-peptide concentrations were markedly, if not significantly, decreased. There was a 30% decrease in 24-h insulin output. The dose response of glucose-induced insulin release after surgery was shifted to the left and upward of that recorded before surgery (Fig. 2 of the online appendix), with a significant increase in the mean slope (Table 1). Potentiation and rate sensitivity were not significantly changed. In comparison with nondiabetic subjects studied 2 years postsurgery with an identical protocol (Table 1), diabetic patients had attained similar body weight and composition, but their fasting and mean plasma glucose and insulin concentrations and 24-h insulin output were still higher (Fig. 1 of the online appendix); insulin sensitivity was slightly, if significantly, lower, but β-cell glucose sensitivity was similar (Fig. 2 of the online appendix).

In the pooled pre- and postsurgery data, mean 24-h glucose was reciprocally related to β-cell glucose sensitivity in a nonlinear fashion ($y = 21 \times x^{-0.31}$, $r = -0.74$, $P < 0.001$). In a multivariate model, treatment-induced changes in 24-h glucose were independently related both to the increase in β-cell glucose sensitivity (partial $r = 0.93$, $P < 0.001$) and to the increase in M (partial $r = 0.71$, $P < 0.001$).

CONCLUSIONS — Two years after malabsorptive surgery, our patients were still obese (BMI 33.1 ± 2.2 kg/m^2), but their glucose tolerance was back to normal as a result of major changes in both insulin sensitivity and β-cell glucose sensitivity. The notion that bariatric surgery can restore glucose tolerance in the majority (over 75%) of severely obese patients is well established (1). Also established is the fact that bariatric surgery leads to a large improvement in insulin sensitivity, which can be detected early after surgery before any substantial weight loss has occurred (4,13,14). Less information is available on the changes in β-cell function and their time course. Morbid obesity per se is associated with profound insulin resistance and marked insulin hypersecretion, but the dynamics of β-cell function, i.e., β-cell glucose sensitivity, rate sensitivity, and potentiation, are preserved (9). Overt diabetes and impaired glucose tolerance, on the other hand, are characterized by a progressive loss of β-cell glucose sensitivity independent of insulin resistance (6). Polyzogopoulou et al. (7) reported improved first-phase insulin response to intravenous glucose 1 year postsurgery. Here, we show that β-cell glucose sensitivity had fully recovered 2 years postsurgery, despite a fall in absolute insulin secretion, and was quantitatively responsible for re-

stored glucose tolerance during free living regardless of the amount of weight lost. Interestingly, equally obese but nondiabetic subjects studied at the same time distance from surgery showed lower plasma glucose levels and insulin secretion rates and higher insulin sensitivity (Table 1). Because at this time β-cell glucose sensitivity was similar in the two groups, the difference in daylong glycemia between nondiabetic and postdiabetic subjects must have been due to the 20% better insulin sensitivity (and, possibly, better potentiation) of the former versus the latter. Whether this finding is a trace of the inherent (obesity-independent) susceptibility to dysglycemia of postdiabetic subjects (predisposing them to relapsing glucose intolerance) remains to be decided by longer-term follow-up studies.

The mechanisms underlying the dramatic effects of malabsorptive surgery on insulin sensitivity and β-cell function are poorly understood. Because major weight loss achieved by predominantly restrictive bariatric surgery does not lead to the striking changes in insulin sensitivity and β-cell function observed with predominantly malabsorptive surgery (3), some specific consequence of BPD must be involved. Candidate mechanisms span from depletion of intracellular fat depots (2) to attenuation of lipotoxicity to changes in the amount and pattern of gastrointestinal hormonal and neural signals triggered by the new route of food transit (15). This surgical modality certainly represents a very useful tool to gain insight into incretin physiology.

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