Restoration of Euglycemia and Normal Acute Insulin Response to Glucose in Obese Subjects With Type 2 Diabetes Following Bariatric Surgery

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Insulin resistance and loss of glucose-stimulated acute insulin response (AIR) are the two major and earliest defects in the course of type 2 diabetes. We investigated whether weight loss after bariatric surgery in patients with morbid obesity and type 2 diabetes could restore euglycemia and normal AIR to an intravenous glucose tolerance test (IVGTT). We studied 25 morbidly obese patients—12 with type 2 diabetes, 5 with impaired glucose tolerance, and 8 with normal glucose tolerance (NGT)—before and after a biliopancreatic diversion (BPD) with Roux-en-Y gastric bypass (RYGBP). Twelve individuals with normal BMI served as control subjects. Twelve months after surgery, in the diabetes group, BMI decreased from 53.2 ± 2.0 to 29.2 ± 1.7 kg/m^2, fasting glucose decreased from 9.5 ± 0.83 to 4.5 ± 0.13 mmol/l, and fasting insulin decreased from 168.4 ± 25.9 to 37.7 ± 4.4 pmol/l (mean ± SE; $P < 0.001$). AIR, the mean of insulin concentration at 2, 3, and 5 min over basal in the IVGTT, increased by 770 and 935% at 3 and 12 months after surgery, respectively (from 24.0 ± 22.7 to 209 ± 43.4 and 248 ± 33.1 pmol/l, respectively; $P <$ 0,001). Conversely, in the NGT group, the AIR decreased by 40.5% (from 660 ± 60 to 393 ± 93 pmol/l; $P =$ 0.027) 12 months after surgery. BPD with RYGBP performed in morbidly obese patients with type 2 diabetes leads to significant weight loss, euglycemia, and normal insulin sensitivity; but most importantly, it restores a normal β-cell AIR to glucose and a normal relationship of AIR to insulin sensitivity. This is the first study to demonstrate that the lost glucose-induced AIR in patients with type 2 diabetes of mild or moderate severity is a reversible abnormality. *Diabetes* 52:1098–1103, 2003

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AIR, acute insulin response; BPD, biliopancreatic diversion; FFM, fat-free mass; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; QUICKI, Quantitative Insulin Sensitivity Check Index; RYGBP, Roux-en-Y gastric bypass.

Epidemiological studies have shown that obesity is a significant risk factor for type 2 diabetes and that 41% of morbidly obese patients have abnormal glycemic control (1). Insulin resistance is more pronounced in obese subjects with type 2 diabetes (2,3). It has been shown that progression from normal to impaired glucose tolerance and diabetes is associated with a reduction in insulin sensitivity and a progressive decrease of the acute insulin response (AIR) to glucose, which is lost at the onset of diabetes (4,5). Moderate weight loss following a hypocaloric diet can improve insulin action and secretion, but the effect is rather weak (6). Metabolic control has been shown to improve the defect of early insulin response only minimally or partially (3,7,8).

Individuals with morbid obesity and type 2 diabetes benefit from weight loss, as this allows better glycemic control and modifies the coexisting risk factors for coronary heart disease, namely hypertension, dyslipidemia, insulin resistance, sleep apnea, and other comorbidities that constitute the metabolic syndrome (9–15). Although weight loss can be achieved by low-calorie diet, exercise, behavior modification, and medical treatment, late weight gain has been an almost universal problem. Conversely Roux-en-Y gastric bypass (RYGBP) maintains a weight loss of ~33% of body weight for >10 years, a result associated with normalization of glucose levels in patients with impaired glucose tolerance (IGT) and type 2 diabetes, in the vast majority of the cases (1,9–16). It also normalizes insulin action and secretion in normal glucose tolerant subjects with morbid obesity (17,18). To our knowledge, there are no other antidiabetic therapies that can produce such effective and long-term glycemic control.

The purpose of the present study was to investigate whether weight loss after gastric bypass can correct the AIR to glucose in morbidly obese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects. Twenty-five patients with morbid obesity were included in the study: 12 with type 2 diabetes, 5 with IGT, and 8 with normal glucose tolerance (NGT) who underwent a biliopancreatic diversion (BPD) with RYGBP. All consecutive patients with diabetes and IGT who agreed to participate were included in the study. The patients with NGT were selected to match the other two groups with regard to BMI, age, and sex. Two of the diabetic patients were on oral hypoglycemic agents that were discontinued 1 month before evaluation, and the other patients had hyperglycemia in the fasting state. The

TABLE 1
Characteristics of the control subjects and the patients in the diabetes group

	Control subjects	Diabetes group			
		Preoperative	3 months	6 months	12 months
n	12	11	11	11	11
M/F	3/9	2/9			
Age (years)	36.8 ± 3.0	40.1 ± 2.5			
Weight (kg)	64.5 ± 3.0	143.3 ± 9.5	112.5 ± 7.0	94.9 ± 6.4	77.8 ± 4.5
BMI (kg/m^2)	22.3 ± 0.5	53.2 ± 2.0	41.7 ± 1.4	35.3 ± 1.6	29.2 ± 1.7
FFM (kg)		75.3 ± 2.9	65.5 ± 5.0	61.9 ± 5.5	55.1 ± 4.7
Fat mass (kg)		60.9 ± 2.9	45.6 ± 3.0	33.1 ± 2.5	22.6 ± 3.4
Fasting glucose (mmol/l)	4.7 ± 0.11 (4.2–5.3)	9.5 ± 0.83 (6.9–15.5)	5.1 ± 0.17 (4.2–5.9)	4.7 ± 0.13 (4.1–5.3)	4.5 ± 0.13 (3.9–5.1)
Fasting insulin (pmol/l)	44.4 ± 6.0	168.4 ± 25.9	55.3 ± 9.1	33.5 ± 6.1	37.7 ± 4.4
QUICKI	0.365 ± 0.007	0.278 ± 0.007	0.357 ± 0.015	0.396 ± 0.019	0.378 ± 0.011
1st phase insulin (pmol/l)	332.4 ± 39.6	24.0 ± 22.7	208.8 ± 43.4	261.8 ± 40.4	248.5 ± 33.1
2nd phase insulin (pmol/l)	207.0 ± 18.6	410.9 ± 57.1	235.9 ± 43.2	172.2 ± 30.2	127.6 ± 22.5

Data are means ± SE (range) unless otherwise indicated.

duration of diabetes ranged from 3 to 5 years. Six of the 12 diabetic patients, 4 of the 5 IGT patients, and 2 of the 8 NGT patients had first-degree relatives with a history of diabetes. The diagnosis of diabetes, IGT, or NGT was established by a 75-g oral glucose tolerance test (OGTT), according to the criteria of the American Diabetes Association (19), 1 month after the initial evaluation. Twelve subjects with normal OGTT and BMI, matched to the diabetes group for age and sex, served as normal control subjects. All subjects were asked to consume a diet rich in carbohydrates for 3 days before testing. The patients were in good health and gave informed consent before surgery. The basic characteristics of the patients are summarized in Tables 1 and 2. Only 11 of the 12 patients in the diabetes group are shown in Table 1; because one of the patients had fasting insulin levels 13.5 standard deviations above the mean of the group, her data were not included in the statistical analysis and are discussed separately.

Surgery. BPD with RYGBP was constructed with a gastric pouch 15 ± 5 ml, a biliopancreatic limb 150–200 cm, a common limb 100 cm, and an alimentary limb composed of the remainder of the small intestine (16). Cholecystectomy and appendectomy were performed in all patients. Postoperatively during the first month, the patients consumed a liquid diet of 600–800 kcal/day composed of 50% carbohydrates, 30% protein, and the remainder lipids. For the next 2 months, they consumed a regular diet of similar composition containing 1,000–1,200 kcal/day and increasing gradually to 1,500–2,000 kcal/day during the 1st year.

AIR to glucose. Intravenous glucose tolerance tests (IVGTTs) were carried out preoperatively and 3, 6, and 12 months postoperatively. At 8:00–9:00 A.M, after a 12-h overnight fast, blood samples were collected at −10 min, immediately before the infusion of 35 g glucose (35% wt/vol, over 2 min), and 2, 3, 5, 10, 20, and 30 min after the end of glucose infusion. The first phase of insulin or acute insulin response was calculated as the difference (Δ) of the mean insulin concentration at 2, 3, and 5 min minus the mean insulin concentration at –10 and 0 min of the test.

Insulin sensitivity. The Quantitative Insulin Sensitivity Check Index (QUICKI) was used to assess insulin sensitivity according to the formula 1/(log [fasting insulin] + log [fasting glucose]). This method of insulin sensitivity estimation is considered reliable and correlates very well with the hyperinsulinemic isoglycemic glucose clamp, especially in the obese population (r = 0.89) (20–22).

Body composition. The percentages of body fat (fat mass) and fat-free mass (FFM) were determined by bioelectrical impedance (TANITA Body Composition Analyzer, Tokyo, Japan).

Assays. Serum glucose was assayed by the glucose oxidase method within 1 h of sample collection, using an automatic analyzer (Olympus, AU640, Medicon). Serum samples were stored at −40°C until they were assayed for insulin by a micro particle enzyme immunoassay (Abbott IMX System, Dainabot, Tokyo, Japan). This assay is specific for insulin and does not recognize proinsulin. Intra- and interassay coefficients of variation were 3.1 and 3.8%, respectively, and the sensitivity of the method was 6.0 pmol/l.

Statistical analysis. Student's t test was used for parametric and Mann-Whitney U test for nonparametric evaluation of differences between groups. Paired t test was used for evaluation of differences between time points within the same group during the follow-up. Statistical significance was set at $P < 0.05$.

RESULTS

Preoperatively. The three groups with morbid obesity had similar BMI, which was higher than that of the control group ($P < 0.01$). Fat mass and FFM were also similar among the three surgical groups (Tables 1 and 2). The diabetes group had a higher waist-to-hip ratio than the NGT group, but it did not reach statistical significance (0.962 ± 0.029 vs. 0.880 ± 0.028, $P = 0.07$).

The diabetes and IGT groups had higher fasting serum glucose ($P < 0.01$) and higher fasting plasma insulin concentrations ($P < 0.05$) than the NGT and control groups (Tables 1 and 2). The NGT group had higher fasting insulin ($P < 0.05$) but similar fasting glucose to that of control subjects. Insulin sensitivity, as expressed by the QUICKI, was reduced in the three surgical groups compared with control subjects ($P < 0.005$), but the NGT group was less insulin resistant than the diabetes and IGT groups ($P < 0.001$) (Tables 1 and 2).

AIR was absent in 8 of the 11 subjects in the diabetes group and substantially reduced in the other 3 subjects (Table 1, Fig. 1*A*). The IGT group had a reduced response ($P < 0.001$) (Table 2, Fig. 2). When AIR was plotted against insulin sensitivity in either group and was compared with the control group (Fig. 3), it was noted that AIR was very diminished for the degree of insulin resistance in the IGT group and virtually absent in the diabetes group. In contrast, the NGT group had two times greater AIR than control subjects ($P = 0.001$) (Table 2, Fig. 2), but this response was appropriate for their insulin resistance (Fig. 3).

The second phase of insulin secretion, calculated as the mean of the total insulin concentration at 10, 20, and 30 min or as the area under the curve, was greatly increased (~200%) in all surgical groups compared with control subjects ($P < 0.05$, Tables 1 and 2).

Postoperatively. Four and two of the eight patients in the NGT group missed their 3-month and 6-month appointments, respectively. All patients were studied 12 months postoperatively. Body weight decreased significantly in all patients. All surgical groups showed similar decreases in BMI (24 kg/m^2 for the diabetes, 21.5 for the IGT, and 18.2 for the NGT group) at the end of the 1st year (Tables 1 and 2). The decline of BMI was greater during the first 3

TABLE 2
Characteristics of the patients in the IGT and NGT groups

	IGT group				NGT group			
	Preoperative	3 months	6 months	12 months	Preoperative	3 months	6 months	12 months
n	5	5	5	5	8	4	6	8
M/F	0/5				0/8			
Age (years)	37.8 ± 4.3				34.1 ± 3.3			
Weight (kg)	125.7 ± 10.5	96.6 ± 9.1	83.5 ± 9.3	74.4 ± 7.8	124.9 ± 6.2	100.7 ± 5.2	88.4 ± 5.0	77.9 ± 4.8
BMI (kg/m^2)	52.2 ± 3.7	39.8 ± 4.6	34.4 ± 4.8	30.7 ± 3.4	46.6 ± 1.8	36.7 ± 1.7	33.0 ± 1.9	28.4 ± 1.7
FFM (kg)	65.2 ± 4.5	61.1 ± 3.9	55.8 ± 3.5	54.5 ± 2.3	65.1 ± 2.5	57.8 ± 1.9	54.8 ± 1.6	55.6 ± 1.5
Fat mass (kg)	60.6 ± 7.0	35.3 ± 7.3	27.7 ± 8.0	19.8 ± 6.5	59.3 ± 4.0	43.0 ± 3.6	33.6 ± 3.7	22.3 ± 3.7
Fasting glucose (mmol/l)	6.1 ± 0.19 (5.6–6.6)	4.2 ± 0.29 (3.1–4.7)	4.4 ± 0.23 (3.7–4.9)	4.5 ± 0.30 (3.8–5.6)	4.9 ± 0.12 (4.3–5.4)	4.3 ± 0.16 (3.9–4.7)	3.9 ± 0.12 (3.5–4.3)	4.1 ± 0.08 (3.8–4.5)
Fasting insulin (pmol/l)	172.2 ± 17.4	48.0 ± 18.6	40.2 ± 13.8	49.2 ± 14.4	79.1 ± 13.6	45.7 ± 3.6	33.9 ± 7.7	34.6 ± 4.4
QUICKI	0.286 ± 0.005	0.378 ± 0.018	0.416 ± 0.034	0.377 ± 0.028	0.33 ± 0.007	0.360 ± 0.007	0.396 ± 0.015	0.385 ± 0.009
1st phase insulin (pmol/l)	276.0 ± 51.6	246.6 ± 55.2	392.4 ± 147.0	372.6 ± 87.0	659.6 ± 60.2	356.4 ± 23.3	428.8 ± 126.9	393.1 ± 92.8
2nd phase insulin (pmol/l)	532.2 ± 120.6	272.4 ± 87.0	246.6 ± 102.6	243.6 ± 78.6	429.3 ± 86.0	206.4 ± 36.6	237.9 ± 89.9	167.7 ± 40.9

Data are means ± SE (range) unless otherwise indicated.

months following surgery and continued to decline thereafter at a slower rate for the rest of the 1st year. All surgical groups also showed a significant and similar decrease in fat mass and FFM postoperatively (Tables 1 and 2), and there were no cases of hypoalbuminemia or other signs of malnutrition. The postoperative decrease in fat mass was proportional to the preoperative fat mass ($r = 0.91$, $P = 0.006$) in the diabetes group, but not in the other two groups.

All patients in the diabetes group had normal fasting glucose 3 months after the operation. Fasting plasma insulin concentration declined significantly in all groups during the early postoperative period and became normal 3 months after surgery (Tables 1 and 2). Insulin sensitivity improved quickly and became normal in all surgical groups after the 3rd postoperative month (Tables 1 and 2).

AIR was restored the 3rd postoperative month in all patients in the diabetes group and continued to improve further during the rest of the 1st year (Fig. 1*B–D* and Fig. 2). The IGT group also showed an improvement of AIR postoperatively (Fig. 2). In both groups, the relationship of AIR to insulin sensitivity that was displaced down and far to the left relative to the control group showed a dramatic shift and became normal (Fig. 3). Conversely, the exaggerated AIR in the NGT group decreased to normal levels in parallel with insulin resistance by the third postoperative month. AIR was similar in all groups 12 months after surgery (Fig. 2, Table 2). Increased second-phase insulin secretion declined gradually to control levels during the postoperative period in all groups and below control levels in the diabetes group ($P = 0.01$) (Tables 1 and 2).

One diabetic patient with preoperative BMI 46 kg/m^2, fat mass 56.1 kg, and fasting glucose 8.7–9.0 mmol/l had a fasting insulin concentration of 1,332 pmol/l, 13.5 SD above the mean of the diabetes group. Therefore, this patient was not included in the statistical analysis of the data, although inclusion of the patient did not modify the results. Three months after the operation, BMI was 36.3 kg/m^2, fat mass was 42.1 kg, fasting glucose was 4.2 mmol/l, fasting insulin was 88.2 pmol/l, and the absent AIR was above normal (670 pmol/l).

DISCUSSION

The BPD with RYGBP procedure was successful in all patients, and weight reduction was impressive, although the patients were still obese 1 year after the operation, with an average BMI 30 kg/m^2. There was a complete remission of diabetes in all cases and reappearance of a normal acute insulin response by the 3rd postoperative month. Insulin sensitivity also became normal within the same period, although the patients were still morbidly obese. The abnormal relationship of AIR to insulin sensitivity became normal. Finally, the greatly increased and prolonged second phase of insulin secretion returned to normal.

Our results confirm the findings of previous studies showing the control of diabetes in morbidly obese patients following BPD with RYGBP (9,11–14). This beneficial effect was evident from the early postoperative period, despite the presence of morbid obesity. Other studies had similar results concerning weight loss and improvement in insulin sensitivity in morbidly obese patients with normal

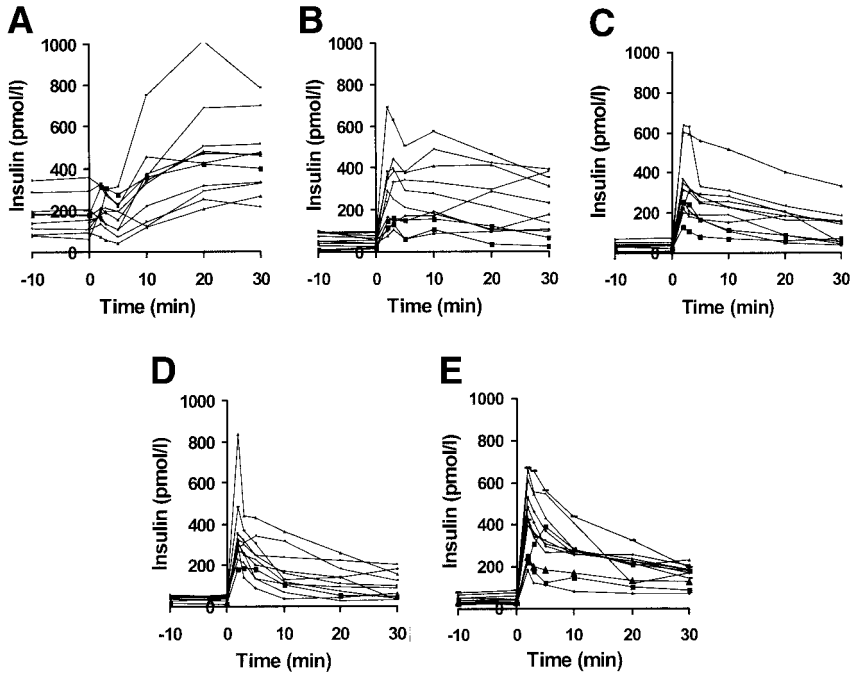

FIG. 1. Insulin response after intravenous glucose infusion (IVGTT) in normal control subjects (*E*) and patients with type 2 diabetes, before gastric bypass (*A*) and 3 months (*B*), 6 months (*C*), and 12 months (*D*) after gastric bypass.

glucose tolerance after bariatric surgery (17,23). In our patients, euglycemia was restored in parallel with the normalization of insulin sensitivity, the reappearance of a normal AIR to glucose, and the restoration of a normal relationship of AIR to insulin sensitivity.

Previous studies have shown that tight metabolic control restores minimally or partially the defect in the first phase of insulin response (7,8). Hughes et al. (24) have reported that in obese patients with type 2 diabetes subjected to Roux-en-Y gastrojejunostomy, the defect in insulin secretion did not improve with weight reduction, although insulin sensitivity did. The possible explanations for these discrepancies between our study and the findings of Hughes et al. (24) are the rather moderate weight loss in their study due to the different surgical procedure, the failure to restore euglycemia and normal insulin sensitivity, and finally, the more severe degree and longer duration of diabetes in their patients.

The preoperative findings in our study are consistent with the changes that occur during the transition from NGT to type 2 diabetes. The NGT group, although insulin resistant, maintained NGT by increasing the AIR proportionally to the degree of insulin resistance, and this is the feature that differentiates this group from the other two (25–28).

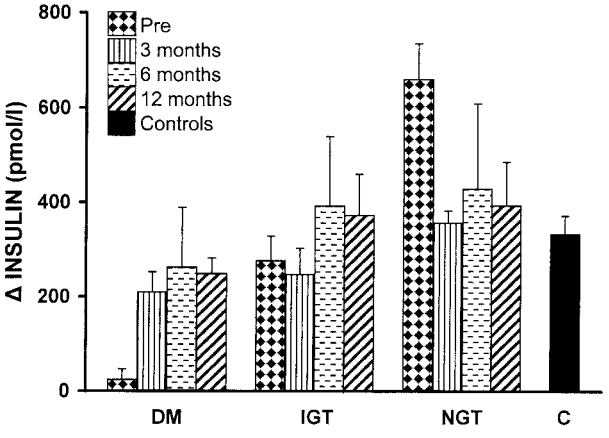

FIG. 2. Acute insulin response during IVGTT. The difference (Δ) in the mean insulin concentration at 2, 3, and 5 min over basal (mean ± SE) is plotted. C, control subjects; DM, diabetes mellitus group; Pre, preoperative.

In contrast, the IGT group had a decreased AIR for the degree of insulin resistance (Fig. 3). This is in agreement with previous studies (4,25–30). Impaired AIR normalized quickly after surgery in parallel with insulin sensitivity, although BMI was still high. It is reasonable to assume that the improvement in the first phase of insulin secretion followed the normalization of insulin sensitivity.

Finally, the diabetes group was the most insulin resistant, but AIR was absent. Because our diabetic patients had diabetes of rather mild to moderate severity, they maintained increased fasting insulin concentration and increased and prolonged second-phase insulin secretion, but they had lost the AIR to glucose. It has been shown that AIR to glucose is lost when fasting glucose concentration exceeds 115 mg/dl (4). It is also known that the β-cell at this stage of type 2 diabetes can respond to other secretagogues, such as glucagon or amino acids, and that the defect is specific to the glucose-induced AIR (3,26).

The relationship of AIR to insulin sensitivity was significantly altered in the IGT and diabetes groups relative to that in control subjects (Fig. 3), as previous studies have shown (27,28,30,31). This altered relationship became normal postoperatively, suggesting that this type of operation, namely BPD with RYGBP, not only normalized insulin sensitivity early after surgery, when the patients were still very obese, but also restored a normal AIR appropriate to the degree of insulin sensitivity. To our knowledge, no other therapeutic intervention has had such an effect so far.

Insulin resistance is inherited and is present many years before the onset of type 2 diabetes (3). Obesity, usually present in patients with type 2 diabetes, further increases

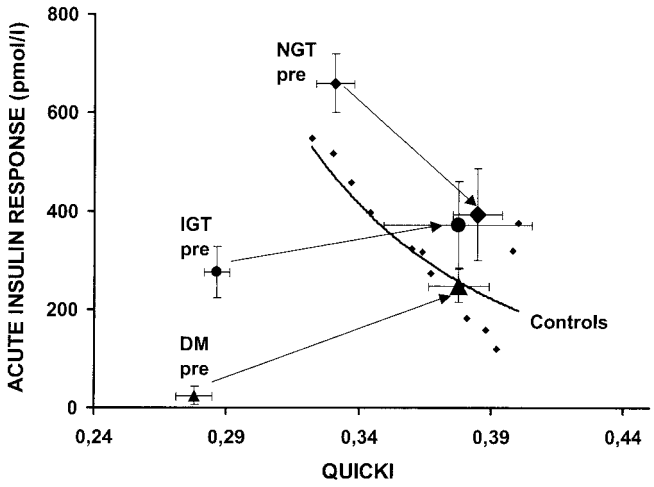

FIG. 3. Relationship between insulin sensitivity and acute insulin response in patients with morbid obesity and diabetes mellitus (DM), IGT, or NGT before and 12 months after BPD with RYGBP (mean ± SE), as compared with normal control subjects (curve). Pre, preoperative.

insulin resistance, which deteriorates with age, but diabetes develops only when the β-cell fails to compensate for the increased insulin demands (27,28). It has been shown that amelioration of insulin resistance after treatment with troglitazone can delay or prevent the onset of type 2 diabetes in Hispanic women at high risk for the development of type 2 diabetes (30). Protection from diabetes, in the same study, was closely related to the degree of reduction in endogenous insulin requirements and the preservation of β-cell compensation for insulin resistance.

In prospective studies it has been shown that normal glucose tolerant subjects with insulin resistance do not develop diabetes if they can increase insulin secretion, in particular the AIR, as insulin resistance deteriorates with time. Alternatively, the subjects who develop IGT and later diabetes exhibit an inappropriate progressive decrease in the AIR to glucose in the presence of increasing insulin resistance (27,28). A reduced AIR for the degree of insulin resistance has been shown in subjects at high risk for the development of type 2 diabetes, such as first-degree relatives of patients with type 2 diabetes, older subjects, women with a history of gestational diabetes or polycystic ovary syndrome (25–31). Insulin secretion, when expressed as an index normalized for insulin sensitivity, is a very useful trait for identifying genetic predisposition to type 2 diabetes (32). We observed that BPD with RYGBP normalized the altered relationship of AIR to insulin sensitivity that characterizes this category of subjects, and this change was probably crucial for the restoration of NGT in our patients.

The detailed mechanisms that lead to normalization of glucose tolerance and insulin secretion in our study are not entirely clear, however. BPD with RYGBP reduces the total caloric intake and particularly carbohydrate consumption in part due to dumping syndrome (33), leading to weight loss and reduction in insulin resistance. It also induces lipid malabsorption, reduces the elevated free fatty acids in the circulation, and therefore reduces their adverse effects on insulin action and secretion (34,35). Changes in ghrelin, glucagon-like peptide-1, enteroglucagon, and gastric inhibitory polypeptide secretion after BPD with RYGBP have also been shown to occur and may contribute to the same results (36–39). Changes in fat distribution after surgery, e.g., preferential loss of intra-abdominal and intramyocellular fat, have a major impact on insulin sensitivity (23). BPD with RYGBP increases IGF-I levels and lowers leptin and pancreatic polypeptide levels in morbidly obese patients with or without type 2 diabetes, as reviewed elsewhere (40). The restoration of normal insulin sensitivity in our morbidly obese patients 3 months after the operation alleviated the high burden imposed upon the β-cell and possibly played a central role in the restoration of the AIR, but it is also possible that changes in the enteropancreatic axis played a significant role.

In conclusion, our findings support the concept that the diminished AIR for the degree of insulin resistance is important for the development of IGT and diabetes. The lack of glucose intolerance in the severely obese and insulin-resistant NGT group that maintained an appropriately exaggerated AIR points in the same direction. Furthermore, our results show that the loss of glucose-induced AIR in obese patients with type 2 diabetes of mild or moderate severity is not permanent but reversible. Finally, the altered relationship of AIR to insulin sensitivity that characterizes subjects with diabetes or IGT or subjects at high risk for the development of type 2 diabetes becomes normal and suggests that this type of surgical operation can be of value in these groups of patients, even in the presence of milder degrees of obesity.

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