Acute Postchallenge Hyperinsulinemia Predicts Weight Gain

A Prospective Study

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The relationships of insulin secretion and insulin action to body weight are incompletely understood. Obesity is associated with reduced sensitivity to insulin and high fasting and postprandial serum insulin levels. However, it is unknown whether insulin secretion rises to compensate for insulin resistance or high insulin secretion promotes body weight gain and the development of insulin resistance. To shed light on this question, we examined weight gain over an interval of 16.7 ± 3.9 years (mean ± SD) in 107 glucose-tolerant offspring (48 men, 59 women) of two parents with NIDDM. The offspring had a baseline intravenous glucose tolerance test, at which time they were aged 32.9 ± 9.7 years, and only those who did not develop diabetes during the follow-up period were included. We estimated insulin sensitivity with the insulin sensitivity index from Bergman's minimal model of glucose disposal and acute insulin secretion from the incremental area under the insulin curve in the first 10 min of the intravenous glucose tolerance test. Weight-gain rate (g/year) was defined as the regression slope of each subject's body weight over time. High acute insulin secretion, young age, and low baseline percent ideal body weight (IBW) were each associated with a high rate of weight gain. After adjustment for differences in age and IBW, statistically significant effects of insulin sensitivity ($P = 0.05$) as well as acute insulin secretion ($P = 0.001$) were obtained. To estimate the effects of acute insulin secretion and insulin sensitivity on the average rate of weight gain (adjusting for age and IBW), the study group was stratified into four subgroups by dividing it at the medians of these two variables. Among those with low acute insulin secretion, weight-gain rate was the same regardless of whether insulin sensitivity was low or high (176 and 152 g/year, respectively). Among those with high acute insulin secretion, mean weight-gain rate was still rather low in those with low insulin sensitivity (271 g/year), but it was quite high in those with high insulin sensitivity (672 g/year; significantly higher than in all other subgroups). Therefore a high first-phase insulin response to intravenous glucose is a risk factor for long-term weight gain, and this effect is particularly manifested in insulin-sensitive individuals. *Diabetes* **46:1025–1029, 1997**

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Received for publication 9 October 1996 and accepted in revised form 24 January 1997.

GTT, glucose tolerance test; IBW, ideal body weight; VMH, ventromedial hypothalamus.

The relationships of insulin secretion and insulin action to body weight are incompletely understood. Overweight adults are typically hyperinsulinemic and resistant to insulin-mediated glucose uptake (1). It is often assumed that the hyperinsulinemia found in these adults is secondary to their insulin resistance, but certain evidence suggests that hyperinsulinemia may cause insulin resistance. For example, intravenous infusion of insulin into humans over a 40-h interval produced insulin resistance (2). Evidence also comes from a cross-sectional study of obese children (3). Those with short-duration obesity (<4.5 years) had normal insulin sensitivity and insulin levels that were high postprandially but not in the fasting state; in contrast, those with longer-duration obesity had low insulin sensitivity and insulin levels that were high in both the fasting and postprandial states, just like many obese adults (3). Thus it appears that an excessive insulin response to food may have preceded the appearance of insulin resistance.

In randomized clinical trials in humans, treatment with insulin or with an insulin secretagogue (a sulfonylurea) leads to weight gain (4–8) and increased fat deposition (7). The largest trial in type II diabetes was a study in the United Kingdom in which subjects were randomized to four alternative treatments: glibenclamide (a sulfonylurea), insulin, metformin (an agent that increases insulin sensitivity but not insulin secretion), and diet alone. Mean weight gain between years 1 and 6 after randomization was 6 kg on the sulfonylurea, 4 kg on insulin, and 1 kg on metformin or diet alone (4,5). The level of glycemic control in the groups on metformin, insulin, and sulfonylurea was equal, so differences in glycemic control could not account for the differences in weight gain. Weight gain was also shown to be a side effect of insulin therapy in patients with type I diabetes enrolled in the Diabetes Control and Complications Trial; patients randomized to intensive therapy with multiple daily insulin injections gained considerably more weight than those randomized to conventional insulin therapy (9).

In laboratory studies, short-term insulin infusion into normal human subjects induces hunger and carbohydrate crav-

ing even when hypoglycemia is prevented (10). Thus an acute hyperinsulinemic response may be an early determinant of obesity and insulin resistance. To determine whether acute postchallenge hyperinsulinemia predicts subsequent long-term weight gain, we examined data from a long-term prospective study of offspring of parents with NIDDM (11,12).

RESEARCH DESIGN AND METHODS

Between 1963 and 1983, offspring of couples who both had type II diabetes mellitus were identified at the Joslin Diabetes Center, Boston, MA. As described previously (11,12), the offspring of these couples were recruited as participants in studies with the goal of identifying characteristic features of glucose and insulin metabolism that might predict the subsequent development of type II diabetes. After a 100-g oral glucose tolerance test (GTT) to detect undiagnosed diabetes, the nondiabetic offspring returned periodically for various glucose challenge tests. We selected the 155 offspring with normal glucose tolerance at baseline who underwent an intravenous GTT. Baseline oral GTTs were performed between 1964 and 1983, and for 95% of them the intravenous GTT was performed within 1 year of the oral GTT. For this analysis, we excluded from this group those who developed diabetes during follow-up (n = 25), because that event may have influenced weight gain. To determine whether exclusion of members of this group did not itself distort the findings, all analyses were repeated with them included. Verification of the absence of diabetes in the remaining 130 subjects was based on a normal oral GTT in 77.7%, normal fasting glucose in 17.7%, and normal postprandial blood glucose measurements in 4.6%. Height and weight were recorded whenever subjects returned for tests, and these data were supplemented with data obtained by questionnaire. Protocols for oral and intravenous GTTs and laboratory measurement of blood glucose and serum insulin have been described previously (11,12).

Acute insulin secretion was defined as the incremental area under the insulin curve in the first 10 min after intravenous injection of glucose and second-phase insulin secretion as the incremental area under the insulin curve between 10 and 120 min after glucose injection. The computer program MINMOD (13) was used to estimate two parameters of the minimal model of glucose disposal during an intravenous GTT (14). The first, the fractional clearance rate (10^{-2}/min) of glucose in the presence of basal insulin, is a measure of non–insulin-dependent glucose uptake. The second parameter is the insulin sensitivity index ($10^{-3} \cdot \text{min}^{-1} \cdot \text{pmol}^{-1} \cdot \text{l}$), which is a measure of the ability of an increase in serum insulin to increase the fractional clearance rate of glucose (14–16).

The outcome variable, rate of weight gain (g/year), was defined as the regression slope of weight over time. Associations with independent variables were examined by ANOVA and multiple regression (17). Percent ideal body weight (IBW) was estimated from the body mass index (weight/height^2) using the sex-specific conversion recommended by the National Diabetes Data Group (18). Fasting serum insulin and acute insulin response were transformed to the common logarithm. Hypoglycemia was defined as a blood glucose <3 mmol/l (<54 mg/dl). The analysis was limited to 107 of the 130 subjects. The reasons for exclusion were an inability to fit the data with the Bergman (14) model (n = 4) and a follow-up interval <8 years (n = 19). Data are presented as means ± SD unless otherwise stated.

RESULTS

Subject and follow-up data are summarized in Table 1. At baseline, age and body habitus ranged widely: from 16 to 59 years (mean 32.9 years) and from 81 to 233% of IBW (mean 121%), respectively. Follow-up time ranged from 8 to 24 years (mean 16.7 years), and the rate of weight gain varied from a loss of 1,145 g/year to a gain of 3,288 g/year (mean 279 g/year).

The rate of weight gain did not differ by sex but varied considerably with age and to some extent with percent IBW at baseline. Young subjects gained weight more rapidly than older ones. Average weight gain decreased 129 g/year with each decade of age (r = –0.20, P = 0.03) so that those in the oldest decade gained very little. Heavy subjects tended to gain weight less rapidly than lean ones, although the difference in slope was not statistically significant. For each 10% increase in percent IBW at baseline, the average rate of weight gain decreased 49 g/year (r = –0.15, P = 0.12).

TABLE 1
Subject characteristics and follow-up

	Baseline	End of follow-up
n	107	—
Sex (M/F)	48/59	—
Age (years)	32.9 ± 9.7	49.7 ± 10.5
Height (cm)	170 ± 11	170 ± 11
Weight (kg)	73.8 ± 17.8	79.1 ± 19.7
% ideal body weight	116 ± 19.6	125 ± 24.0
Length of follow-up (years)	—	16.7 ± 3.7
Number of visits	—	16.6 ± 12.1
Total weight gain (kg)	—	5.3 ± 10.4
Mean rate of weight gain (g/year)	—	279 ± 603

Data are means ± SD.

The results of univariate analyses of the rate of weight gain according to quartiles of the distribution of selected characteristics are summarized in Table 2. For insulin sensitivity, weight gain varied in a nonlinear manner across the quartiles, although the average weight gain in the two quartiles above the median was 40% faster than the average of the two below the median (P = 0.39). In contrast, weight gain increased steadily across quartiles of the distribution of acute insulin secretion (r = 0.21, P = 0.03). Subjects in the highest quartile of acute insulin secretion gained weight at almost three times the rate of the lowest quartile, and those in the middle two quartiles had intermediate rates of weight gain. Weight gain was completely unrelated to second-phase insulin secretion (r = 0.07, P = 0.45), fasting serum insulin (r = 0.09, P = 0.35), or glucose effectiveness (r = 0.06, P = 0.52).

To examine the effect of acute insulin secretion, adjusted for baseline differences in age and percent IBW, these variables were tested in a multivariate model as continuous variables. To see whether the effect of acute insulin secretion was dependent on the level of insulin sensitivity, the latter was included in the model. Based on preliminary analyses that its effect was limited to high values of insulin sensitivity, it was entered as an indicator variable for insulin sensitivity above its median value (Table 3). In this model, high insulin sensitivity (above the median) was associated with a 235 g/year greater weight-gain rate than low sensitivity, an effect that was just barely significant (P = 0.05). The evidence for the effect of the acute insulin response was much stronger (P = 0.001) than in the univariate analysis. To represent the effect of this continuous variable, we estimated the difference in weight-gain rate between the highest and lowest quartiles of the acute insulin response, approximately equivalent to a six-fold difference in response. The rate of weight gain (adjusted for insulin sensitivity, age, and IBW) in the highest quartile was 521 g/year greater than in the lowest quartile, double the difference obtained in the univariate analysis (Table 2). Addition of glucose effectiveness, fasting serum insulin, second-phase insulin secretion, and fasting and 2-h blood glucose did not improve the model's ability to explain the rate of weight gain.

To visualize the interdependence of the effects of acute insulin secretion and insulin sensitivity in the multivariate model, the study group was stratified into low and high by dividing the group at the medians of these variables. The

TABLE 2
Weight gain as a function of selected metabolic variables

	Weight gain rate (g/year)
Insulin sensitivity ($10^{-3} \cdot min^{-1} \cdot pmol^{-1} \cdot l$)	
<3.9	226 ± 567
3.9–6.94	232 ± 473
6.95–9.89	414 ± 905
≥9.9	248 ± 356
Acute insulin secretion ($pmol \cdot l^{-1} \cdot min^{-1}$)	
<1,872	151 ± 529
1,872–3,077	257 ± 458
3,078–4,799	294 ± 626
≥4,800	414 ± 762
Second-phase insulin secretion ($pmol \cdot l^{-1} \cdot min^{-1}$)	
<6,300	273 ± 548
6,300–10,019	252 ± 480
10,020–16,499	203 ± 618
≥16,500	380 ± 748
Glucose effectiveness (min^{-1})	
<1.55	240 ± 481
1.55–2.28	225 ± 513
2.281–3.016	186 ± 598
≥3.017	461 ± 774
Fasting serum insulin (pmol/l)	
<66	166 ± 521
66–84	323 ± 611
90–114	232 ± 400
≥120	374 ± 798

Data are means ± SD. Subjects are grouped by quartiles of each variable. Acute insulin secretion was calculated as the incremental area under the curve of serum insulin over the first 10 min of the intravenous GTT and second-phase insulin secretion as the incremental area under the same curve over minutes 10–120 of the intravenous GTT. Insulin sensitivity and glucose effectiveness were determined using Bergman's (14) minimal model.

TABLE 3
Multiple linear regression model to predict weight gain rate

Independent variables	Regression	P	R^2
Age (per decade)	–119	0.044	
% ideal body weight (per 10% change)	–67	0.036	
Insulin sensitivity (above median vs. below)	235	0.050	
Acute insulin secretion (per sixfold increase)	521	0.001	
Model (Root means square error = 564)		0.001	0.16

In this regression model, age and percent ideal body weight were represented as continuous variables, acute insulin secretion ($pmol \cdot l^{-1} \cdot min^{-1}$) was logarithmically transformed, and one unit corresponds to a 5.3-fold increase, i.e., the difference between the geometric means of the lowest and highest quartiles of acute insulin secretion. Insulin sensitivity was coded as an indicator variable: 1 for insulin sensitivity above the group median of 6.95×10^{-3} $min \cdot pmol^{-1} \cdot l^{-1}$, and 0 for insulin sensitivity below this value. Each of the four variables is a significant independent predictor of subsequent weight gain.

mean rate of weight gain for each group, adjusted for differences in age and percent IBW, are shown in Fig. 1. For subjects with low acute insulin secretion, weight gain was the same regardless of whether insulin sensitivity was low or high (176 or 152 g/year, respectively). In contrast, for subjects with high insulin secretion, weight-gain rate was strongly influenced by insulin sensitivity. The rate of weight gain was rather low if insulin sensitivity was low, but it was very high if insulin sensitivity was above the median (271 and 672 g/year, respectively). The rate of weight gain in the subgroup with high insulin secretion and high insulin sensitivity was significantly higher (P = 0.003) than that of every other group. This analysis was repeated with the group of offspring who developed diabetes included. The figure was different in only trivial ways.

Hypoglycemia-induced snacking might be a mechanism through which high acute insulin secretion and high insulin sensitivity could contribute to increased weight gain. If so, this might be reflected in low blood glucose at 120 min during the GTT in the group with the greatest weight gain in Fig. 1. The mean blood glucose at 120 min among subjects with high insulin sensitivity and high acute insulin secretion was 5.0 ± 0.8 mmol/l, right in the middle of the means for the other three groups, which ranged from 4.7 ± 1.0 to 5.3 ± 0.9 mmol/l (NS). Similar results were found for the 180-min blood glucose. Furthermore, hypoglycemia, defined as blood glucose <3.0 mmol/l at any point in the oral GTT, occurred no more frequently in the group with high insulin sensitivity and high acute insulin secretion than it did in the other three groups combined (data not shown).

DISCUSSION

The novel finding in this study was that acute insulin secretion is a potent predictor of subsequent weight gain and that this effect is independent of age and percent IBW and persists when insulin sensitivity is taken into account. Precise characterization of the interdependence of the effects of acute insulin response and insulin sensitivity is problematic. An association between insulin sensitivity and weight gain has been described in Pima Indians (19), but in this analysis insulin sensitivity's effect was demonstrable only among offspring with relatively high values. As suggested by Fig. 1, it is plausible that insulin sensitivity plays a permissive role such that a minimum value (threshold) is necessary for acute insulin secretion to have any effect on weight gain. Replacement of the insulin secretion and insulin sensitivity terms with a single term representing this type of threshold effect gives a model that fits the data about as well as the one in Table 3 (data not shown). We can only conclude that the data are consistent with both interpretations.

The mechanisms underlying the weight gain are unknown. If a vigorous acute insulin response and insulin sensitivity combine to produce hypoglycemia, a pattern of frequent snacking could accelerate weight gain. However, hypoglycemia during the oral GTT in these subjects was infrequent regardless of the acute insulin response, making this explanation unlikely. Furthermore, the second phase of insulin secretion during the intravenous GTT (after the first 10 min)

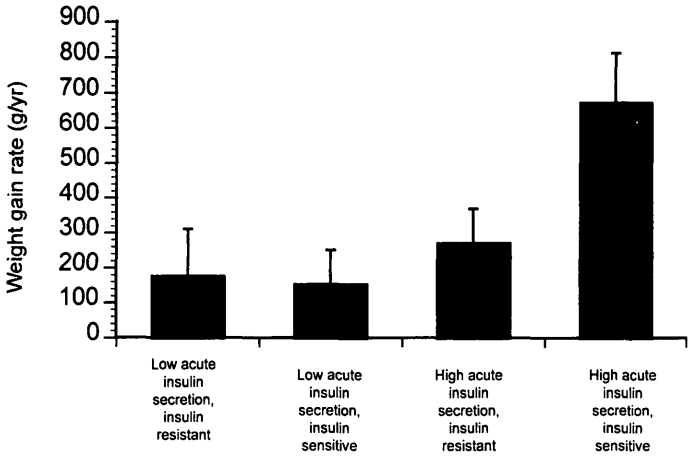

FIG. 1. Weight-gain rate (adjusted for age and percent ideal body weight) as a function of insulin sensitivity and acute insulin secretion. Subjects are grouped with respect to median values for insulin sensitivity and acute insulin. By the Bergman (14) minimal model insulin sensitivity index: insulin sensitive and resistant >6.95 and ≤6.95 × 10^{-3} · min^{-1} · $pmol^{-1}$ · l, respectively. Based on incremental area under the curve of serum insulin in the first 10 min of the intravenous GTT: high and low secretion ≤3,078 and <3,078 pmol · l^{-1} · min^{-1}, respectively. Error bars represent SE of the least-squares means.

was not associated with the rate of weight gain. Thus the weight-gain effect seems to be specific to the acute phase of the insulin response, rather than the prevailing insulin level after an intravenous glucose challenge.

One possible mechanism by which acute insulin secretion might affect body weight is through the stimulation of hunger without the intermediate step of hypoglycemia. This issue was examined in experiments performed by Rodin et al. (10). Insulin and glucose infusions were used to vary plasma glucose and insulin independently in 20 lean healthy control subjects. Acute hyperinsulinemia resulted in increased hunger, heightened palatability of sucrose, and greater intake of a carbohydrate-containing fluid. This was equally true in hyperglycemic and hypoglycemic conditions. Thus hypoglycemia was not necessary for the appetite-stimulating effect of an acute increase in plasma insulin.

Findings in rats with lesions of the ventromedial hypothalamus (VMH) imply an important role for acute insulin secretion, specifically, in both appetite regulation and fat deposition. At 1 week after the lesions are made in the VMH, blood glucose is normal; the rats are exquisitely sensitive to insulin and have a very high acute insulin response compared with their own presurgical results and with control rats who underwent sham surgery (20). Soon thereafter, the rats develop extreme hyperphagia, become morbidly obese (21), and then become insulin resistant a few weeks after the development of obesity (20). However, if the parasympathetic innervation of the pancreas is severed at the same time by vagotomy, the changes in pancreatic insulin secretion are prevented and hyperphagia does not occur (22). Similarly, if a rat undergoes chemical pancreatectomy and receives transplanted (and denervated) islet cells before the VMH lesions, the insulin hypersecretion, hyperphagia, and obesity are prevented (23). These studies support a role for acute insulin secretion in mediating the hyperphagia and weight gain in rats with VMH lesions.

Different results have been obtained in animal studies using chronic infusions of insulin (24–27). In these experiments, food intake decreased after insulin was infused over periods of several days. These results suggest that the effect of chronic hyperinsulinemia may be opposite to the acute effect of a short burst of insulin.

Instead of weight gain being an effect of acute insulin secretion, an alternative hypothesis—that both are the effects of a common underlying hormonal or neural stimulus—must be considered. However, the demonstration by Rodin and colleagues (10) that an acute infusion of exogenous insulin increased appetite and nutrient consumption supports a direct effect of a rapidly increasing insulin concentration as an appetite stimulant, regardless of any secondary mechanisms.

The contrast in the effects of sulfonylureas and metformin on weight gain in patients with NIDDM has generally been attributed to more frequent hypoglycemia in subjects taking sulfonylureas or to gastrointestinal side effects of metformin. However, our findings suggest a plausible alternative explanation. Weight gain during treatment with sulfonylureas may result in part from the increased acute insulin secretion that is the mode of action of this class of agents. Metformin's mode of action, on the other hand, is to increase insulin sensitivity while decreasing acute insulin secretion. This combination of effects would have no net effect (or a net negative effect) on weight gain based on the findings of this study.

A study of acute insulin secretion and weight-gain rate in Pima Indians found an inverse relationship (28), the opposite of the findings of this study. However, the two studies differ in a number of regards that might contribute to these differences. The Pima study group was more obese at baseline, corresponding roughly to the heaviest quartile of our study group, and more insulin resistant. Although different measures of insulin sensitivity were used in the studies, it is likely that none of the Pimas had a level of insulin sensitivity above the median of our subjects, the range in which the relationship between acute insulin response and weight gain was most clear in our data. Moreover, the study designs differed with regard to the length of follow-up and the measure of weight gain. In the study of Pima Indians, weight gain was calculated from two measurements of weight separated by an average of 3.5 years. The last was subtracted from the first, and the difference was expressed as a percentage of baseline weight per year. When we replicated their analysis (and measure of weight gain) in those subjects in our study group who were in both the highest quartile of the relative body weight distribution and the lower half of the insulin sensitivity distribution, we also found an inverse relationship between weight gain and acute insulin secretion, although it was not statistically significant. However, this inverse relationship disappeared if we extended follow-up to the full 16.7 years or included the entire study group in the analysis. This suggests that, within this subgroup of our study population, the apparent inverse relationship might be an artifact arising in the use of a two-point measure of percent weight change over a short interval or a "regression toward the mean" phenomenon arising in an extreme tail of the weight distribution.

It is important to consider what limitations should be imposed on the interpretation of the findings of this study. The study population consisted of subjects with normal glucose tolerance who had two parents with NIDDM. They were aware of being at high risk of NIDDM, and some of them

strove very hard to avoid gaining weight. These efforts would have obscured the full expression of their propensity to gain weight and may account for the mean weight gain in this group being somewhat lower than has been reported in other studies of nondiabetic subjects in the United States (29). Moreover, there was a relative paucity of very overweight individuals in the older age groups, so inferences about that subgroup should be cautious. Neither of these issues could produce a spurious finding; they can only diminish the power of the study to detect the effect of the acute insulin response. Finally, one must consider whether the relationship between acute insulin response and weight-gain rate observed in this population is unique to a population enriched with susceptibility to NIDDM. The studies of Rodin and colleagues (10,30–32) suggest that is not the case. Moreover, this enrichment was diminished by excluding all subjects who developed NIDDM during follow-up.

In conclusion, acute hyperinsulinemia (as reflected in first-phase insulin secretion following intravenous glucose) is a risk factor for rapid weight gain and obesity, particularly among individuals who are sensitive to insulin. The fact that obese individuals are typically insulin resistant suggests that the weight gain induced by acute hyperinsulinemia in this study was accompanied by a concomitant decrease in insulin sensitivity.

ACKNOWLEDGMENTS

Supported in part by a grant from the Diabetes Association of Greater Fall River (J.H.W.), National Institute of Diabetes and Digestive and Kidney Diseases Grant R01-DK-47475 (A.S.K.), Swiss National Science Foundation Grant 32-9257.87 (B.C.M.), and a grant from the Joslin Diabetes Center. R.J.S. was supported by fellowships from the Canadian Diabetes Association and the Juvenile Diabetes Foundation International.

We thank the study subjects for their time and patience, Theresa Smith, RN, for intravenous GTTs, Anna Karass for glucose measurements, Marta Grinsbergs for insulin assays, Derek Jones and Mary Jane Campbell for collecting blood samples and follow-up data, and the physicians who assisted in the long-term follow-up of study patients: G. Boden, M.J. Garcia, R.F. Williams, D.M. Beardwood, T. Pozefsky, L. Rojas, C.B. Kahn, P.H. Sonksen, J.D. Tobin, M.R. Santis, B.N. Park, L. Koncz, J.L. Kyner, E.G. Wilmshurst, M.H. Tan, A.A. Rossini, R.L. Kaufman, O.P. Ganda, R.A. Cole, J.L. Day, J.J. Connon, R.H. Rhie, P.J. Dunn, M.H. Blanc, and H.S. Starkman.

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