Glucose-Insulin Response to Oral Glucose in a Healthy Obese Population

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SUMMARY

The characteristics of the glucose and insulin responses during the glucose tolerance test (GTT) in obese people as a group have not been established. We analyzed glucose and insulin levels during GTT in 160 healthy obese patients who averaged 42% over ideal body weight. Statistical upper limit of normal for 2-h glucose was 260 mg/dl in women and 206 mg/dl in men. Although there was a significant correlation between insulin and glucose levels in both sexes and between insulin and degree of obesity in women, r values were relatively low (r < 0.4 for all). High insulin levels and delayed peak insulin were present in the majority of patients with normal GTT and absent in many of the most obese patients. Results indicate that upper limits of normal glucose for GTT in the obese are much higher than currently accepted criteria. DIABETES *28:* 208–212, March 1979.

In spite of numerous studies on the interrelationship among obesity, plasma glucose, and insulin levels, some very practical problems have not been addressed. Current criteria for abnormal glucose tolerance were determined in populations that were primarily nonobese.[1,2] Previous studies on glucose dynamics in the obese utilized these criteria to separate normal from chemical diabetes.[3–10] Since the original criteria for the glucose tolerance test (GTT) were established, it has been demonstrated that obesity is usually associated with abnormalities of insulin receptors that could cause abnormal glucose tolerance independent of the presence or absence of diabetes.[11,12] One recent study indicated that there is a general decrease in carbohydrate tolerance in mildly obese women that is independent of drugs or age.[13]

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The characteristic of the glucose and insulin levels during the oral glucose tolerance test (OGTT) in moderately obese people as a group have not been established. To help define these characteristics more accurately, we performed GTTs in 160 healthy obese outpatients on no medications. The results were analyzed in an attempt to define the plasma glucose and insulin response to an oral 100-g glucose load. In addition, the effects of sex, weight, percent body fat, and age on glucose and insulin levels were evaluated.

MATERIALS AND METHODS

The general characteristics of the group from which these patients were drawn have been described previously.[14] The initial group included 202 patients. For the purpose of this study, patients on birth control pills, diuretics, or any other medicine that might affect blood sugar were excluded. Two patients who had previously been told that they had diabetes were likewise excluded.

The resultant group consisted of 160 patients: 109 women and 51 men (Table 1). According to standard height and weight tables all patients were ≥18 kg over their ideal body weight. Both sexes averaged 27 kg over ideal body weight. Corrected for age and height, both sexes were 42% over ideal body weight. They were then given written instructions for a 300-g carbohydrate diet and after they had been on the diet for 3 days a GTT was given, using 100 g oral glucose. The 100-g glucose load was used to allow comparison with previous standards.

Plasma sugars were determined by using the glucose oxidase method. Plasma insulin levels were determined in our laboratory by utilizing a double antibody technique. All insulin samples were run in duplicate and the average of the two was used for analysis. Values exceeding the values of the standard curve were diluted and redetermined. Percent body fat was estimated by using four different areas of caliper-measured skinfold thicknesses in each patient. We recognize that percent body fat determined by this method is an estimate. However, when applied to groups of patients as is done in this report it does correlate well with other methods of determining total body fat.[15]

TABLE 1
Baseline descriptive statistics

Variable	Men (N = 51)	Women (N = 109)
Age (yr)	31 (9.4)*	33 (10)
Height (cm)	177 (8)	161 (6)
Weight (kg)	100 (11)	86 (15)
Percent body fat†	31 (2.6)	44 (2.8)

* Mean (SD).
† Calculated from skinfold measurements.[14]

Since histograms of the data and the Kolmogorov-Smirnov test for normality suggested that many of the variables were not normally distributed, statistical analysis was performed by utilizing both parametric and nonparametric techniques.[16] Comparison of one variable with another was done by utilizing Spearman rank order correlation coefficients. The data were also inspected for bimodality at each time point during the GTT for all variables. Total area of the glucose, insulin, and glucose/insulin ratio curves were calculated as an estimate of the total response during the test. Area curves were determined by utilizing both a zero baseline and fasting values as a baseline.

RESULTS

Glucose and insulin results for all patients. During the GTT the glucose and insulin levels were significantly different between men and women ($P < 0.05$) at several points during the test (Table 2). There was an extremely wide range of insulin response at all time periods in both men and women. Median insulin levels had not returned to baseline by 3 h in either sex (Table 2).

In addition to the wide range of values as a group (see percentiles, Table 2), there were wide fluctuations in glucose levels for individual patients during the test. In 74 patients, the 1-h value was actually less than the 2-h value, and seven patients had a 1-h glucose value of less than 60 mg/dl, without hypoglycemic symptoms. Three-hour glucose values of 60 mg/dl or less, 50 mg/dl or less, and 40 mg/dl or less occurred in 31, 13, and 3 patients, respectively, in the absence of hypoglycemic symptoms. The blood sugar did not vary by more than 30 mg/dl during the GTT in 11 patients (excluding ½-h value).

Since these data usually were not normally distributed, nonparametric estimates of the 5th and 95th percentiles are the most appropriate way to describe the reasonable statistical lower and upper limits (Table 2). Previous "normal" curves usually have been derived by using parametric statistics. For the purpose of comparison, we determined the 95–90% tolerance limits by utilizing the assumption that the data were normally distributed. The upper limits from the two types of analysis happen to be similar. The differences in glucose compared with previous studies in nonobese patients cannot be attributed to the use of parametric statistics in earlier studies. For the purpose of comparison with previous standards, mean values are also presented in Table 2, with the realization that they do not reflect the population as well as medians.

Correlation of insulin and glucose levels with sex and obesity. As previously stated, data from each time period during the GTT was correlated with various other variables. In addition, areas under the curve for glucose insulin and glucose insulin ratio were also correlated with each variable. The two methods of calculating total area revealed similar statistics in all determinations. In the interest of clarity and brevity, correlations with area above a zero baseline will be used here. Individual time periods will be mentioned when they are of particular importance or reflect a correlation that was not apparent from total area analysis.

In addition to the general differences in insulin and glucose response in men and women already mentioned, there were also significant differences in weight and percent body fat ($P < 0.001$). Although the men weighed more than the women (100 vs. 86 kg mean), they had a lower percent body fat (31% vs. 44% mean) (Table 1). In men, the high glucose and insulin levels found during the GTT could not be correlated with either weight or percent body fat (Table 3). In women, there was a correlation, predominantly with percent body fat. A significant correlation with weight was found only in the fasting insulin and glucose level in women (Table 3). In general, the r values for even the significant correlations were not extremely high and they do not establish

TABLE 2
Median, 5th, and 95th percentiles of insulin and glucose values during an OGTT in obese men and women

Time	Sex	Plasma glucose (mg/dl)				Serum insulin (μU/ml)			
		5th	Median	95th	Mean	5th	Median	95th	Mean
Fasting	Men	86	100†	128	105	14	24*	40	25
	Women	76	96†	124	97	11	20*	39	23
½ h	Men	120	170	238	166	38	132†	354	152
	Women	106	154	256	162	31	89†	272	110
1 h	Men	94	156†	254	160	50	183†	394	200
	Women	58	120†	248	134	32	92†	331	123
2 h	Men	80	120*	206	132	25	150†	335	158
	Women	84	138*	260	157	29	92†	324	117
3 h	Men	42	70†	156	79	16	39	195	69
	Women	50	92†	152	96	16	47	144	66

OGTT, Oral glucose tolerance test.
* $P < 0.05$.
† $P < 0.01$ for results of comparison of data between men and women using the Kruskel and Wallis H test.[16]

TABLE 3
Correlations between insulin, glucose, weight, and percent body fat in obese men and women during a 3-h GTT

Variables correlated	r value‡ Men	Women
WT/FG	0.112	0.193*
WT/FI	0.009	0.347†
PBF/FG	−0.186	0.127
PBF/FI	−0.169	0.439†
WT/TAG	0.126	0.187
WT/TAI	−0.023	0.133
PBF/TAG	0.031	0.245*
PBF/TAI	0.196	0.343†

GTT, Glucose tolerance test; WT, weight; FG, fasting plasma glucose; FI, fasting serum insulin; PBF, percent body fat; TAG, total area under the glucose curve; TAI, total area under the insulin curve.
* P < 0.05.
† P < 0.01.
‡ Spearman rank order correlation coefficient.

a cause-and-effect relationship. There was a wide range of insulin secretion at any level of percent body fat (Figure 1). The woman with the highest percent body fat had an insulin area very similar to the woman with the lowest percent body fat (Figure 1). It is apparent that in any analysis of insulin and glucose dynamics in obese patients, men and women must be analyzed separately.

Insulin and glucose ratios. There was a significant correlation between total area of the glucose curve and total area of the insulin curve in both men and women as groups (r = 0.290, P = 0.05 and r = 0.320, P = 0.001, respectively). As would be expected from the relatively low r value, there was a wide range of insulin values for any given total area of glucose, even in the women (Figure 2).

As a group, the men had higher insulins than the women. The total areas for glucose in men and women were similar—401 for men vs. 411 for women (P > 0.1). The total area for insulin in men was 434 compared with 299 in women (P < 0.001). The difference between insulin levels in men and women was most pronounced at ½, 1, and 2 h (Table 2).

Insulin levels in patients with varying degrees of glucose tolerance. To evaluate whether there was any characteristic increase or decrease in the insulin secretion pattern associated with various levels of glucose tolerance, we analyzed patients with "normal" glucose tolerance separately (group A). Levels of plasma glucose in this subgroup, in mg/dl, were all less than all of the following: fasting, 130; 1 h, 185; 2 h, 140; and 3 h, 130. These values are normal by Fajans and Conn criteria and would constitute a score of zero by Public Health Service criteria.[1] There were 27 men and 55 women in group A. Patients who were not in group A fell into several subgroups of carbohydrate intolerance, as defined by current standards. Six men and 31 women had isolated values exceeding the limits defined for group A at only the 1-, 2- or 3-h value. Four men and seven women (group B) had elevated values at both 1 and 2 h, which was consistent with an abnormal test by Fajans and Conn criteria.[1] Two additional patients of each sex had elevated values at 1, 2, and 3 h (group C), consistent with an abnormal test by Public Health Service criteria. Insulin levels in groups B and C were compared with those in group A by utilizing an H test for statistical analysis (Table 4). At every time period for which insulin levels of patients in either group B or C differed significantly from those in group A, group B or C had higher insulin levels associated with their higher glucose levels. These results are consistent with our previous overall analysis, indicating a positive correlation between plasma sugar and serum insulin.

In addition to the previously mentioned subgroups, there were three women with fasting glucose values of over 130 mg/dl. They also had 2-h glucose values over 400 mg/dl and 3-h values over 200 mg/dl. Their fasting and 3-h insulin levels were both significantly higher than those in group A (P < 0.05), with median values of 54 and 86 μU/ml, respectively. These three patients also had evidence of insulin deficiency. Median insulin values at 1 and 2 h were 74 and 88 μU/ml, in spite of the marked hyperglycemia.

Although the obese patients reported here had high insulin levels during the GTT as a group, there were individual patients who had normal insulin levels throughout

FIGURE 1. Distribution of total area under the insulin curve during oral glucose tolerance tests (OGTTs) for various degrees of percent body fat in 109 obese women.

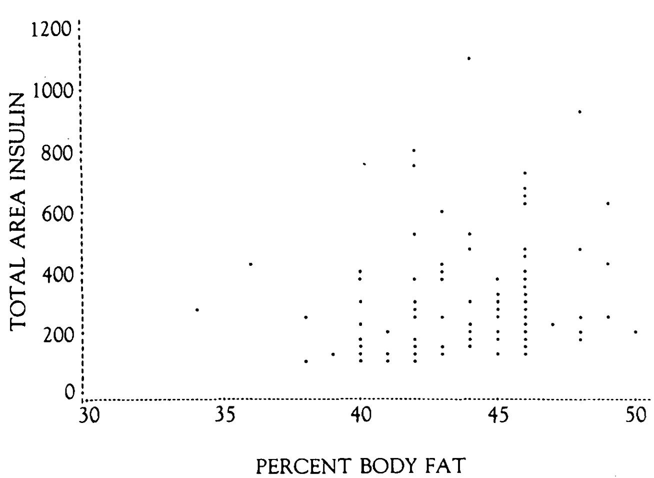
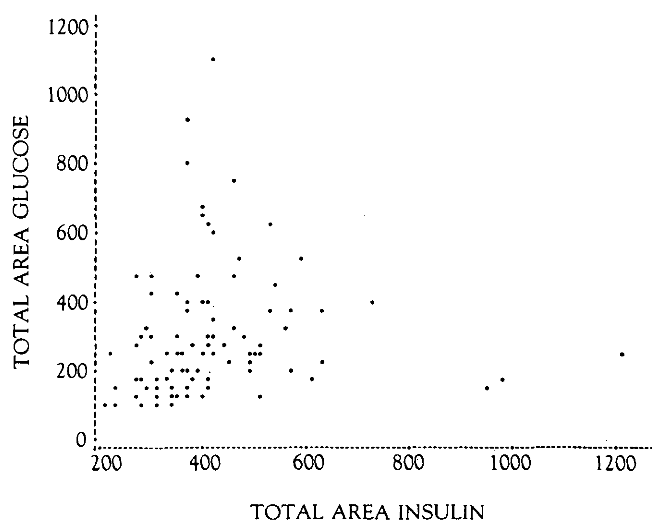


FIGURE 2. Total area under the insulin curve versus total area under plasma glucose curve during oral glucose tolerance tests (OGTTs) in 109 obese women. See text for further description of the three women with the highest total area glucose.



the test. Exact upper limits of normal for insulin levels in a nonobese population have not been established. Some studies report mean insulin levels in nonobese subjects with standard error of the mean or standard deviation.[3,5–8,17,18] Utilizing these previous studies, we calculated an upper limit of normal for insulin response in lean subjects to identify patients from this study who did not have insulin elevations, in spite of their obesity. The insulin (in microunits per milliliter) levels during the GTT were less than all of the following values in all of the patients so defined as having normal insulin levels: 0 h, 35; ½ h, 170; 1 h, 150; 2 h, 85; and 3 h, 55. Thirty-two (39%) of our obese patients in group A had normal insulin levels during the GTT by these criteria.

Age effect on glucose and insulin dynamics. There is a well-established effect of age on carbohydrate tolerance in the general population.[13,19–21] We found a significant age effect on total area for glucose in women but not in men (r = 0.305, P = 0.003, and r = 0.241, P = 0.095, respectively). There was no significant effect of age on total area for insulin for either sex (P = 0.95 and 0.84). Grouping of data for decades of life is outlined in Table 5. The small number of patients in each age subgroup and wide range of values within each subgroup prevented any meaningful age correction of the glucose during the GTT in our patients. The age effect did not account for the general increase in either glucose or insulin seen in our obese patients. The increase in glucose and insulin levels during the GTT and also the positive correlation between glucose and insulin response persisted when corrected for age.

We also analyzed the effect of a family history of diabetes. None of the patients had two first degree relatives with diabetes. A positive family history was defined as one blood relative who had been told he had diabetes. The reliability of such a history is questionable since the majority of patients also had a positive family history of obesity.

Forty percent of the women had a "positive" family history. The insulin levels and glucose levels did not differ in those with and without such a family history (P > 0.05).

DISCUSSION

In general, an increase in plasma sugar levels in our obese patients was accompanied by an increase in serum insulin levels, confirming the presence of "insulin resistance" in obesity observed by numerous other studies.[3–10] The finding was not uniform and correlations between insulin levels and degree of obesity had relatively low r values. Twenty percent of our obese patients did not manifest high insulin levels. Analyses of weight, percent body fat, levels of carbohydrate tolerance, age, and sex failed to reveal any single parameter to account for the high insulin or the wide range in insulin response.

Most previous studies of insulin levels and carbohydrate tolerance in the obese have indicated that with increasing glucose tolerance there is a delay in peak insulin levels plus a reduced overall secretion.[3–9] Others indicate an overall increase in insulin release in obese "diabetics."[10] Inclusion of patients with fasting hyperglycemia among the "chemical diabetics" may account for some of these discrepancies. Our data indicate that if fasting glucose is normal, then there is a general increase in insulin with increased glucose and delayed peak insulin levels occurring at all levels of carbohydrate tolerance. The three patients with fasting hyperglycemia in our study did have an overall reduced insulin secretion. The clinical significance of exaggerated insulin response during the GTT is not clear. The question of whether insulin resistance is a precursor to diabetes has been extensively reviewed in previous publications and definitive conclusions could not be drawn.[11,12,17,18]

Although insulin glucose dynamics are undoubtedly of pathophysiologic importance, the majority of physicians are more concerned with the practical problem of interpreting the plasma glucose levels with a given GTT. There is a substantial body of evidence that the classic diagnostic criteria for "chemical diabetes" misdiagnoses diabetes even in the general population.[19,20] One reason for this may be that the general population contains more obese people than the groups from which present criteria were derived.

We do not have information to address the problem of glucose tolerance in the general population. Our data addresses only a subpopulation of obese patients. Ninety-five percent of our obese women had plasma glucose values (in mg/dl) less than the following values: fasting, 124; 1 h,

TABLE 4
Insulin levels during OGTT in obese patients with normal GTT (group A), those meeting Fajans and Conn (group B), and Public Health Service criteria (group C) for an abnormal GTT[1]*

Time	Sex	Group A Serum insulin (μU/ml)	Group B Serum insulin (μU/ml)	Group C Serum insulin (μU/ml)
Fasting	Men	26 (11–42)†	20 (14–24)	35 (33–37)§
	Women	20 (9–48)	18 (16–38)	28 (23–33)
½ h	Men	143 (33–420)	120 (78–194)	151 (133–169)
	Women	99 (11–520)	83 (41–142)	124 (115–133)
1 h	Men	184 (18–428)	176 (115–223)	240 (220–260)§
	Women	104 (9–380)	108 (87–168)	130 (91–169)
2 h	Men	154 (12–335)	210 (136–278)§	322 (280–364)§
	Women	122 (17–399)	134 (21–355)	142 (95–189)
3 h	Men	37 (16–182)	50 (37–58)	240 (138–343)§
	Women	41 (11–296)	79 (29–115)‡	230 (121–340)§

* All groups mutually exclusive. See texts for numbers of patients in each group and definition of normal.
† Median (range).
‡ P < 0.05.
§ P < 0.01 comparison with group A.

TABLE 5
Total area of glucose curve (TAG) and total area of the insulin curve (TAI) for each decade

Age (yr)	TAG Men	TAG Women	TAI Men	TAI Women
<20	325 (1)*	408 (9)	245	418
20–29	385 (23)	380 (34)	470	278
30–39	404 (19)	394 (35)	418	291
40–49	430 (5)	416 (23)	464	284
≥50	454 (3)	585 (8)	217	335
P value†	0.564	0.011	0.454	0.450

* Mean of area for age group (number of patients in age group).
† Probability associated with a test of differences among the means for the five age groups.

248; 2 h, 260; and 3 h, 152. This is a statistically derived normal in a specific subgroup and some limitations for any such "normal" curve must be kept in mind. Values in men and women differ significantly (Table 2). The values derived here apply specifically to the 20–50 yr age group more than 20% over ideal body weight.

Given our previous discussion on insulin resistance, it is apparent that one need not invoke a second diagnosis such as diabetes to account for some elevation of glucose in obese patients. There is, however, evidence that obese patients with "chemical diabetes" are more likely to have subsequent deterioration in the GTT than thinner patients with similar GTTs.[22] In the most obese patients, the deterioration rate was 37%.[22] How much of this deterioration was due to overt diabetes versus more prolonged obesity and/or weight increase causing more insulin resistance is uncertain. The addition of obesity and insulin resistance to a person who was destined to ultimately develop diabetes could certainly hasten the onset of overt hyperglycemia. The use of current criteria for interpretation in the obese may therefore identify a population at risk, but does not establish a diagnosis. If the term "chemical diabetes" as currently used is to be applied to the obese, then the standards for abnormality should be raised. Unfortunately there appears to be no way to correct the GTT for obesity which applies to all degrees of overweight. In a largely nonobese population, Boyns et al. found no correlation between degree of obesity and glucose levels during the GTT.[2] Wingerd and Duffy found a predictable increase in glucose in a population containing some patients who were less obese than our patients.[13] In our population, all of whom were obese, analysis of individual time periods during the GTT plus total area curves provided no means of predicting glucose based on weight or percent body fat. The factor least affected by obesity was the fasting plasma glucose. Upper limits of normal derived here are quite consistent with the currently accepted 130 mg/dl.[1] The fasting glucose appears to be the most specific blood test for the diagnosis of diabetes in the obese.

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