Insulin Resistance and Insulin Secretion Are Determinants of Oral Glucose Tolerance in Normal Individuals

GERALD M. REAVEN, RICHARD J. BRAND, Y.-D. IDA CHEN, ASHWINI K. MATHUR, AND IRA GOLDFINE

Plasma glucose values after oral glucose challenge vary widely in nondiabetic subjects. We have now evaluated the role of insulin resistance in determining the plasma glucose response to oral glucose in 74 volunteer subjects with normal glucose tolerance. In these subjects, we determined the plasma glucose and insulin responses over a 3-h period to a 75-g oral glucose challenge, and the steady-state plasma glucose concentration during a continuous infusion of somatostatin, glucose, and insulin (a quantitative measure of insulin resistance). The plasma glucose response was defined as the incremental increase in plasma glucose concentration above the fasting value for 3 h after the oral glucose challenge. Multiple regression analysis was used to define the relationship between the dependent variable (plasma glucose response) and various predictors of this response. These analyses indicated that both the steady-state plasma glucose and the incremental insulin response during the first 30 min after the glucose load were significant predictors of the plasma glucose response. In those individuals in whom insulin action was impaired and the 30-min plasma insulin response was decreased, plasma glucose values reached higher levels. When standardized regression coefficients were determined, the incremental glucose response was directly correlated with steady-state plasma glucose ($r = 0.700$, $P < 0.001$) and inversely with the insulin response during the first 30 min ($r = 0.268$, $P = 0.023$). Furthermore, the correlation between steady-state plasma glucose and glucose response was significantly greater ($P < 0.005$) than that between the glucose response and 30-min insulin concentration. These data demonstrate that both insulin action and insulin secretion are determinants of the plasma glucose response to oral glucose in individuals with normal glucose tolerance. ***Diabetes*** **42:1324–32, 1993**

From the Department of Medicine, Stanford University School of Medicine and Geriatric Research, Education and Clinical Center, Palo Alto; the Department of Veterans Affairs Medical Center, Palo Alto; the Mount Zion Hospital and Medical Center, San Francisco; and the University of California at Berkeley, Berkeley, California.

Address correspondence and reprint requests to Dr. G.M. Reaven, GRECC (182-B), VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

Received for publication 1 February 1993 and accepted in revised form 22 April 1993.

NIDDM, non-insulin-dependent diabetes mellitus; NGT, normal glucose tolerance; SSPG, steady-state plasma glucose; BMI, body mass index; IBW, ideal body weight; NDDG, National Diabetes Data Group; HSA, human serum albumin; FPG, fasting plasma glucose; ΔI_{30}, incremental insulin response above basal 30 min after glucose challenge; OGTT, oral glucose tolerance test; HDL, high-density lipoprotein.

Plasma clearance of glucose after ingestion of an oral glucose load is a function of both the ability of the pancreatic β-cell to secrete insulin and the efficiency of the liver and peripheral tissues to respond to insulin. Typically, in individuals with NIDDM, defects exist in both the secretion and action of insulin (1,2). As a consequence, these two variables have been extensively studied in patients with NIDDM (1–3). In contrast, much less attention has been paid to the relative importance of insulin secretion and action in the regulation of oral glucose tolerance in nondiabetic individuals.

In nondiabetic individuals, a wide variation in plasma insulin levels occurs after an oral glucose challenge (4), and we have reported (5) that, in 100 individuals with NGT, the values for insulin-stimulated glucose disposal display wide variations. Strikingly, 25% of this population was nearly as insulin resistant as patients with NIDDM (1,3). The plasma insulin responses varied in the entire group, and a significant relationship existed between degree of insulin resistance and degree of hyperinsulinemia, i.e., in individuals with greater insulin resistance, higher plasma insulin concentrations were present. We concluded that, in the insulin-resistant normal subjects, the increased insulin secretion had compensated for the insulin resistance and thus prevented the appearance of overt diabetes mellitus.

Although the glucose tolerance tests in these subjects were normal (6), considerable variability occurred in the

plasma glucose responses to oral glucose. Because both insulin action and insulin secretion can modulate glucose tolerance, it seemed important to determine the relative contributions of these variables in the disposal of oral glucose in normal individuals. Therefore, we measured the plasma glucose and insulin responses to oral glucose and insulin-stimulated glucose disposal in 74 nonobese individuals with NGT. A predictive model was used to evaluate the roles played by insulin action and insulin secretion in disposing of an oral glucose load, taking into account the additional variables of fasting glucose concentration, age, degree of obesity, and sex. The results of these studies indicated that both ability of insulin to stimulate glucose uptake and the plasma insulin response 30 min after the administration of oral glucose were significantly related to the plasma glucose response to oral glucose in individuals with NGT.

RESEARCH DESIGN AND METHODS

Seventy-four individuals (27 men and 47 women) volunteered for this study. Ages ranged from 19 to 71 yr with a mean ± SD of 44 ± 13 yr. BMI, which was used as an estimate of degree of obesity, ranged from 18.8 to 29.5 kg/m^2 with a mean ± SE of 23.8 ± 3.1 kg/m^2. The protocol was approved by the Stanford University Committee for the Protection of Human Subjects, and written informed consent was obtained from all subjects. The volunteer subjects were instructed to maintain their usual diet and activities before they were admitted to the Stanford Medical Center General Clinical Research Center (Palo Alto, CA), and tests were performed in random order. All subjects were in good health, as determined by a medical history, physical examination, and screening routine laboratory analyses. The study population was confined to individuals with a BMI <30 kg/m^2 to prevent individuals with substantial obesity from having undue influence on the results. This cutoff was based on the notion that a BMI >30 kg/m^2 defines an individual >20% above IBW (7).

OGTT. After an overnight fast, blood was drawn for measurement of plasma glucose (8) and insulin (9) concentrations before and 30, 60, 120, and 180 min after the ingestion of a 75-g oral glucose challenge. Only volunteer subjects with a normal OGTT by the criteria of the NDDG (6) were included in the study.

Insulin resistance test (SSPG). After an overnight fast, intravenous catheters were placed in each arm. Blood was sampled from one arm for plasma glucose and insulin concentration, and the contralateral arm was used for administration of test substance. As described previously (10,11), somatostatin was administered at 350 μg/h in a solution containing 2.5% (wt/vol) HSA by Harvard infusion pump to suppress endogenous insulin secretion. Simultaneously, insulin and glucose were infused at 25 mU and 240 mg · m^{-2} · min^{-1}, respectively. Blood was sampled hourly until 2 h into the study, and then every 10 min at 150, 160, 170, and 180 min. Insulin concentrations typically plateaued after 30 min, whereas glucose concentrations plateaued after 120 min. The four glucose and insulin values obtained from 150 to 180 min were averaged and considered to represent the SSPG and insulin concentrations.

Statistical analysis. The relationships between the experimental variables measured (predictors) and glucose response were analyzed by standard methods of multiple regression analysis using SAS (Cary, NC), PROC REG. In these analyses, the incremental glucose response served as the dependent variable and the following six individual predictors as the independent variables. The predictors of the plasma glucose response evaluated were *1*) insulin resistance (as estimated by the SSPG); *2*) insulin secretion (as estimated by the incremental insulin response above basal 30 min after the glucose challenge or ΔI_{30}); *3*) FPG concentration; *4*) age; *5*) sex; and *6*) obesity as defined by BMI. The incremental increase in plasma insulin concentration during the first 30 min after the glucose challenge was selected as the measure of the insulin secretory response because insulin values at later time points reflect to an increasing degree the impact of the prevailing plasma glucose concentration on the β-cell.

For this study, estimates of the magnitudes of specified relationships of interest and the associated uncertainties in these estimates have been calculated to summarize the results. For a graphic representation of the direct relationship between a specific predictor and the incremental glucose response after adjusting for the remaining predictors, partial regression leverage plots have been used (12). Because of the lack of a normal distribution, Spearman's correlation coefficients were calculated to determine the relationship between resistance to insulin-mediated glucose uptake and various measures of the plasma insulin response to glucose.

RESULTS

Plasma glucose and insulin response to oral glucose. The frequency distribution of plasma glucose and insulin concentrations before and at all time points after the oral glucose challenge are shown in Figs. 1 (glucose) and 2 (insulin). As can be seen, the values for both glucose and insulin varied considerably from subject to subject, and the means and ranges are given in Table 1.

Measurement of insulin resistance. Figure 3 illustrates the frequency distribution of the measurements of insulin-mediated glucose disposal (SSPG concentrations). As with the plasma glucose and insulin responses, considerable variability existed in the estimate of in vivo insulin action, ranging from 2.3 to 16.7 mM (Table 1).

Regression analysis of variables modifying oral glucose response. To analyze the relative effects of the different variables on the plasma glucose response to an oral challenge, we used the total integrated area above the FPG concentration (incremental glucose area) as our measurement of the plasma glucose response. We then studied the relationship between this measure and the following six predictors: FPG concentration, ΔI_{30}, SSPG, age, sex, and BMI. For this purpose, a linear regression model was fitted to predict the plasma glucose response based on the six above-defined variables, and the numerical results of this analysis are shown in Table 2.

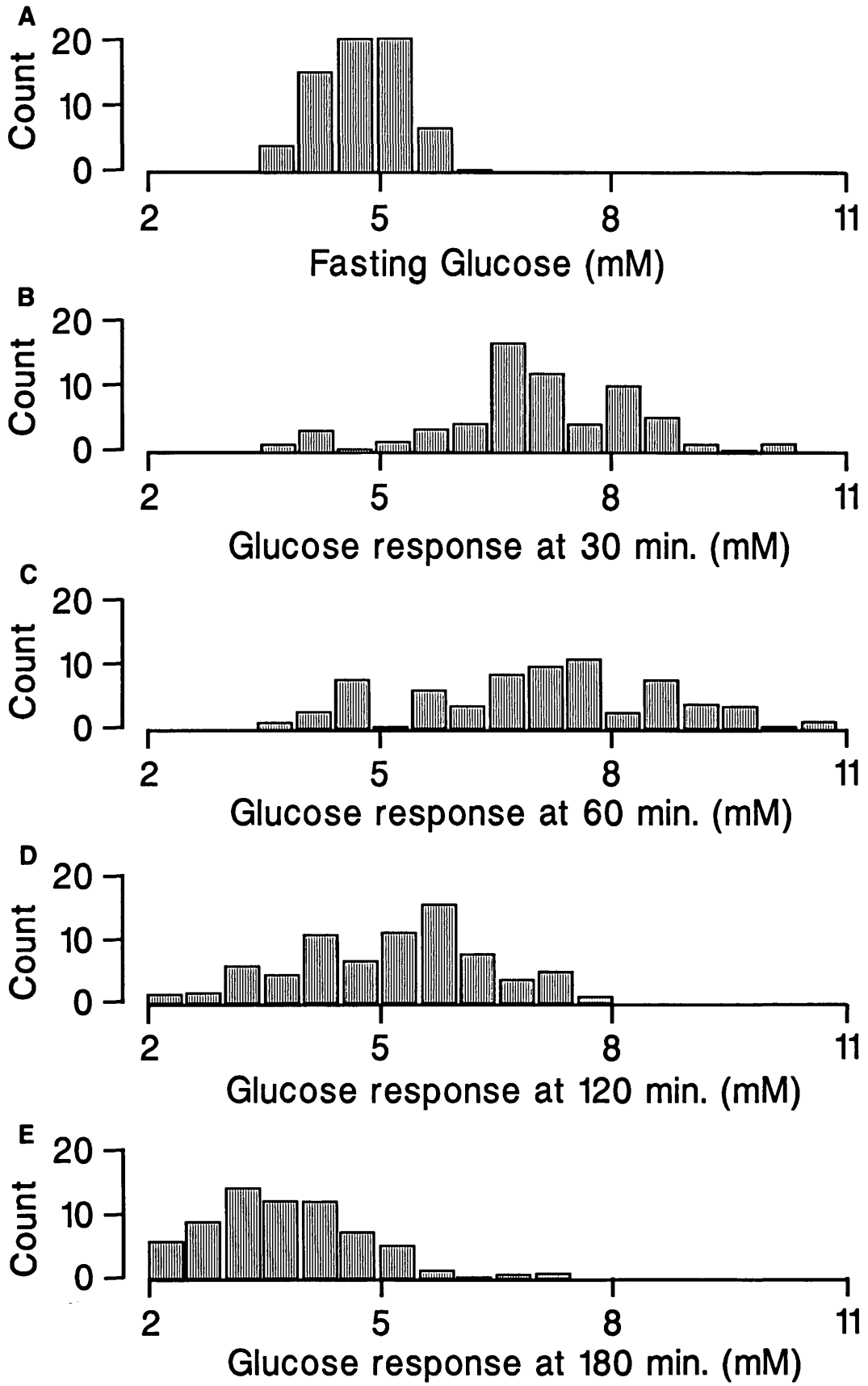

FIG. 1. Distributions of plasma glucose concentration before (*A*) and 30 (*B*), 60 (*C*), 120 (*D*), and 180 (*E*) min after oral glucose load.

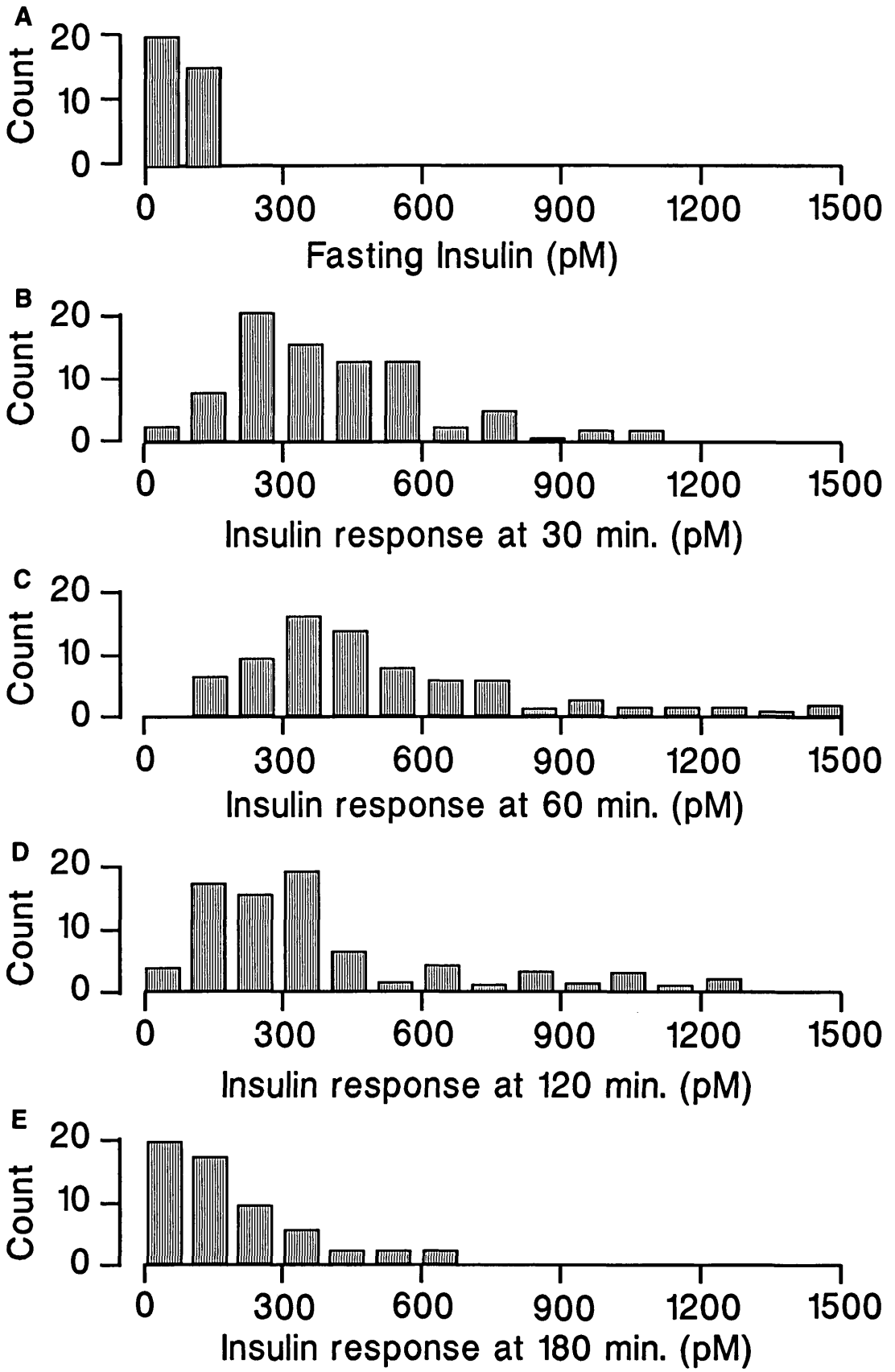

FIG. 2. Distributions of plasma insulin concentration before (*A*) and 30 (*B*), 60 (*C*), 120 (*D*), and 180 (*E*) min after oral glucose load.

TABLE 1
Metabolic measurements

Variable	
Plasma glucose response (mM)	
Fasting	4.9 ± 0.5 (3.7–6.2)
30 min	7.2 ± 1.4 (3.8–10.3)
60 min	7.2 ± 1.6 (3.8–10.9)
120 min	5.3 ± 1.2 (2.4–7.4)
180 min	3.9 ± 1.0 (2.3–7.4)
Plasma insulin response (pM)	
Fasting	68 ± 34 (4–157)
30 min	377 ± 197 (57–1040)
60 min	471 ± 255 (143–1456)
120 min	359 ± 257 (43–1277)
180 min	131 ± 117 (28–602)
SSPG (mM)	6.9 ± 3.5 (2.3–16.7)

Data are means ± SD (range); n = 74 (27 men and 47 women).

Considering both the estimate of the regression coefficient and its estimated SE, SSPG ($P < 0.001$) and ΔI_{30} ($P = 0.023$) were significant predictors of the plasma glucose response. The relationship between the incremental glucose response and ΔI_{30} was negative, i.e., the greater the insulin response, the lower the glucose response. The relationship between glucose and insulin responses at time points other than 30 min was either neutral or positive, i.e., the insulin response at these time points was unrelated to the degree of glucose tolerance, or correlated positively with a higher plasma glucose response. Most likely, the relationships between plasma insulin and glucose concentrations at the later time points were secondary to the stimulatory effect of a greater degree of hyperglycemia on β-cell insulin secretion. As such, they support our use of the ΔI_{30} predictor as the estimate of insulin secretory function in this study. Of the demographic variables, only BMI ($P = 0.020$) was a significant predictor of the plasma glucose response. The relationship between BMI and glucose response was negative, i.e., the more obese, the lower the glucose response with all other variables being kept constant.

The estimated regression coefficients shown in Table 2 describe the change in plasma glucose response per unit change in each variable keeping all other predictors constant. However, because the six predictors have inherently different units of measurement, the actual values of the regression coefficients shown in Table 2 are not comparable. To make them commensurate, the regression coefficients were divided by the ratio of the SD of the incremental glucose response to the SD of the specific predictor variable. These standardized regression coefficients indicate the change in incremental glucose response (in SD units) with one SD change in the predictor. These calculations appear in Table 2 under the heading of standardized regression coefficients, and the larger the absolute value, the more important the variable in predicting incremental glucose response. With the use of this approach to assess the relative strengths of the predictive relationships, Table 2 shows that the insulin resistance, as measured by SSPG, was ~3 times stronger than the early insulin response (ΔI_{30}) in predicting the plasma glucose response. Furthermore, when the difference between the standardized regression coefficients was compared by Student's t test, the magnitude of the relationship between incremental plasma glucose response and SSPG was significantly greater ($P < 0.005$) than that between plasma glucose response and 30-min insulin level.

Graphic representations. To graphically assess the data, a series of partial regression leverage plots were constructed. First, two separate linear regression models were constructed: one to predict the glucose response and the other to predict any one of the other variables, for example, SSPG, from the remaining variables. Then the difference between the observed and predicted glucose response (i.e., residual glucose response) and the difference between the observed and predicted SSPG (i.e., residual SSPG) were plotted to give a graphical description of the direct relationship between incremental glucose response and SSPG after adjustment for the other predictors of the glucose response. The results of these analyses are illustrated in Fig. 4. Note that, for each predictor variable included in Fig. 4, the horizontal scale is different. Because these scales differ, the slopes of the plotted trend lines are not comparable visually. Instead the numerical value given for the standardized regression coefficients in Table 2 should be used to compare the slopes. The plots in Fig. 4 also show that the scatter is fairly evenly distributed on either side of the trend line,

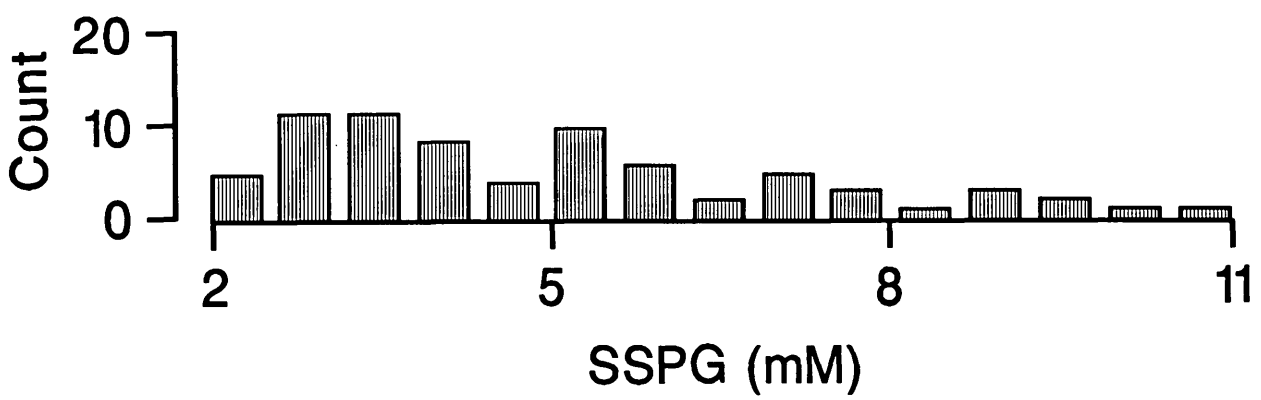

FIG. 3. Distribution of steady-state plasma glucose determined by insulin suppression test.

TABLE 2
Regression analysis of variables modifying incremental plasma glucose response

Variable	Regression coefficient	SE	Standardized regression coefficient	*P* value
Fasting glucose (mM)	−0.028	0.474	−0.006	0.951
ΔI_{30} (pM)	−0.013	0.005	−0.268	0.023
SSPG (mM)	0.442	0.090	0.700	<0.001
Age (yr)	0.031	0.019	0.183	0.110
BMI (kg/m^2)	−0.261	0.110	−0.349	0.020
Sex	0.500	0.130	0.229	0.606

indicating that the linear model was adequate for the purpose of this analysis.

Results presented to this point have focused on defining the variables that account for differences in the incremental plasma glucose response within a group of healthy individuals with NGT. Although not the primary goal of this study, it is difficult to view the wide range of SSPG values seen in Fig. 3 and not attempt to explain how this extreme degree of variability in insulin-mediated glucose uptake could exist in individuals classified as normoglycemic. An obvious possibility is that the more insulin resistant a subject, the greater the insulin response, thus preventing gross decompensation of glucose tolerance in insulin-resistant individuals. Table 3 displays the relationship between SSPG and various measures of the plasma insulin response. Every relationship was statistically significant, providing support for the view that the greater the degree of insulin resistance in individuals with NGT, the higher the insulin response.

DISCUSSION

This study demonstrates that, in normal individuals, the increase in plasma glucose concentrations after an oral glucose challenge is strongly associated with the degree of insulin resistance. In individuals with higher SSPG values during the insulin suppression test, greater increases occurred in plasma glucose concentrations during an OGTT. Furthermore, this relationship was highly statistically significant ($P < 0.001$) when differences in age, sex, BMI, and various measures of the insulin secretory response were taken into consideration. The plasma incremental insulin response 30 min after the oral glucose was also significantly ($P = 0.023$) related in an inverse fashion to the plasma glucose response, and this relationship persisted when controlled for the other variables measured. Thus, it can be concluded that both degree of insulin resistance and insulin response during the first 30 min were independent predictors of the plasma glucose response to oral glucose in individuals with NGT. However, note that the relationship between incremental plasma glucose response and SSPG was significantly greater than that between the glucose response and the insulin concentration 30 min after administration of the glucose load.

To directly compare the impact of these two variables, independent of any other predictors, standardized regression coefficients were calculated. Using this analysis, we observed that the height of the early insulin response was not as powerful as was the degree of insulin resistance in predicting the magnitude of the incremental plasma glucose response to oral glucose. However, these results do not necessarily provide an accurate quantitative comparison of the importance of insulin action and insulin secretion in regulation of glucose tolerance. More specifically, a relative sensitive method was used to quantitate insulin action, whereas the 30-min insulin response may not be the most sensitive method to evaluate β-cell function. For example, in retrospect it may have been preferable to have used the plasma insulin concentration 15 min after oral glucose as the estimate of insulin secretion.

We and others (1,3,13–18) have shown that insulin resistance is present in the majority of patients with NIDDM, independent of other variables that are known to modulate insulin action. However, although insulin resistance may be necessary for states of glucose intolerance to develop in most individuals, significant fasting hyperglycemia and manifest NIDDM does not develop until the β-cells are no longer able to compensate for impaired insulin action (1,3,14,18,19). In support of this hypothesis are the results of cross-sectional studies that show resistance to insulin-mediated glucose uptake is relatively constant over a wide range of FPG concentrations in patients with NIDDM, whereas once manifest hyperglycemia develops, the magnitude of the increase in fasting hyperglycemia is inversely related to the decline in insulin secretory response (1,3,18,20–23). Furthermore, prospective longitudinal studies have demonstrated that hyperinsulinemia in nondiabetic individuals is a significant predictor of the development of NIDDM and that resistance to insulin-mediated glucose uptake can be documented before any discernible decrease in insulin secretory response (24–27). Finally, it should be emphasized that the cross-sectional and longitudinal studies have been performed in a wide variety of ethnic groups.

If insulin resistance precedes the onset of NIDDM, this abnormality should be detected in a certain fraction of nondiabetic subjects. This prediction is supported by this study, which demonstrates that great variability occurred in the values for insulin-stimulated glucose disposal (SSPG) in healthy, nonobese individuals with NGT, similar to data previously reported from our group (5). In that study, we found that ~25% of individuals with NGT were approximately as insulin resistant as were patients with NIDDM. Given the direct positive relationship between insulin resistance to glucose uptake and enhanced insulin secretion in nondiabetic subjects shown in this and previous studies (3,5,28,29), it appears that NGT can be

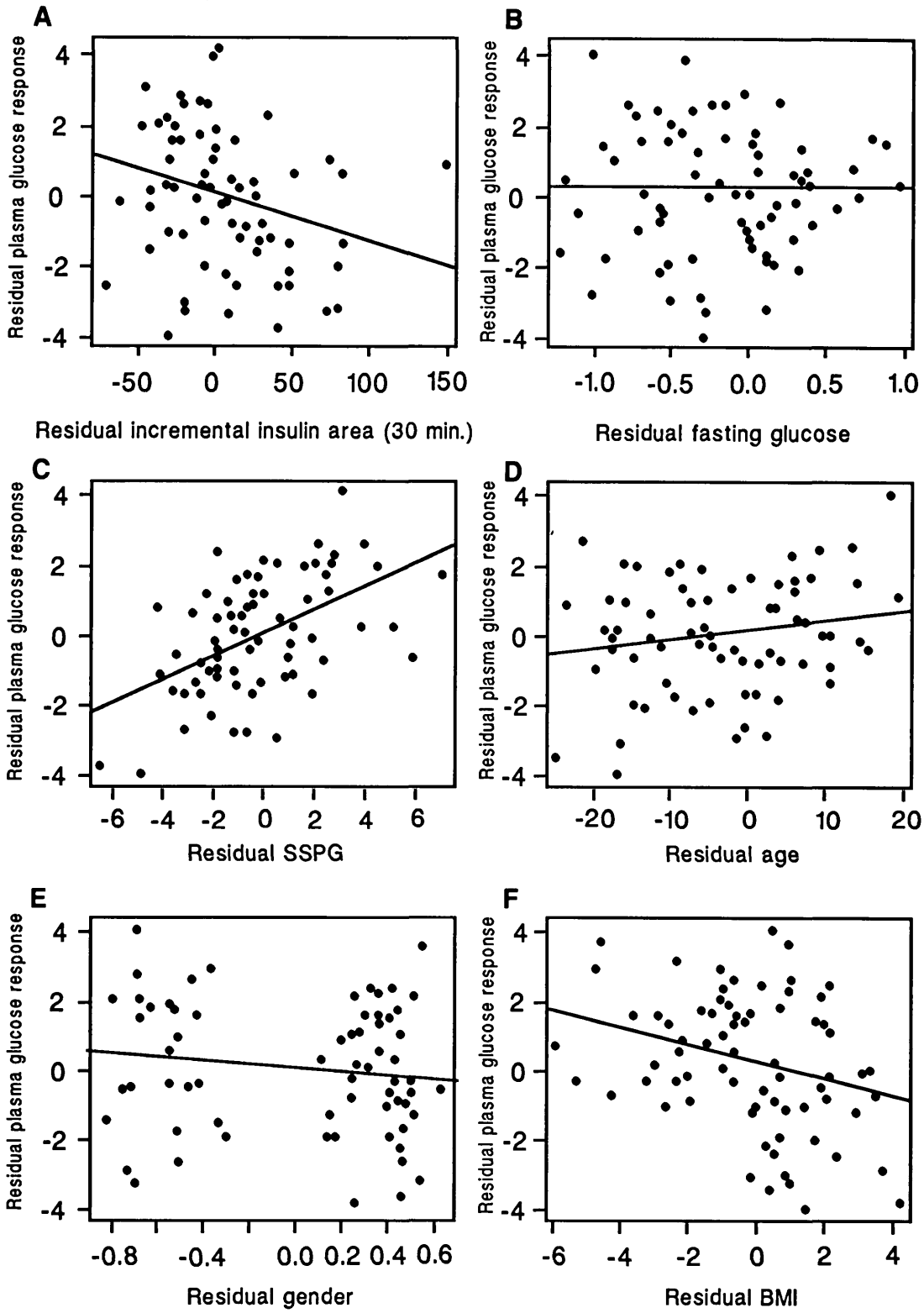

FIG. 4. Partial regression leverage plots showing relationship between plasma glucose response and each of 6 predictors (incremental insulin area at 30 min [*A*], fasting glucose [*B*], steady-state plasma glucose [*C*], age [*D*], sex [*E*], and BMI [*F*]), after adjusting for the other 5 predictors.

maintained in insulin-resistant individuals, providing that they can sustain a state of compensatory hyperinsulinemia. Once this capacity is lost and insulin secretory capacity declines, NIDDM occurs.

That an increase in β-cell insulin secretion may prevent the development of NIDDM in insulin-resistant subjects does not mean that insulin resistance and compensatory hyperinsulinemia are benign events. Hypertriglyceridemia, a low HDL-cholesterol concentration, and high blood pressure (1,10,30–35) have been shown to be

TABLE 3
Relationship between insulin resistance (SSPG) and plasma insulin concentration

Variable	*r*	*P* value
Fasting insulin	0.47	<0.001
Insulin at 30 min−fasting insulin	0.44	<0.001
Insulin at 60 min−fasting insulin	0.64	<0.001
Insulin at 120 min−fasting insulin	0.55	<0.001
Insulin at 180 min−fasting insulin	0.53	<0.001
Incremental insulin (0–180 min)	0.68	<0.001

associated with both insulin resistance and hyperinsulinemia and an increased risk of coronary heart disease (36–38). Furthermore, hyperinsulinemia, per se, has been identified as an independent risk factor for coronary heart disease (39,40). Thus, a defect in insulin-mediated glucose uptake, whether or not it is compensated for by an increase in β-cell function, can have grave consequences.

In conclusion, plasma glucose and insulin responses to an oral glucose challenge and values of insulin-stimulated glucose disposal vary widely in healthy subjects with NGT. The major factors affecting the plasma glucose response during a conventional OGTT are the degree of insulin resistance and the incremental insulin response during the first 30 min after the administration of the oral glucose challenge. Thus, the importance of insulin resistance in modulating glucose homeostasis is not confined to patients with states of glucose intolerance (1) but plays a role in regulation of the plasma glucose response to oral glucose challenge in normal individuals. Finally, these data demonstrate the great variability in insulin action in individuals with NGT and the role of compensatory hyperinsulinemia in the maintenance of glucose homeostasis in these individuals.

ACKNOWLEDGMENTS

The study was supported in part by National Institutes of Health Grants DK-38985, RR-00070, and DK-30732.

REFERENCES

1. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–607, 1988
2. Porte D Jr: β-Cells in type II diabetes mellitus. *Diabetes* 40:166–80, 1991
3. Reaven GM, Hollenbeck CB, Chen Y-DI: Relationship between glucose tolerance, insulin secretion, and insulin action in non-obese individuals with varying degrees of glucose tolerance. *Diabetologia* 32:52–55, 1989
4. Reaven GM, Olefsky JM: Relationship between heterogeneity of insulin responses and insulin resistance in normal subjects and patients with chemical diabetes. *Diabetologia* 13:201–06, 1977
5. Hollenbeck CB, Reaven GM: Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance. *J Clin Endocrinol Metab* 64:1169–73, 1987
6. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–57, 1979
7. Thomas AE, McKay DA, Cutlip MB: A nomograph method for assessing body weight. *Am J Clin Nutr* 29:302–04, 1976
8. Kadish AH, Litle RL, Sternberg JC: A new and rapid method for determination of glucose by measurement of rate of oxygen consumption. *Clin Chem* 14:116–31, 1968
9. Hales CN, Randle PJ: Immunoassay of insulin with insulin antibody precipitate. *Biochem J* 88:137–46, 1963
10. Shen D-C, Shieh S-M, Fuh MM-T, Wu D-A, Chen Y-DI, Reaven GM: Resistance to insulin-stimulated glucose uptake in patients with hypertension. *J Clin Endocrinol Metab* 66:580–83, 1988
11. Swislocki ALM, Hoffman BB, Reaven GM: Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. *Am J Hypertens* 2:419–23, 1989
12. Myers RH: *Classical and Modern Regression with Applications*. Boston, MA, Duxbury, 1986
13. Ginsberg H, Kimmerling G, Olefsky JM, Reaven GM: Demonstration of insulin resistance in untreated adult onset diabetic subjects with fasting hyperglycemia. *J Clin Invest* 55:454–61, 1975
14. Reaven GM, Bernstein R, Davis B, Olefsky JM: Non-ketotic diabetes mellitus: insulin deficiency or insulin resistance? *Am J Med* 60:80–88, 1976
15. Kolterman OG, Gray RS, Griffin J, Burstein P, Insel J, Scarlett JA, Olefsky JM: Receptor and post-receptor defects contribute to the insulin resistance in non-insulin dependent diabetes mellitus. *J Clin Invest* 68:957–69, 1981
16. Reaven GM: Insulin resistance in noninsulin-dependent diabetes mellitus. Does it exist and can it be measured? *Am J Med* 74:3–17, 1983
17. DeFronzo RA, Ferrannini E, Koivisto V: New concepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. *Am J Med* 74:52–81, 1983
18. Bogardus C, Lillioja S, Howard B, Reaven GM, Mott D: Relationships between insulin secretion, insulin action and fasting plasma glucose concentration in non-diabetic and non-insulin-dependent diabetic subjects. *J Clin Invest* 74:1238–46, 1984
19. Fraze E, Donner CC, Swislocki ALM, Chiou Y-AM, Chen Y-DI, Reaven GM: Ambient plasma free fatty acid concentrations in noninsulin-dependent diabetes mellitus: evidence for insulin resistance. *J Clin Endocrinol Metab* 61:807–11, 1985
20. Reaven GM, Miller R: Study of the relationship between glucose and insulin responses to an oral glucose load in man. *Diabetes* 17:560–69, 1968
21. Savage PJ, Dippe SE, Bennett PH, Gorden P, Roth J, Rushforth NB, Miller M: Hyperinsulinemia and hypoinsulinemia: insulin responses to oral carbohydrate over a wide spectrum of glucose tolerance. *Diabetes* 24:362–68, 1975
22. Zimmet P, Whitehouse S, Alford F, Chisholm D: The relationship of insulin response to a glucose stimulus over a wide range of glucose tolerance. *Diabetologia* 15:23–27, 1978
23. Reaven GM, Miller RG: An attempt to define the nature of chemical diabetes using a multidimensional analysis. *Diabetologia* 16:17–24, 1979
24. Saad MF, Pettitt DJ, Mott DM, Knowler WC, Nelson RG, Bennett PH: Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. *Lancet* 1:1356–59, 1989
25. Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK: Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution. *Diabetes* 39:283–88, 1990
26. Sicree RA, Zimmet PZ, King HOM, Coventry JS: Plasma insulin response among Nauruans: prediction of deterioration in glucose tolerance over 6 yr. *Diabetes* 36:179–86, 1987
27. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Khan CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–15, 1990
28. Hollenbeck CB, Chen N, Chen Y-DI, Reaven GM: Relationship between the plasma insulin response to oral glucose and insulin-stimulated glucose utilization in normal subjects. *Diabetes* 33:460–63, 1984
29. Facchini F, Chen Y-DI, Hollenbeck CB, Reaven GM: Relationship between resistance to insulin-mediated glucose uptake urinary uric acid clearance, and plasma uric acid concentration. *JAMA* 266: 3008–11, 1991
30. Reaven GM, Lerner RL, Stern MP, Farquhar JW: Role of insulin in endogenous hypertriglyceridemia. *J Clin Invest* 46:1756–67, 1967
31. Olefsky JM, Farquhar JW, Reaven GM: Reappraisal of the role of insulin in hypertriglyceridemia. *Am J Med* 57:551–60, 1974
33. Laws A, Reaven GM: Evidence for an independent relationship between insulin resistance and fasting plasma HDL-cholesterol, triglyceride and insulin concentrations. *J Intern Med* 231:25–30, 1992
34. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–98, 1990
35. Ferrannini E, Haffner SM, Mitchell BD, Stern MP: Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 3:416–22, 1991
36. Miller GJ, Miller NE: Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. *Lancet* 1:16–19, 1975

37. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH: Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 335:827–38, 1990
38. Austin MA: Plasma triglyceride and coronary heart disease. *Arterioscler Thromb* 11:2–14, 1991
39. Pyörälä K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care* 2:131–41, 1979
40. Ducimetiere P, Eschwege E, Papoz L, Richard JL, Claude JR, Rosselin G: Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia* 19:205–10, 1980