Comparison of Insulin Secretion and In Vivo Insulin Action in Nonobese and Moderately Obese Individuals with Non-insulin-dependent Diabetes Mellitus

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SUMMARY

Insulin secretion and in vivo insulin action were quantified in nonobese and moderately obese patients (approximately 30% overweight) with non-insulin-dependent diabetes mellitus (NIDDM), matched for severity of diabetes. Insulin secretion was assessed by determining plasma insulin responses to a test meal given at noon, and in vivo insulin action by the insulin clamp technique. No significant differences were noted between the two groups for either variable. Thus, it cannot be assumed that the cause of hyperglycemia in patients with NIDDM differs between nonobese and moderately obese subjects. DIABETES 31:382–384, May 1982.

Patients with non-insulin-dependent diabetes mellitus (NIDDM) have varying degrees of insulin resistance and insulin deficiency.[1] Although loss of normal insulin sensitivity has been well documented in nonobese patients with NIDDM,[2–4] it is often assumed that it is in the obese patient that insulin resistance plays the more important role in the development of diabetes. In contrast, there seems to be general agreement that insulin deficiency is the major metabolic defect seen in thin patients with NIDDM. Indeed, the belief that there are substantial differences in the metabolic characteristics of these two groups of patients with NIDDM is so pervasive that a distinction between nonobese and obese subjects is made in the new system of classification of diabetes mellitus proposed by the National Diabetes Data Group.[5] Although this differentiation may have a good deal to recommend it, we are unaware of any studies in which insulin secretion and in vivo insulin action have actually been compared in obese and nonobese patients with NIDDM matched for degree of glucose intolerance. Given the wide acceptance of the notion that the two groups must differ substantially, it seemed reasonable that a study be performed in order to quantify these putative differences. The present investigation was conducted to supply this information.

MATERIALS AND METHODS

The experimental subjects, all of whom were volunteers, were admitted to the Stanford General Clinical Research Center. They consumed a weight-maintaining liquid formula diet, with a caloric distribution of 43% carbohydrate, 42% fat, and 15% protein. This diet was consumed for at least 3 days before any study. The daily intake was divided into three meals, containing $^1/_5$, $^2/_5$, and $^2/_5$ of total calories, and consumed at 0800, 1200, and 1800 h. Relative body weight (RBW) was determined from standard tables.[6] The obese subjects were approximately 30% overweight, none had a history of childhood obesity, and all were diet failures. The nonobese subjects had not lost weight. All subjects had NIDDM according to recently suggested criteria.[5] Participants had never taken insulin, and were not taking any medication or had any medical problems, other than diabetes, known to affect glucose metabolism. Hepatic, renal, and thyroid function were normal. Some relevant clinical characteristics of the patients are given in Table 1.

Insulin secretion was estimated by measuring plasma insulin concentrations for 3 h following an oral glucose challenge. In order to avoid excessive hyperglycemia and hyperosmolality, a conventional oral glucose tolerance test was not performed. Instead, we determined the plasma glucose and insulin responses to the noon feeding. In this in-

TABLE 1
Clinical characteristics (mean ± SEM)

Group	N	Age (yr)	RBW (%)	Fasting glucose
NIDDM, nonobese	13	57 ± 2	98 ± 2	280 ± 18
NIDDM, obese	13	55 ± 3	129 ± 6	265 ± 13

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stance, blood was drawn at 1200 h (before the formula was given), at 1230 h (when the feeding was completed), and 1 (1300 h), 2 (1400 h), and 3 h (1500 h) after the meal was started. The amount of carbohydrate ingested at this meal varied with body weight, e.g., a 70-kg individual received a carbohydrate challenge equivalent to 105 g of glucose.

In vivo insulin action was estimated by the insulin clamp technique. Since this method has been previously described in detail,[7] only the general procedure will be outlined. Blood samples were obtained every 5 min from an indwelling catheter in a hand vein. The hand was kept in a radiant warmer at 70°C to provide arterialized samples. Plasma was immediately separated in a Beckman microfuge (Beckman Model S, Fullerton, California), and glucose determined in triplicate using a Beckman Glucose Analyzer II (Beckman Instruments). After establishing the baseline plasma glucose concentration, a primed continuous infusion of insulin at 42.6 mU/m²/min was started. Plasma glucose was determined every 5 min. At 4 min after the start of the insulin infusion, a variable infusion of glucose was administered using a negative feedback algorithm. This infusion was adjusted to maintain the plasma glucose within 10% of the baseline value. The amount of glucose metabolized (M) between 20 and 120 min of the study was computed from the amount of glucose infused, with corrections made for urinary glucose loss and changes in glucose pool size.[7]

The use of the glucose clamp to assess glucose utilization is based on the assumption that the amount of glucose infused to maintain basal glucose levels is equal to the rate of glucose utilization. However, this is the case only when hepatic glucose production is suppressed. In order to quantify glucose utilization rate, total glucose turnover must also be determined during the clamp studies. This was done by modification of techniques previously described from our laboratory.[8] [^{3}H-3]-Glucose (62 μCi) was injected as an intravenous bolus 3 h before the start of the clamp study, followed by a constant infusion of 0.25 μCi/min for a total of 5 h. Aliquots of plasma were precipitated with $BaOH_2$ and $ZnSO_4$ at 20-min intervals, centrifuged, and the protein-free supernatant evaporated in a scintillation vial. Plasma glucose concentration and radioactivity were determined, and glucose specific activity calculated.

The rate of appearance of glucose (Ra) and the rate of disappearance of glucose (Rd) were calculated at 20-min intervals before and during the insulin infusion, using the non-steady-state equation of Steele.[9] Ra and Rd should be equal during the period before the administration of insulin, and is assumed to equal basal hepatic glucose output. Subtraction of the glucose infusion rate from the value of Ra during the clamp study yields hepatic glucose output (HGO) under the condition of hyperinsulinemia, and comparison of these two values defines the degrees to which insulin inhibited HGO.

Plasma glucose[10] and insulin concentrations[11] were measured by standard methods. Statistical analysis was performed using the Statistical Package for the Social Sciences.

TABLE 2
Mean (± SEM) hepatic glucose output (mg/kg/ml)

Group	HGO-Basal	HGO-Infusion
Nonobese	2.62 ± 0.4	0.15 ± 0.09
Obese	2.67 ± 0.6	0.17 ± 0.04

RESULTS

The estimates of insulin secretion and action in the two groups are summarized in Figure 1. It is apparent that the plasma glucose and insulin responses of the two groups were quite comparable. Glucose utilization rates during insulin clamp studies were expressed in terms of both body weight and surface area, but it is clear that the results are the same: glucose utilization rates were the same in both groups of subjects, and this occurred at comparable steady-state plasma insulin levels (98 ± 9 and 96 ± 7 μU/ml in nonobese and obese subjects, respectively). For comparison's sake, it is worth pointing out that these mean values for M are approximately 50% that of normal subjects we have studied.[12,13] However, since the elevated plasma glucose levels of patients with NIDDM promote glucose uptake, this comparison minimizes the loss of in vivo insulin action seen in patients with NIDDM.

Table 2 indicates that HGO was comparable in the two groups in the basal state. Furthermore, the insulin infusion essentially totally suppressed HGO in both groups. This latter result, which is not surprising given the degree of hyperglycemia and hyperinsulinemia that was obtained dur-

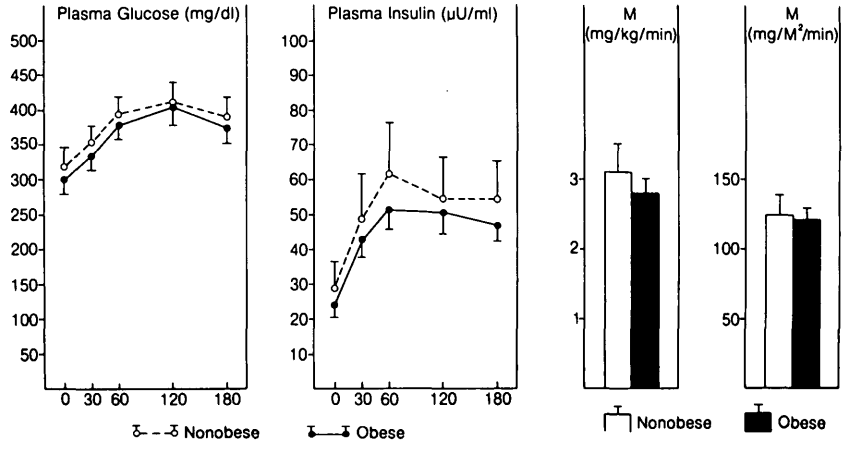

FIGURE 1. Mean (± SEM) plasma glucose and insulin responses to a test mixed meal and glucose utilization rates (M) in nonobese and obese subjects with non-insulin-dependent diabetes mellitus.

ing these studies, indicates that the values for M seen in Figure 1 closely approximate total glucose utilization.

DISCUSSION

The results presented indicate that essentially identical estimates of insulin secretion and in vivo insulin action were found when we compared obese and nonobese patients with NIDDM matched for severity of diabetes. As a corollary, these data suggest that the metabolic defects responsible for development of diabetes must be similar in both groups. This conclusion is at variance with the usual notion that nonobese patients are insulin deficient and obese patients insulin resistant. As such it is important to make sure that the data are not misleading. However, there are no obvious reasons why this should be the case, particularly as regards our estimates of the insulin secretory response to oral glucose. The techniques used are quite straightforward, and the number of subjects in the two subgroups of patients with NIDDM is substantial. The situation concerning our estimates of in vivo insulin action is more complicated. The glucose clamp technique is not a simple one, but we have had considerable experience with its use,[12] and the clamps were technically excellent by all the usual criteria.[7] Since the steady-state insulin concentrations of obese and nonobese subjects were also quite comparable during the clamp period, this cannot explain the fact that glucose utilization rates (M) were similar in obese and nonobese subjects with NIDDM. Finally, HGO was suppressed to an equal degree during the clamp studies in both groups. Given all of these considerations, it seems most likely that our data are not flawed, and that insulin secretion and in vivo insulin action were similar when nonobese and obese patients were matched for degree of glucose tolerance.

On the other hand, the fact that our results indicate that insulin secretion and in vivo action were similar in obese and nonobese patients when matched for severity of diabetes does not mean that changes in obesity will not affect these variables. In the first place, our patients were not massively obese. Second, we did not perform full insulin dose-response curves, and it is possible that glucose utilization would be lower if obese subjects were compared with nonobese subjects at much higher steady-state insulin levels. (Parenthetically, one could also question the significance of differences in the ability of insulin to stimulate in vivo glucose uptake at insulin levels far beyond those that occur in vivo.) Furthermore, there is certainly evidence that in vivo insulin action improves with weight loss.[14] Thus, there is good evidence that obesity modulates insulin action. However, the fact that obesity can modify insulin action does not negate the fact that it is only one of many factors that have this capacity. Thus, our inability to document an effect of moderate obesity on insulin resistance in a cross-sectional study, as contrasted to a longitudinal one, simply testifies to the complexity of the situation.

Finally, the observation that nonobese and moderately obese subjects had similar values for insulin secretion and action under our experimental conditions does not necessarily mean that the metabolic defects responsible for diabetes are the same in both groups. It is clear that patients with NIDDM, both obese and nonobese, have defects in both insulin secretion and action, and the relative roles played by these two abnormalities in the genesis of the hyperglycemia in either situation remains an unanswered question.[15] The results presented here do not help solve the dilemma, but strongly suggest that whatever answer does emerge will be relevant to both nonobese and moderately obese patients with NIDDM.

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