Effect of Obesity on Insulin Resistance in Normal Subjects and Patients With NIDDM

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Insulin resistance (IR) is a characteristic feature of non-insulin-dependent diabetes mellitus (NIDDM) as well as obesity, and a majority of NIDDM patients are obese. To assess the effect of obesity independent of NIDDM on IR, we studied the relationship between IR and obesity in 65 normal and 58 NIDDM subjects; we used body mass index (BMI) as a measure of obesity and glucose infusion rate (GINF) during a euglycemic hyperinsulinemic (120 mU · $m^{-2} \cdot min^{-1}$) glucose clamp as a measure of IR. In lean normal subjects, GINF was 57.7 ± 2.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (10.4 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$) and the lean NIDDM subjects were markedly insulin-resistant, with a GINF of 34.4 ± 2.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (6.2 ± 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$). Obese normal subjects were also insulin-resistant compared with lean normal subjects, with a GINF of 36.1 ± 2.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (6.5 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$), and obesity caused an increase in IR in NIDDM, with a GINF of 21.1 ± 1.4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (3.8 ± 0.25 $mg \cdot kg^{-1} \cdot min^{-1}$) in the obese NIDDM subjects. Therefore, ~61% of the IR in obese NIDDM subjects is due to NIDDM, with 39% due to obesity, demonstrating a greater impact of NIDDM than of obesity in causing IR. The correlation between GINF and BMI was much better in normal subjects ($r = -0.75$) than in NIDDM subjects ($r = -0.50$) as was the relationship between fasting insulin level and BMI ($r = -0.59$ in normal subjects, $r = -0.48$ in NIDDM subjects). As expected, the fasting insulin level was also strongly correlated to GINF in normal subjects ($r = -0.61$); however, this relationship was weaker in NIDDM subjects ($r = -0.46$). In conclusion, *1*) obesity has a major impact to cause insulin resistance in nondiabetic subjects, but the effect of obesity on IR in NIDDM is less; *2*) NIDDM per se is the major contributor to IR in NIDDM; and *3*) the fasting insulin level is a better surrogate marker of IR in nondiabetic subjects than in NIDDM patients. *Diabetes* 44:1121–1125, 1995

Obesity and non-insulin-dependent diabetes mellitus (NIDDM) are characterized by insulin resistance (1). Most patients with NIDDM are obese; however, the contribution of obesity to the insulin resistance of NIDDM remains a matter of controversy. Although it is well known that weight loss improves insulin sensitivity and glycemic control in obese NIDDM patients (2–5), the effect of obesity on insulin resistance, independent of NIDDM, has not yet been defined thoroughly.

Several studies have addressed the correlation between insulin action and obesity in NIDDM. Reaven et al. (6) and Hollenbeck et al. (7) found no difference in insulin resistance between lean and obese subjects. These data were confirmed by Firth et al. (8), who found no correlation between glucose utilization and obesity in NIDDM subjects. In contrast to these findings, when Campbell and Carlson (9) investigated the impact of obesity on insulin action in NIDDM using a sequential insulin infusion protocol, they found a significant correlation between the degree of obesity and insulin action in NIDDM during the lower insulin infusion rates. However, they were not able to demonstrate a significant correlation between body mass index (BMI) and glucose disposal in nondiabetic control subjects.

In the present study, we have evaluated this issue by assessing the relationship between the degree of insulin resistance and obesity in a larger number of nondiabetic and NIDDM subjects over a wide range of BMI.

RESEARCH DESIGN AND METHODS

Subjects. We studied the relationship between insulin resistance and obesity in 65 nondiabetic subjects and 58 patients with NIDDM in sequential euglycemic clamp studies performed in this unit. The clinical characteristics of the study subjects are shown in Table 1. The subjects were subdivided further into lean (BMI < 28 kg/m^2) normal subjects (n = 30, BMI = 24.7 ± 0.4 kg/m^2), lean NIDDM patients (n = 16, BMI = 24.6 ± 0.5 kg/m^2), obese (BMI ≥ 28 kg/m^2) normal subjects (n = 35, BMI = 34.6 ± 0.7 kg/m^2), and obese NIDDM patients (n = 42, BMI = 35.0 ± 1.0 kg/m^2). All participants were admitted 3 days before the study to the San Diego VA Medical Center's Special Diagnostic and Treatment Unit and consumed a weight maintenance diet containing 55% carbohydrate, 30% fat, and 15% protein. Diabetic subjects had fasting plasma glucose (FPG) values >7.8 mmol/l, and control subjects had FPG values <6 mmol/l and a normal oral glucose tolerance test result based on the criteria published by the National Diabetes Data Group (10). No diabetic patients were taking insulin, and in those taking oral hypoglycemic agents medication were withdrawn at least 3 weeks before the study. The purpose, nature, and potential risks of the study were explained in detail to all subjects before obtaining their written consent. The study protocol was reviewed and approved by the Human Subjects Committee of the University of California, San Diego.

Experimental protocol. All studies were performed at 8.00 A.M. after a 10- to 12-h overnight fast.

Oral glucose tolerance test. Blood was drawn for measurement of FPG and insulin concentrations. A 75-g oral glucose load was then administered. Blood was drawn for repeated measurements of glucose and insulin levels at 30, 60, 90, 120, and 180 min.

Glucose clamp study. The glucose clamp was performed as described previously under euglycemic conditions to measure quantitatively glucose uptake and maintain plasma glucose and insulin at the required concentrations (11,12). Using this approach, an antecubital vein was cannulated in an antegrade manner to administer infusates. A dorsal hand vein was cannulated in a retrograde fashion and kept in a warming device (72°C) to facilitate venous sampling and provide arterialized

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BMI, body mass index; FPG, fasting plasma glucose; GINF, glucose infusion rate; HGO, hepatic glucose output; NIDDM, non-insulin-dependent diabetes mellitus.

TABLE 1
Clinical characteristics of the study subjects

	Control subjects	NIDDM patients
n	65	58
Sex (M/F)	59/6	49/9
Age (years)	44.4 ± 1.0	53.1 ± 1.2*
Fasting glucose (mmol/l)	5.3 ± 0.1	11.7 ± 0.4*
Fasting insulin (pmol/l)	80 ± 10	125 ± 14†

Data are means ± SE. *$P < 0.0001$, †$P < 0.01$, NIDDM vs. control.

venous blood. A loading dose of insulin was administered in a logarithmically decreasing manner over the next 10-min period and was followed immediately by a constant infusion rate (120 mU · m^{-2} · min^{-1} for the next 300 min). The plasma glucose was maintained at the desired concentration throughout the study by monitoring the plasma glucose at 5-min intervals and adjusting the infusion rate of a 20% dextrose solution using a servo-control negative-feedback principle. Thus, plasma glucose and insulin concentrations were kept constant whereas the glucose infusion rate varied. Potassium and phosphate were given intravenously to compensate for the intracellular movement of these ions and to maintain normal serum levels. The mean glucose infusion rate (GINF) during the final hour of the clamp that was required to maintain euglycemia served as an overall measure of insulin action on glucose metabolism. The insulin levels resulting from the insulin infusion rate chosen (120 mU · m^{-2} · min^{-1}) have been shown to suppress almost completely hepatic glucose output (HGO) (13), which precludes the use of isotopic tracer to estimate HGO. Thus, the glucose infusion rate was assumed under these conditions to equal glucose disposal.

Analytical techniques and calculations. Glucose was measured with a YSI automated glucose analyzer (Yellow Springs, OH). Insulin was assayed by a double-antibody radioimmunoassay according to the method of Desbuquois and Aurbach (14). The GINF required to maintain euglycemia was measured at 20-min intervals during the final hour of the clamp, and the results are expressed as the mean of these three measurements. The degree of obesity was expressed as BMI (weight in kg/height in m^2).

Statistical analysis. Data are expressed as means ± SE. Statistical analyses were performed with nonpaired Student's *t* tests, simple and multiple linear regression, and $P < 0.05$ was considered significant.

RESULTS

Relationship between GINF and BMI in control subjects and NIDDM patients. Figure 1 shows the results for the entire study population and demonstrates a continuous relationship in the nondiabetic subjects (negative correlation coefficient $r = -0.75$, $P < 0.0001$), whereas in the diabetic subjects not only is the correlation coefficient lower ($r = -0.50$, $P < 0.0001$), but the relationship appears to be discontinuous at the lower levels of BMI. When GINF was expressed as μmol · m^{-2} · min^{-1} (which minimizes the effect of body mass), the negative correlations were weaker in both the nondiabetic subjects ($r = -0.58$, $P < 0.0001$) and the diabetic patients ($r = -0.32$, $P = 0.015$). To illustrate this further, these subjects were divided into lean (BMI < 28 kg/m^2) and obese (BMI > 28 kg/m^2) and the relationship between BMI and GINF was examined separately in the lean or obese nondiabetic and diabetic subjects. The correlation between GINF and BMI remained highly significant in the nonobese control subjects ($r = -0.50$, $P < 0.01$); however, in the nonobese diabetic patients no significant correlation was found between these two variables ($r = -0.03$, $P = 0.91$). When GINF was expressed as μmol · m^{-2} · min^{-1}, the negative correlation in the nonobese control subjects lost significance ($r = -0.31$, $P = 0.09$). When this relationship was examined in the obese groups, a significant relationship was demonstrated in the obese nondiabetic subjects ($r = -0.53$, $P < 0.001$). In the obese diabetic patients, a significant relationship was observed ($r = -0.34$, $P < 0.05$), but the magnitude of this relationship was less in the obese diabetic group compared with the obese nondiabetic group. Expressing the GINF as micromoles per meters squared per minute reduced the correlation in the obese nondiabetic patients ($r = -0.42$, $P = 0.012$) and caused the weak correlation in the obese diabetic patients to lose significance. Multiple regression analyses were performed, controlling for age and level of FPG. Holding these variables constant had only a minor effect on the correlation between BMI and GINF. In the normal group the correlation coefficient changed from −0.75 to −0.70, and in the NIDDM group it changed from −0.50 to −0.52. Among the subgroups, the effects were also minimal. Only FPG had an independent correlation with GINF, and then only in the control group (see below).

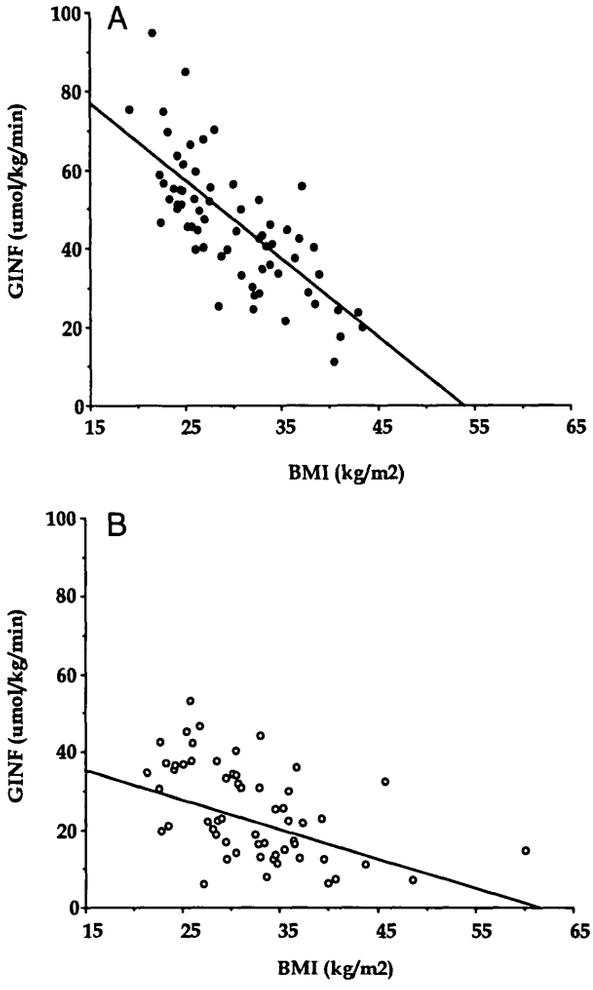

FIG. 1. Correlation between GINF and BMI in normal subjects (*A*, ●; $r = -0.75$; $P < 0.0001$) and NIDDM patients (*B*, ○; $r = -0.50$; $P < 0.0001$).

Relationship between glucose infusion rate and fasting serum insulin level in control subjects and NIDDM patients. Figure 2 shows that a significant inverse correlation existed between GINF and fasting serum insulin in both the control subjects ($r = -0.61$, $P < 0.0001$) (Fig. 2*A*) and NIDDM patients ($r = -0.46$, $P < 0.001$) (Fig. 2*B*); however, the correlation was weaker in NIDDM patients than in the control subjects.

Relationship between BMI and fasting serum insulin level in control subjects and NIDDM patients. A statistically significant positive relationship existed between fast-

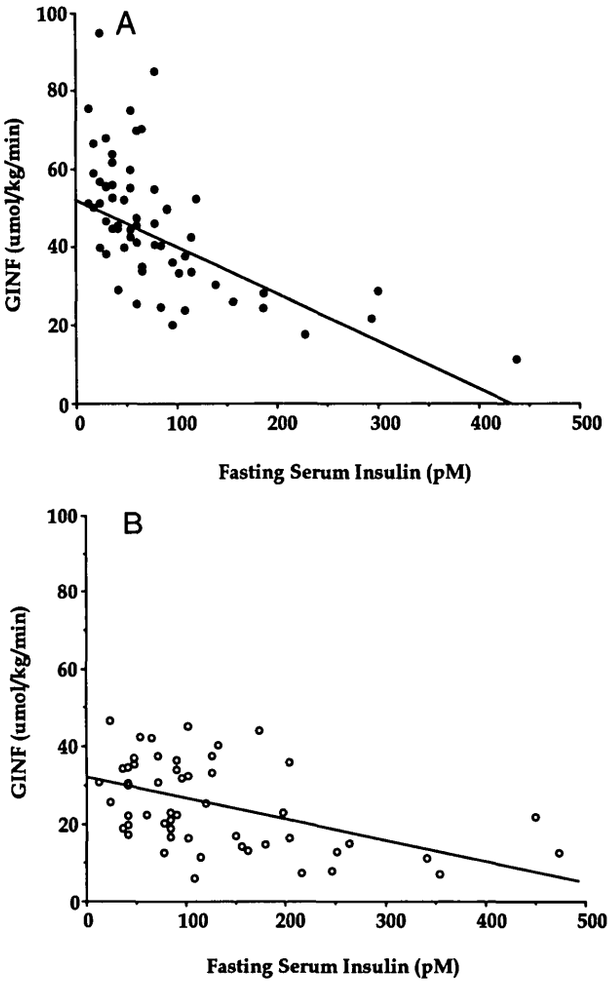

FIG. 2. Correlation between GINF and fasting serum insulin in normal subjects (*A*, ●; $r = -0.61$; $P < 0.0001$) and NIDDM patients (*B*, ○; $r = -0.46$; $P < 0.001$).

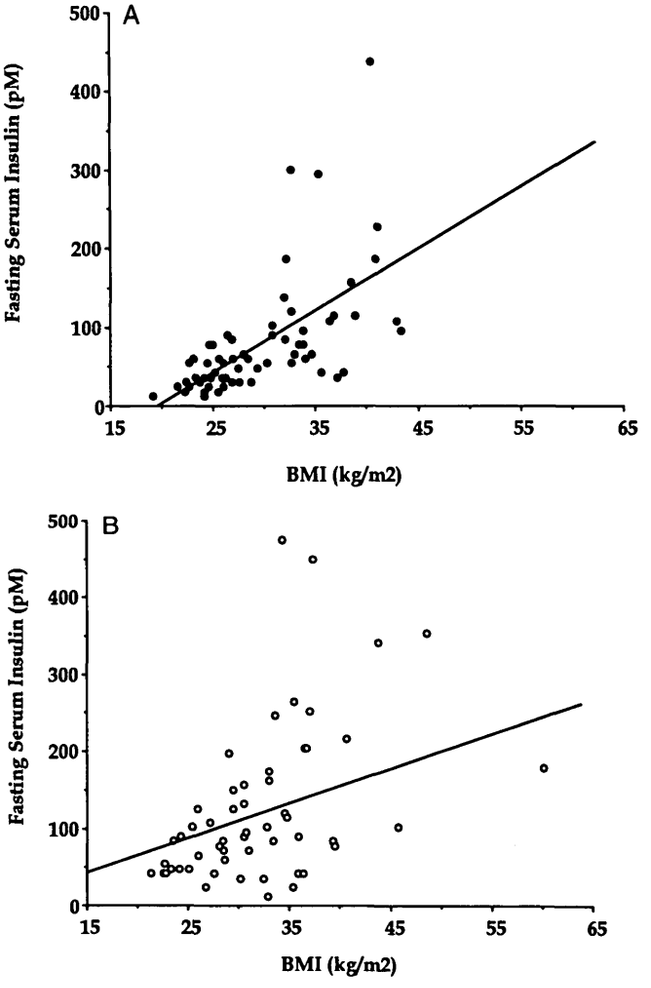

FIG. 3. Correlation between BMI and fasting serum insulin in normal subjects (*A*, ●; $r = 0.59$; $P < 0.0001$) and NIDDM patients (*B*, ○; $r = 0.48$; $P < 0.001$).

ing serum insulin and BMI in both control subjects ($r = 0.59$, $P < 0.0001$) (Fig. 3*A*) and NIDDM patients ($r = 0.48$, $P < 0.001$) (Fig. 3*B*). However, this correlation was weaker in the NIDDM group.

Magnitude of insulin resistance in the subject groups. The GINF values (means ± SE) for the various study groups are presented in Fig. 4. As shown in Fig. 4*A*, GINF was 57.7 ± 2.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (10.4 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$) in lean control subjects, 36.1 ± 2.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (6.5 ± 0.4 $mg \cdot kg^{-1} \cdot min^{-1}$) in obese control subjects ($P < 0.0001$ vs. lean control subjects), 34.4 ± 2.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (6.2 $mg \cdot kg^{-1} \cdot min^{-1}$) in lean NIDDM patients ($P < 0.0001$ vs. lean control subjects), and 21.1 ± 1.4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (3.8 $mg \cdot kg^{-1} \cdot min^{-1}$) in obese NIDDM patients ($P < 0.0001$ vs. lean control subjects, $P < 0.001$ vs. lean NIDDM patients). These data indicate that both NIDDM and obesity make independent contributions to the level of insulin resistance and that in obese NIDDM patients ~61% of the insulin resistance is due to NIDDM per se, with 39% due to obesity. When expressed as $mmol \cdot m^{-2} \cdot min^{-1}$ (Fig. 4*B*), the values for GINF were 2.26 ± 0.8 and 1.72 ± 0.1 $mmol \cdot m^{-2} \cdot min^{-1}$ in the lean and obese control subjects, respectively, and 1.35 ± 0.12 ($P < 0.0001$ compared with control subjects) and 1.01 ± 0.07 $mmol \cdot m^{-2} \cdot min^{-1}$ ($P = 0.016$ compared with control subjects) in the lean and obese NIDDM patients, respectively. In this formulation, ~75% of the insulin resistance in obese NIDDM patients is due to NIDDM per se, with only 25% attributable to obesity.

The FPG level showed a significant negative correlation with GINF in normal subjects ($r = -0.41$, $P < 0.001$) but not in NIDDM patients ($r = -0.12$, $P = 0.36$).

DISCUSSION

It has been clearly shown that insulin resistance is a prominent feature in nondiabetic obese subjects and NIDDM patients, independent of obesity (1). However, the relationship between obesity and insulin resistance in NIDDM remains poorly defined. Three studies have failed to demonstrate a significant correlation between obesity and insulin resistance in NIDDM patients. Hollenbeck et al. (7) and Reaven et al. (6) found no difference in glucose clearance rates between lean and obese NIDDM patients during hyperglycemic glucose clamps. These findings have been supported by Firth et al. (8), who demonstrated no significant correlation between BMI and glucose disposal in diabetic patients. Thus, these authors have concluded that the insulin resistance in NIDDM is unaffected by the degree of obesity. However, these results are difficult to reconcile with the well-known effect of weight loss in decreasing insulin resistance and improving metabolic control in NIDDM patients (5). Consistent with this, Campbell and Carlson (9) have

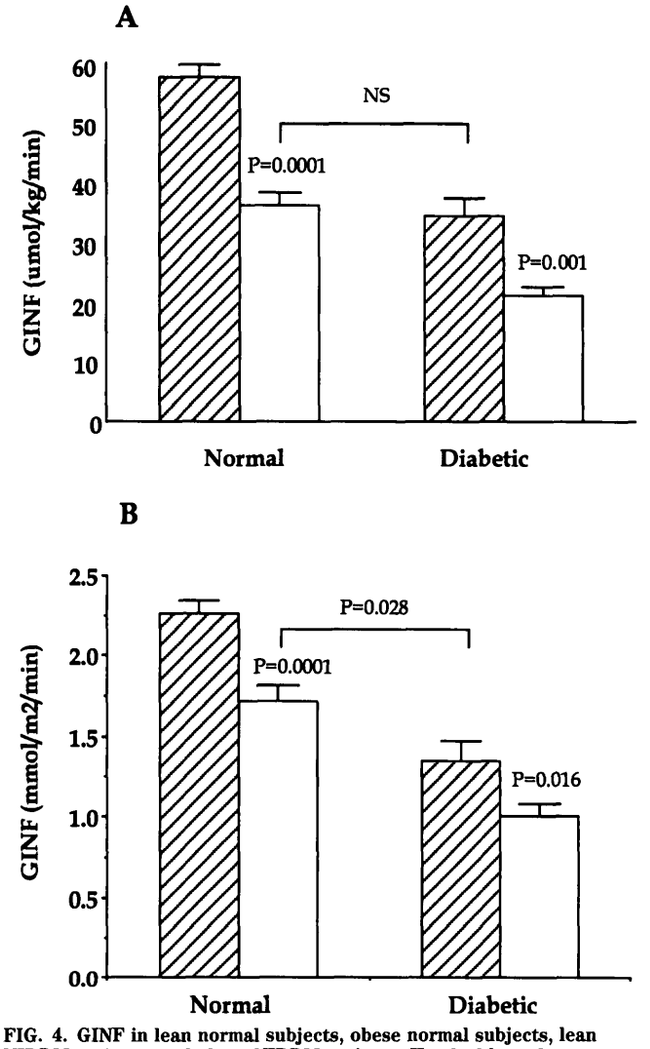

FIG. 4. GINF in lean normal subjects, obese normal subjects, lean NIDDM patients, and obese NIDDM patients. Hatched bars, lean subjects; open bars, obese subjects. *A:* GINF expressed in $\mu mol \cdot kg^{-1} \cdot min^{-1}$. *B:* GINF expressed as $mmol \cdot m^{-2} \cdot min^{-1}$.

reported a significant relationship between obesity and insulin resistance in NIDDM patients.

The reasons for these apparently discrepant results (6–9) are not clear. They may relate to the fact that these studies quantitated insulin resistance through different procedures and that relatively small numbers of subjects were studied. In the current report, we have assessed insulin resistance in obesity by standard measurements (euglycemic hyperinsulinemic glucose clamp and BMI) in a fairly large group of subjects (n = 123), representative of a wide range of BMI. In this study, all clamp studies were carried out for 300 min to ensure reliable steady-state measures of glucose disposal. Because of delays in activation, shorter clamp studies can fail to detect underlying differences in insulin-mediated glucose disposal. Our results show that obesity does contribute to the degree of insulin resistance in obese NIDDM patients but, for any given level of BMI, the impact of obesity is less in NIDDM patients than in nondiabetic subjects. In fact, if one examines only lean subjects (BMI <28 kg/m^2), then no relationship exists between BMI and insulin resistance in the diabetic patients, whereas a highly significant correlation still exists in the nondiabetic group. We interpret this to mean that the relationship between increasing adiposity and insulin resistance is a continuous inverse function in nondiabetic subjects. In NIDDM, because a large degree of insulin resistance is conferred by diabetes per se, the added effect of increasing adiposity is only appreciable when true obesity (BMI >28 kg/m^2) is superimposed. Furthermore, when GINF data were recalculated as micromoles per meters squared per minute, all correlations with BMI were weaker. The correlations lost significance in the lean normal subjects and the obese diabetic patients. Expressing glucose disposal per meters squared, and thereby lessening the effect of increased body mass, further supports the hypothesis that the major component of insulin resistance in NIDDM is diabetes, obesity being an even more minor component.

The relationship between insulin resistance and fasting plasma insulin levels was also of interest. An inverse relationship existed in both groups, such that the greater the degree of insulin resistance the higher the insulin level. However, the correlation coefficient was higher in the nondiabetic subjects, and the slope of the relationship was steeper. Note that for any given degree of insulin resistance, the fasting insulin level was greater in the nondiabetic subjects than in the diabetic patients. This raises the question: What is the feedback loop connecting insulin resistance to hyperinsulinemia? Clearly, peripheral glucose levels represent one important feedback signal in this loop, and this is supported by our findings that a significant positive correlation (r = 0.41, $P < 0.001$) existed between the FPG level and GINF in the nondiabetic subjects. However, it is also possible that other regulatory signals exist that modify the feedback relationship between the presence of insulin resistance and the degree of hyperinsulinemia. Regardless of the metabolic determinants of hyperinsulinemia, it is apparent that either the set points or the regulatory factors differ in diabetic patients compared with nondiabetic subjects. It is also possible that the defective β-cell function that exists in NIDDM is also manifested in the fasting insulin level, such that for a given level of insulin resistance basal insulin levels are lower in diabetic patients compared with nondiabetic subjects. Regardless of the mechanisms, these findings suggest that the fasting insulin level is a better marker for insulin resistance in nondiabetic subjects than in NIDDM patients.

The current results allow certain conclusions concerning the relative impact of obesity and diabetes in causing insulin resistance. For example, in nonobese NIDDM patients, the insulin resistance is obviously due entirely to diabetes, with no contribution from obesity. Judging from the obese NIDDM group, one can infer that ~60% of the insulin resistance in obese NIDDM patients is due to NIDDM, with 40% due to obesity (75 and 25% if the results are expressed per meters squared). Thus, one could argue that a majority of insulin resistance in NIDDM is attributable to the diabetes per se and less is attributable to obesity. This scenario is consistent with the clinical manifestations of most NIDDM patients. A majority of NIDDM patients are overweight, and the obesity usually presages the onset of NIDDM. After the onset of NIDDM, the insulin resistance becomes more severe. These comments should not be taken to mean that the insulin resistance of obesity and NIDDM is additive in a mechanistic sense. The cellular causes of the two may be completely different and, indeed, considerable evidence indicates that this is the case (1,11,12). Thus, our results only apply to the overall physiological manifestation of cellular insulin resistance, that is, decreased in vivo insulin-stimulated glucose uptake.

The above conclusions depend on the reliability of the BMI as an obesity index. BMI has been shown to have the strongest correlation with skinfold thickness and body density (15). Because the vast majority of the subjects studied were men, a possible gender-related difference in the validity of the BMI in the assessment of body composition has been minimized.

In conclusion, the results of this study indicate that obesity has a major impact on insulin resistance in nondiabetic subjects, but its effects on insulin resistance in NIDDM patients are more modest. Thus, diabetes per se is the major contributor to insulin resistance in NIDDM, whereas the effect of increasing obesity is less significant. Finally, the fasting insulin level is a better surrogate marker of insulin resistance in normal subjects than it is in NIDDM patients.

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