Insulin Binding in Non–Insulin-Dependent Diabetes Mellitus (NIDDM) Is Correlated With Glycemic Control: Clinical Evidence for Abnormal Receptor Regulation in NIDDM

Catherine M. Kelly, and I. George Fantus

Insulin binding has been reported to be decreased in non–insulin-dependent diabetes mellitus (NIDDM). Although elevated basal insulin concentrations have been correlated with decreased insulin binding in obesity, this relationship has not been found in NIDDM. To determine the potential cause(s) of the decrease, we measured ^{125}I-insulin binding to circulating monocytes isolated from 31 non–insulin-treated patients with NIDDM who had a fasting plasma glucose (FPG) concentration greater than 7.8 mmol/L and 13 control subjects. We examined the influence of obesity, insulin concentration, glycemic control, and treatment with oral hypoglycemic agents on insulin binding in a cross-sectional study. Insulin binding was significantly decreased in the entire NIDDM group (mean ± SEM, %/10^7 monocytes: 4.65 ± 0.33) as compared with controls (6.45 ± .70, $P < .02$). Subgroups defined by obesity (relative body weight > 1.2) and poor glycemic control (FPG > 11.1 mmol/L) and those not taking oral hypoglycemic agents had significantly lower insulin binding ($P < .02$). However, neither relative body weight nor insulin concentrations (basal or stimulated) correlated with insulin binding. Stepwise linear regression analysis showed that only FPG significantly correlated with insulin binding ($r = -.45$, $P = .002$) even when oral hypoglycemic agent–treated patients were removed from the analysis ($r = -.50$, $P = .003$). There was no significant contribution to explain insulin binding by the other variables, including diagnosis of diabetes, obesity, insulin concentration, or treatment with oral hypoglycemic agents. We conclude that poor metabolic control is associated with an alteration in insulin receptor regulation in NIDDM.

IN NON–INSULIN-DEPENDENT diabetes mellitus (NIDDM), defects in both insulin secretion[1-3] and insulin action[3-5] have been described. In nondiabetic obese subjects, insulin resistance is manifested as insulin insensitivity and has been attributed at least in part to reduced insulin binding.[6,7] This has been demonstrated by measurement of the in vivo insulin dose-response curve for glucose disposal with the euglycemic glucose-clamp technique and quantification of insulin binding to both adipocytes and monocytes.[7,8] In obese subjects, insulin binding has been found to correlate inversely with basal insulin concentrations.[7,9] The hyperinsulinemia has been postulated to play an important role in downregulating insulin receptors.[9,10] Similarly, Olefsky and Reaven[11] have shown that basal insulin concentrations correlated negatively with insulin binding to monocytes in a combined group of "chemical" diabetics (impaired glucose tolerance) and normal controls. In contrast, similar studies in patients with NIDDM, ie, with fasting hyperglycemia, have not shown such a relationship.[11-15] Although, on average, insulin binding is lower than normal in these individuals,[11,12] in some studies insulin binding has been reported as normal[15] or heterogeneous.[13] Furthermore, neither insulin binding nor receptor number correlated with basal insulin concentrations in these patients.[11] These data imply that factors other than insulin must influence insulin binding in NIDDM. In vivo glucose-clamp studies in NIDDM have shown both a rightward shift of the insulin dose-response curve, similar to that in obese subjects, and an unresponsiveness to insulin, attributed to a postbinding defect.[14] Thus, although it is physiologically important in determining insulin sensitivity, the regulation of insulin binding in NIDDM remains unclear.

The purpose of this study was to measure insulin binding to monocytes in a diverse group of patients with NIDDM and examine its relationship to body weight, insulin concentration, glycemic control, and drug treatment. Our results emphasize the heterogeneity of insulin binding in all subgroups of NIDDM patients. Although insulin binding was not related to basal or stimulated insulin concentrations, we found a significant inverse correlation with postabsorptive glucose concentrations. This association suggests the possibility that an abnormality of receptor regulation is associated with poorly controlled NIDDM and that improvement of metabolic control results in an increase in insulin binding.

SUBJECTS AND METHODS

Subjects

Thirteen normal control subjects and 31 patients with NIDDM were studied in the Metabolic Day Center of the Royal Victoria Hospital. Written informed consent was obtained from all subjects. All subjects were in stable health as judged by medical history, physical examination, and standard laboratory determinations. To confine our study to patients with NIDDM, all patients were screened to ensure that fasting plasma glucose (FPG) concentration was more than 7.8 mmol/L. The patients were on a standard diet consisting of 45% carbohydrate, 35% fat, and 20% protein and had maintained a stable weight for at least 6 weeks. Control subjects were instructed to eat 200 g carbohydrate for 3 days before the binding studies; oral glucose tolerance tests were performed to ensure normal carbohydrate tolerance. Studies were performed in the follicular phase of the menstrual cycle in all premenopausal

From the Protein and Polypeptide Hormone Laboratory, Department of Medicine, Royal Victoria Hospital, McGill University, Montreal, Quebec; and the Department of Medicine, Mount Sinai Hospital and Banting and Best Diabetes Centre, University of Toronto, Toronto, Ontario, Canada.

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Address reprint requests to I. George Fantus, MD, Mount Sinai Hospital, 600 University Ave, Suite 780, Toronto, Ontario, M5G 1X5 Canada.

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women. Weight and activity level were maintained constant for 6 weeks.

Oral Glucose Tolerance Tests

Oral glucose tolerance tests were begun at 9 AM after an overnight fast. Before and at 0.5, 1, 1.5, 2, and 3 hours after a 75-g oral glucose load, venous blood was withdrawn for determination of glucose and insulin concentrations. At time 0, an additional 120-mL blood sample was taken for insulin binding studies. Plasma glucose concentrations were determined by the glucose oxidase method, and insulin, by double-antibody radioimmunoassay as described previously.[16]

^{125}I-insulin Binding to Monocytes

Whole blood was diluted 1:1 with Dulbecco's phosphate-buffered saline at room temperature. Mononuclear cells were isolated by centrifugation through a Ficoll (0.9%)-Hypaque (33.9%) gradient (Pharmacia, Baie d'Urfe, Canada) using the method reported by Boyum.[17] The cell suspension was washed and resuspended in 100 mmol/L HEPES buffer with 1% bovine serum albumin (Sigma Chemical, St Louis, MO) at an approximate concentration of 50×10^6 cells/mL. Porcine monocomponent insulin (Nordisk Laboratories, Gentofte, Denmark) was labeled with Na^{125}I (New England Nuclear, Boston, MA) at a specific activity of 130 to 180 μCi/μg by a modification of the chloramine-T method.[18] The cells were incubated with 0.2 ng/mL ^{125}I-insulin and varying concentrations of unlabeled insulin (0 to 100 μg/mL). The binding assay was performed as previously described,[9] except that the incubation was at 15°C for 3 hours. Preliminary experiments showed that equilibrium binding was achieved under these conditions. The percentage of monocytes in the mononuclear cell preparation was determined by phagocytosis of latex beads[19] (Seragen Diagnostics, Indianapolis, IN). There were no differences in the percentage of monocytes between control subjects and patients. Nonspecific binding, determined as the amount of ^{125}I-insulin bound in the presence of 100 μg/mL unlabeled insulin, was less than 1% of total radioactivity and was subtracted from total binding to yield specific binding. Specific binding was corrected to 10^7 monocytes per milliliter.

Analysis of Data

Insulin binding data were analyzed as competition curves and Scatchard plots.[20] Since extrapolation of Scatchard plots to the x-axis is associated with uncertainty, the R_0 was calculated at the insulin concentration of 100 ng/mL (17 mmol/L).[11] The insulin area under the curve (AUC) above basal was calculated as previously described.[16] Statistical comparisons of binding data were performed using two-tailed Student's t test unless otherwise indicated. Linear regression analysis by the least-squares method was used to determine correlation coefficients.

To determine the relative contribution of the multiple clinical parameters (variables), a stepwise and a backward-selection method for multiple regression models was used to determine the best combination of variables to explain insulin binding using the program SAS/STAT Version 6.0 (SAS Institute, Cary NC).

RESULTS

The control group consisted of 13 healthy young volunteers with a mean ±SE age of 26.9 ± 2.8 years. The mean age of the NIDDM group was 51.8 ± 2.4 years, which was significantly greater ($P < .001$). NIDDM patients were subgrouped according to relative body weight, level of fasting glycemia, and presence or absence of treatment with oral hypoglycemic agents (Table 1). The lean group (NIDDM-lean) was defined by a relative body weight of less than 1.20. Well-controlled diabetic patients (NIDDM-WC) were defined by a FPG of less than 11.1 mmol/L (200 mg/dL). Poorly controlled patients (NIDDM-PC) were those with FPG ≥ 11.1 mmol/L. The drug-treated group consisted of 11 subjects who were taking sulfonylurea drugs, either chlorpropamide or glyburide. There were no significant differences in mean ages among NIDDM subgroups. The duration of NIDDM varied from 6 months to 21 years.

Table 1. Clinical Characteristics of Controls and Patients With NIDDM

	No. of Subjects	Men	Women	Age (yr)	Relative Body Weight
Controls	13	9	4	26.9 ± 2.8	1.01 ± .02
NIDDM-all	31	18	13	51.8 ± 2.4†	1.35 ± .05†
NIDDM-lean	12	9	3	53.5 ± 3.6	1.08 ± .02*
NIDDM-obese	19	9	10	51.8 ± 2.5	1.52 ± .06‡
NIDDM-WC	10	8	2	58.4 ± 3.5	1.40 ± .09†
NIDDM-PC	21	10	11	50.5 ± 2.3	1.32 ± .07†
NIDDM–drug-treated	11	7	4	48.2 ± 3.7	1.36 ± .09†
NIDDM–no drug	20	11	9	55.5 ± 2.4	1.35 ± .07†

NOTE. Values are the mean ± SE. Relative body weight was calculated from Metropolitan Life Insurance Tables.

*$P < .05$, †$P < .001$ v controls.

‡$P < .001$ v NIDDM-lean.

The mean fasting glucose concentration was significantly greater in the NIDDM group as compared with controls (12.2 ± 0.49 v 4.5 ± 0.07 mmol/L, $P < .001$; Table 2). The separation of lean and obese subgroups was confirmed by calculation of the mean ±SEM body mass index (weight in kilograms divided by height in meters squared), which was significantly greater in the obese group (obese 32.5 ± 1.7 v lean 23.7 ± 0.7, $P < .001$). The NIDDM-WC subgroup had a lower FPG than the NIDDM-PC subgroup (9.5 ± 0.28 v 13.4 ± 0.51 mmol/L, $P < .001$). It should be noted that the subgroup on drug treatment also had a significantly lower FPG as compared with those treated with diet alone

Table 2. Glucose and Insulin Concentrations and Insulin Binding in NIDDM

	FPG (mmol/L)	FPI (pmol/L)	Insulin AUC (pmol/L/h)	% Specific ^{125}I-insulin Bound per 10^7 Monocytes
Controls	4.5 ± .07‡	87.2 ± 7.8	680 ± 134	6.45 ± .70
NIDDM-all	12.2 ± .49	143.6 ± 19.3	438 ± 86	4.65 ± .33†
NIDDM-lean	11.7 ± .87	117.2 ± 24.0	429 ± 156	5.0 ± .54
NIDDM-obese	12.4 ± .59	160.3 ± 27.5*	445 ± 99	4.43 ± .59†
NIDDM-WC	9.5 ± .28	138.6 ± 27.0	396 ± 99	5.13 ± .50
NIDDM-PC	13.4 ± .51‖	146.0 ± 25.9	456 ± 117	4.42 ± .42†
NIDDM–drug-treated	10.4 ± .45	138.9 ± 23.3	389 ± 54	5.01 ± .62
NIDDM–no drug	13.1 ± .62§	146.2 ± 27.5	464 ± 130	4.45 ± .38†

NOTE. Results are the mean ± SEM.

*$P < .05$ v controls.

†$P < .02$ v controls.

‡$P < .001$ v all other groups.

§$P < .01$ v NIDDM–drug-treated.

‖$P < .001$ v NIDDM-WC.

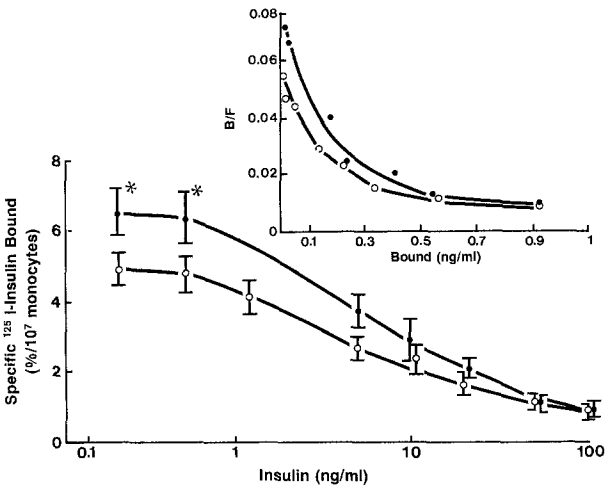

Fig 1. Insulin binding in NIDDM. Competition curves and Scatchard plots (inset) of ^{125}I-insulin binding to monocytes isolated from (●) controls (n = 13) and (○) patients (n = 31) with NIDDM. Mean ± SEM. *$P < .05$.

(NIDDM–drug-treated 10.4 ± 0.45 *v* no drug 13.1 ± 0.62 mmol/L, $P < .01$). Fasting plasma insulin (FPI) concentrations tended to be slightly elevated in the entire group of NIDDM patients and in all subgroups. However, mean values did not differ significantly from values in control subjects, except in the obese subgroup (Table 2). Insulin AUCs tended to be decreased as compared with control AUCs in the entire NIDDM group. However, the difference in mean values did not quite reach statistical significance ($.05 < P < .1$) (Table 2).

^{125}I-insulin binding (mean ± SEM, %/10^7 monocytes) was lower in NIDDM patients as compared with controls (NIDDM 4.65 ± 0.33 *v* controls, 6.45 ± 0.70, $P < .02$) (Table 2). Examination of the insulin binding–inhibition curves showed that binding was lower at low insulin concentrations but approached the normal curve at higher concentrations of unlabeled hormone, suggesting a change in receptor affinity. Means of the receptor number per cell (R_o) calculated from total insulin bound at 100 ng/mL hormone on Scatchard analysis in the two groups were not different (mean ± SEM receptors per cell, control 10,697 ± 1,989 *v* NIDDM 10,067 ± 1,573, NS) (Fig 1). There was no relationship between duration of diabetes and insulin binding (data not shown).

One factor previously associated with decreased insulin binding is basal hyperinsulinemia.[6-10] Indeed in the subgroup of obese NIDDM patients mean insulin binding was significantly lower than in controls (4.43% ± 0.59% per 10^7 monocytes, $P < .02$), whereas in the lean NIDDM subgroup this was not the case (5.0% ± 0.59% per 10^7 monocytes) (Table 2). At the same time, mean FPI concentration was significantly elevated in the obese group (160.3 ± 27.5 *v* control 87.2 ± 7.8 pmol/L, $P < .05$), whereas it was not significantly different in the lean patients (117.2 ± 24.0 pmol/L) (Table 2). Although this suggested that hyperinsulinemia was a contributing factor to the decreased insulin binding in some patients, basal insulin concentrations of the entire NIDDM group were not significantly increased as compared with control levels (Table 2). Furthermore, elevated mean basal insulin concentrations were not observed in the two other subgroups that were found to have significantly decreased insulin binding, ie, NIDDM-PC and NIDDM–no drug treatment (Table 2). In examining the entire study population, there was no correlation between FPI concentrations and insulin binding ($r = -.126$). It may be noted that insulin AUC in response to oral glucose tended to be decreased in the NIDDM population, but did not differ in any of the subgroups (Table 2).

To determine whether a metabolic factor could account for the lower insulin binding in NIDDM, the patients were divided according to glycemic control as outlined earlier. Those with poor glycemic control had a significantly decreased mean insulin binding (4.42% ± 0.42% per 10^7 monocytes, $P < .02$) as compared with controls, whereas the well-controlled subgroup (5.13 ± 0.50) did not (Table 2). Competition curves showed that the difference between NIDDM-WC and NIDDM-PC was also apparent at higher concentrations of unlabeled insulin (Fig 2). Scatchard analysis (Fig 2, inset) demonstrated that this was associated with a higher R_o in NIDDM-WC (mean ± SEM receptors per cell, 14,891 ± 2,727 *v* 7,560 ± 1,465, $P < .05$).

Since it has been demonstrated in some studies that therapy with sulfonylurea drugs is associated with an increase in insulin binding,[21,22] we subdivided the patients on the basis of oral hypoglycemic therapy. Insulin binding was significantly decreased in patients not receiving drug treatment as compared with controls (4.45 ± 0.38, $P < .02$), but was not different from control values in those receiving therapy (5.01 ± 0.62) (Table 2). However, in contrast to NIDDM-WC and NIDDM-PC groups, there were no significant differences in the insulin binding competition curves between drug-treated and untreated subgroups (data not shown). We also noted that the drug-treated group had a significantly lower FPG than those not treated with drugs (10.4 ± 0.45 *v* 13.1 ± 0.62 mmol/L, $P < .01$), consistent with better metabolic control (Table 2).

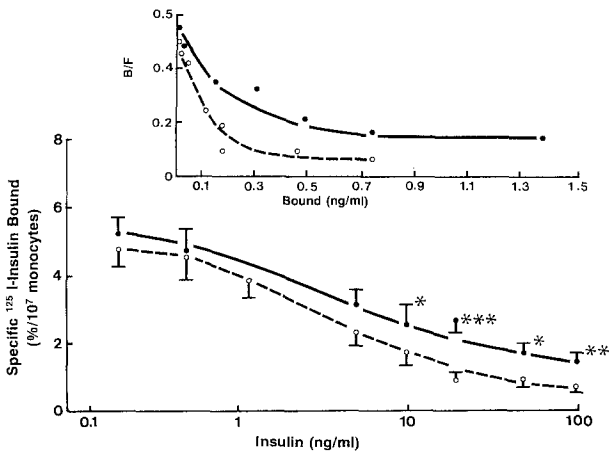

Fig 2. Comparison of insulin binding in (●) NIDDM-WC (n = 8) and (○) NIDDM-PC (n = 23). Groups are defined as in Table 1. Competition curves and Scatchard plots (inset). Mean ± SEM. *$P < .05$, **$P < .01$, ***$P < .001$.

To further test the hypothesis that insulin binding was related to metabolic control, FPG concentration was plotted versus insulin binding in the entire study population. A significant inverse correlation was observed ($r = -.452$, $P = .002$; Fig 3). To eliminate the possible confounding effects of sulfonylurea therapy, drug-treated patients were removed from the analysis. A significant inverse correlation between FPG and insulin binding persisted ($r = -.496$, $P = .003$).

Since we examined a number of clinical parameters that may influence insulin binding and it was possible that some of these may be interrelated, we performed a stepwise linear regression analysis to determine variables that best explained the variability in insulin binding. Including all study subjects, the only parameter significantly correlated with insulin binding was FPG (estimated regression equation: ^{125}I-insulin specific binding = 7.52 − 0.01 × FPG, $P = .002$). Neither diabetes status ($P = .897$), FPI ($P = .819$), nor obesity ($P = .601$) significantly correlated with binding either alone or in combination. Thus, the correlation of insulin binding with FPG could not be explained merely by a division of the population into NIDDM and control groups. A repeated analysis excluding the patients receiving oral hypoglycemic agents yielded similar results.

DISCUSSION

Insulin binding to circulating monocytes in patients with NIDDM was found to be significantly lower than in normal subjects. This difference was most closely associated with subgroups characterized by obesity and poor metabolic control and those not receiving oral hypoglycemic agents. Significant basal hyperinsulinemia, known to be present in nondiabetic subjects with obesity and decreased insulin binding, was observed in the obese subgroup with NIDDM. This finding is consistent with the documented effect of insulin to downregulate its own receptor. This process may have contributed to the decreased insulin binding in this subgroup. However, in NIDDM-PC, basal hyperinsulinemia was not observed. In fact, insulin concentrations in NIDDM-WC subjects were, on average, slightly higher. Thus, one (or more) factor(s) other than insulin apparently associated with poor metabolic control appears to have a significant influence on insulin binding in NIDDM. Further evaluation of our data showed that although basal insulin concentrations in the entire study population did not correlate with insulin binding ($r = .126$, P = NS), fasting glucose concentrations showed a significant inverse correlation ($r = -.452$, $P = .002$). The latter correlation could not be explained by differences in age, since previous studies have shown that insulin binding to monocytes remains constant until age 65, after which it may decrease,[23,24] and in this study insulin binding did not correlate with age (data not shown).

To be certain that the inverse relationship between insulin binding and FPG was not merely a reflection of differences in both parameters between control and diabetic populations, as well as to determine the possible

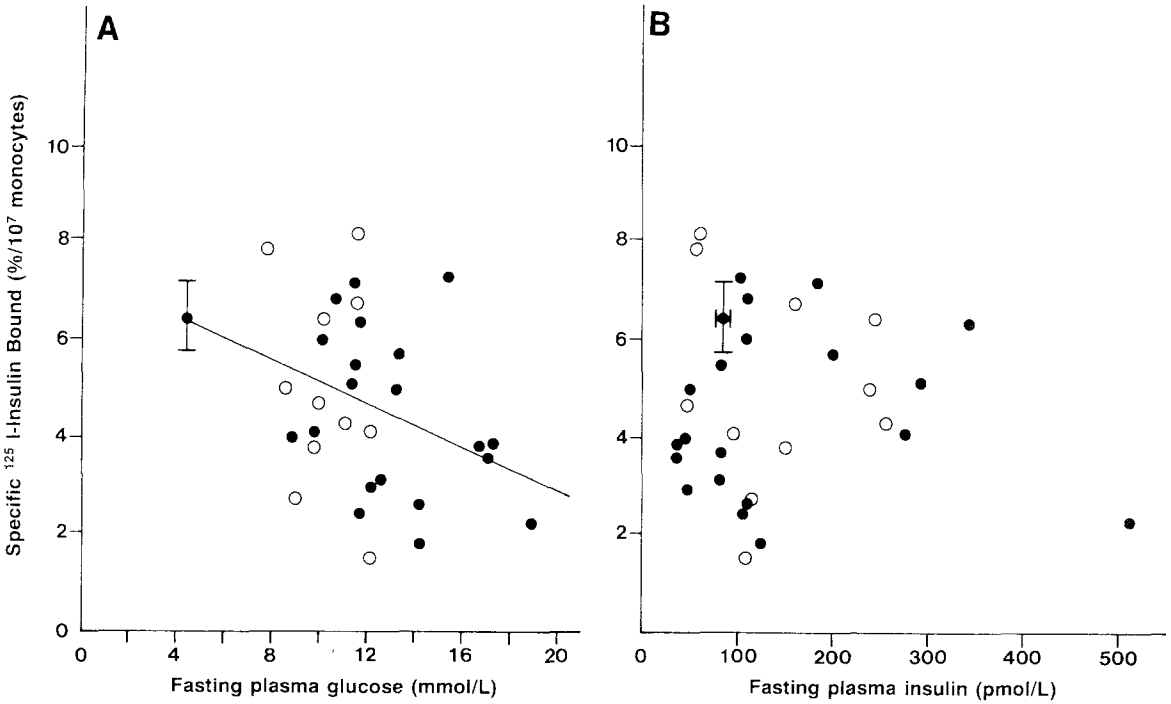

Fig 3. Relationships between ^{125}I-insulin binding and FPG and FPI concentrations. Correlations between ^{125}I-insulin binding and FPG concentrations (A) and between ^{125}I-insulin binding and FPI concentrations (B) in control subjects (n = 13) and patients with NIDDM (n = 31), (●) untreated (n = 20) or (○) treated with sulfonylurea drugs (n = 11). Mean ± SE values for ^{125}I-insulin-specific binding in control subjects are indicated by horizontal bars. The entire range was 3.4% to 10.5% per 10^7 monocytes. A significant inverse correlation between insulin binding and FPG was apparent either including ($r = -.452$, $P = .002$) or excluding ($r = -.496$, $P = .003$) drug-treated patients.

contribution of the other clinical parameters, obesity and FPI, a stepwise multiple linear regression analysis was performed. This showed that FPG alone significantly correlated with insulin binding in the entire study population without any contribution from the other variables, including diabetes status.

In previous studies, the relationship between insulin concentration and insulin binding in obesity was confirmed by decreasing the insulin concentration in obese individuals by diet and documenting the associated changes in insulin binding.[9] Similarly, our hypothesis that metabolic control may be an important factor in determining the level of insulin binding in NIDDM is supported by several studies of NIDDM patients before and after improvement of glycemic control. Thus, diet therapy is well known to improve plasma glucose concentrations in obese NIDDM patients and has been associated with an increase in insulin binding.[25] Sulfonylurea drugs have also been shown to improve glycemia and increase insulin binding without altering insulin concentrations.[21,22] In this instance, the increased binding was attributed to direct actions of the drugs on insulin receptors. We considered that the treatment of some patients with sulfonylurea drugs was a potentially confounding variable in our study. However, there are three reasons that suggest that this did not account for our observations: (1) it has been difficult to demonstrate consistently direct receptor effects of these agents in vitro,[26,27] (2) the patients treated with the drugs had a significantly lower mean fasting glucose concentration, indicating better metabolic control, and (3) the inverse correlation of fasting glucose concentration with insulin binding remained significant in a stepwise linear regression analysis even when drug-treated patients were excluded ($r = -.50$, $P = .003$). We and others have also demonstrated that the biguanide metformin increased insulin binding after 1 week of therapy in NIDDM patients with initially low binding.[28,29] This was accompanied by a decrease in glucose concentrations but no change in insulin concentrations.[28] Finally, Foley et al[30] demonstrated that intensive insulin therapy of obese NIDDM Pima Indians resulted in increased insulin binding, and Firth et al[31] found a small increase in binding in a group of NIDDM patients with a mean fasting glucose concentration of 10 mmol/L (180 mg/dL) treated with either sulfonylurea or insulin. Together with the present study, these data strongly suggest that the improvement of metabolic control plays a major role in influencing insulin binding in NIDDM.

We noted that the decrease in insulin binding in the entire NIDDM group was associated in our study with a lower receptor affinity. On the other hand, in the group with better glycemic control the higher binding was associated with a higher receptor number. Although this suggests the possibility of separate phenomena, the inaccuracies inherent in Scatchard analysis[32] make us cautious with regard to this interpretation. Furthermore, receptor number changes have frequently been preceded or accompanied by changes in receptor affinity during physiologic or pharmacologic studies in vivo.[9,28,33]

The mechanism of the inverse association between metabolic control and insulin binding is not clear. The effect of glucose on insulin receptors has been investigated. Although oral ingestion of glucose in normal subjects results in an increase in insulin receptor affinity,[34-36] this effect appears to be indirect. A 5-hour intravenous glucose infusion either did not alter[37] or decreased[38] insulin receptor affinity in monocytes. Longer-term in vitro incubations have been performed using different cell types. However, results of these studies in cultured human lymphocytes,[39,40,43] hepatoma cells,[40] and adipocytes[41,42] have been contradictory and inconclusive. Furthermore, we[43] and others[44-46] found that insulin binding to monocytes in hyperglycemic IDDM patients was heterogeneous, supporting the concept that a factor other than glucose is responsible.

Apart from decreased glucose, improved metabolic control is associated with changes in the concentrations of various other circulating metabolites. Hypertriglyceridemia without hyperglycemia has been associated with decreased insulin binding.[47] However, in the patients of the present study, insulin binding did not correlate with triglyceride levels ($r = .014$, data not shown). Circulating free fatty acid levels are also elevated in obesity and poorly controlled diabetes mellitus. Exposure of rat hepatocytes in vitro for 30 minutes to 3 hours to high physiologic concentrations of a number of free fatty acids (oleic, palmitic, stearic, or eicosapentaenoic) resulted in a significant decrease in cell surface insulin binding.[48,49] Of further interest, Svedberg et al[50] demonstrated that there were no effects of free fatty acids on hepatocytes isolated from obese rats that already demonstrated decreased insulin binding.[50] Treatment of these rats in vivo with etomoxir, an inhibitor of free fatty acid oxidation, resulted in an increase in hepatocyte insulin binding. The mechanism of these effects of free fatty acids is not known, and whether free fatty acids influence insulin binding to monocytes or insulin target tissues other than hepatocytes needs to be determined.

A decreased internalization rate in monocytes in obesity and NIDDM has been demonstrated.[51,52] Although receptor recycling was not specifically examined, Trischitta et al[52] showed a slower rate of release of internalized insulin. The regulation of receptor internalization and recycling is incompletely understood but clearly involves postreceptor (intracellular) events.[53] In this context, the degree of elevation of fasting glucose concentration has been found to correlate with the severity of the postreceptor defect in NIDDM.[54] Basal glucose concentration is thus a marker for these intracellular abnormalities. It is important to emphasize that the correlation between fasting glucose and insulin binding in our cross-sectional study does not prove cause and effect. Also, although monocytes are convenient to obtain and have been found to provide an overall accurate reflection of insulin binding to target tissues, the possible variability of receptor regulation in different tissues must be considered.

Clearly, the defect in insulin binding alone does not explain the degree of insulin resistance in NIDDM. How-

ever, the decrease in insulin binding that accompanies poor metabolic control in many patients will exacerbate the resistance. Both postreceptor defects in insulin action and pancreatic endocrine function are improved after therapy for NIDDM.[55] Improvement in insulin binding would be another factor contributing to the maintenance of metabolic control after therapy, particularly if the additional receptors are functionally normal. A defective insulin receptor tyrosine kinase activity in NIDDM has been demonstrated by several investigators[56-58] and appears to be at least partly reversible.[59]

In summary, we have demonstrated a significant inverse correlation between FPG concentration and insulin binding to monocytes in NIDDM. This relationship is not explained by degree of obesity, insulin concentration, or oral hypoglycemic drug therapy. We suggest that fasting hyperglycemia, not necessarily by a direct effect, is associated with an intracellular defect that alters insulin binding. This association may explain, in part, the heterogeneity of insulin binding in NIDDM.

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