Henry Ford Hospital Medical Journal

Volume 28
Number 2 *Richmond W. Smith Jr. Testimonial Issue*

Article 16

6-1980

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Henry Ford Hosp Med J
Vol 28, No 2 and 3, 1980

Insulin-Resistant Diabetes Mellitus and Insulin Receptor Antibodies

Variable association with acanthosis nigricans

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Two patients with severe insulin-resistant diabetes mellitus and anti-insulin receptor autoantibodies are reported here. A marked decrease in the number of accessible insulin receptors was found in the monocytes of one patient. Otherwise, the insulin receptors were of normal affinity compared to those of normal controls. Acanthosis nigricans was not present in one patient, and in the other patient it preceded the diagnosis of diabetes by ten years. We conclude that although acanthosis nigricans and insulin resistance are frequently associated, they probably do not bear a pathogenetic relationship to each other. Therefore, the investigation of anti-insulin receptor antibodies is advisable in unexplained insulin-resistant diabetes even if acanthosis nigricans is absent.

Insulin resistance may develop as a result of a number of mechanisms, namely, excessive plasma levels of insulin antagonists (1), secretion of abnormal insulin (2,3), and target cell defects (4,5). Recent advances in our knowledge of the physiology of insulin action have shed light on this last category of causes for insulin insensitivity. Insulin receptor deficiencies of either primary or secondary origin have been demonstrated in maturity-onset diabetes mellitus (6,7), obesity (8-10), and the type A syndrome of acanthosis nigricans and insulin resistance (11). Also, defects occurring distally to the insulin receptor interaction (12-13) and circulating autoimmune antibodies directed against the insulin receptor (4,11,14-16) have been shown to occur in insulin-resistant diabetics. These anti-insulin receptor antibodies account for the insulin unresponsiveness in the type B syndrome of acanthosis nigricans and insulin resistance (11). We are reporting here two cases of diabetes associated with severe insulin resistance and anti-insulin receptor antibodies, one of which had the unusual feature of lacking acanthosis nigricans. Such a feature indicates that this skin disorder does not necessarily accompany the type B syndrome of insulin resistance.

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Case Reports

Case 1

This 69-year-old obese white woman had diabetes mellitus diagnosed 13 months previously, without diabetic ketoacidosis or any long-range complications. Because her diabetes was uncontrolled with treatment consisting of a 1400 calorie diet, insulin therapy was initiated. However, an increasing insulin dosage of up to 200 units of pork Lente insulin per day failed to improve her metabolic control. The patient's past medical history included bronchial asthma, essential hypertension, ischemic heart disease with angina pectoris, status postmyocardial infarction and congestive heart failure, peripheral deep vein thrombosis, pulmonary embolism, hiatal hernia, and reflux esophagitis. Additional therapy consisted of aldactazide two tablets, aldomet 750 mg, digoxin 0.25 mg, and terbutaline 10 mg daily. Both her mother, who had died at age 70, and a sister had uncomplicated adult onset diabetes mellitus. Physical examination failed to reveal any evidence of acanthosis nigricans.

Optimal diabetic control could not be attained despite dietary compliance and insulin replacement as described above. The patient died suddenly of a cardiorespiratory arrest associated with an acute myocardial infarction 18 days after her hospital admission.

Case 2

A 31-year-old white woman had an eleven-year history of diabetes complicated by peripheral neuropathy, proliferative retinopathy, and vitreous hemorrhage; these latter problems had been treated with laser therapy and vitrectomy. No ketoacidosis or other late diabetic complications were present. Additional medical problems included essential hypertension, severe depression, obesity, and recurrent galactorrhea associated with phenothiazine

treatment. Galactorrhea resolved after this medication was discontinued. The patient's one pregnancy had ended prematurely in miscarriage. She never used oral contraceptives. Her therapy consisted of a 1200 calorie diet, single peak NPH pork insulin 200 units, dyazide two tablets, minipress 20 mg, and haldol 10 mg daily. Acanthosis nigricans had been noted first at age 10 and was confirmed during the physical examination. A sister of the patient apparently had acanthosis nigricans, but she was not known to have diabetes and was not available for clinical studies.

Methods

Insulin antibodies were measured by a previously reported procedure (17). Insulin was labeled with ^{125}I (Amersham Corporation, Arlington, IL) according to a modification of the method of Freychet, et al (18). Plasma free insulin and C-peptide immunoreactivities were assessed by the procedures of Nakagawa, et al (19) and Kuzuya, et al (20), respectively. Plasma globulins were isolated by precipitation with 50% ammonium sulfate. Circulating mononuclear blood cells were isolated with Ficoll-Hypaque gradients (21), and monocytes were counted after cytochemical staining with a nonspecifc esterase method (22). Insulin reserve was measured by means of a glucagon stimulation test (23).

Responsiveness to insulin was assessed by a modification of the procedure of Shen, et al (24), which consists of a constant rate intravenous infusion of insulin (80 mU/min) and glucose (6 mg/Kg/min). Epinephrine and propanolol used in the original procedure were omitted in the infusate because of their effect on the hepatic production of glucose (25-30). Felig and Wahren (31) have shown that at levels of plasma insulin comparable to those attained in this study, splanchnic production of glucose is suppressed. Therefore, the corresponding steady state plasma glucose levels reflect the subject's responsiveness to insulin. The omission of epinephrine and propanolol in the infusate resulted in persistent endogenous insulin secretion which was assessed by measurement of plasma C-peptide levels.

Control subjects were 34 lean, normal individuals, 15 men and 19 women; all were within ± 15% of ideal body weight according to standard Metropolitan Life Insurance Co tables. All other assays were done by standard radioimmunoassays and clinical methods. Single component pork insulin was a gift of Dr. Ronald E. Chance of Eli Lilly and Co, Indianapolis, Ind. Dr. Ake Lernmark of the Hagedorn Research Laboratory, Gentoften, Denmark, supplied the antibody for the insulin radioimmunoassay.

Results

The first patient had average daily random plasma glucose levels of 185 mg/dl (range: 99-249 mg/dl), and glycosylated hemoglobin measurements amounted to 13.2%. Plasma cortisol and growth hormone levels were within the normal range, and insulin antibodies were undetectable. Fasting plasma insulin and C-peptide concentrations were 36.5 μU/ml and 5.4 ng/ml, respectively, and the insulin and C-peptide responses to intravenous glucagon stimulation indicated that a normal pancreatic beta cell reserve was present (Table I).

TABLE I

Glucagon Stimulation Test

Patient	Time (min)	Plasma Insulin (μU/ml)	Plasma C-Peptide (ng/ml)
1	0	36.5	5.4
	5	62.5	6.5
	10	52.4	6.4
	20	36.4	6.0
2*	0	28.2	2.1
	5	61.0	3.3
	10	37.6	3.2
	20	50.8	3.0

* Free plasma insulin and C-peptide levels were measured because insulin antibodies were present.

The second patient showed an average fasting plasma glucose of 165 mg/dl (range: 93-265 mg/dl), and a mean random plasma glucose value of 205 mg/dl (range: 97-377 mg/dl). Glycosylated hemoglobin was 13.5%. Fasting plasma-free insulin and C-peptide values were 28.2 μU/ml and 2.1 ng/ml, respectively (Table I). Plasma insulin antibody titers were 0.9 and 1.5 units/liter on two different occasions. Intravenous glucagon stimulation resulted in a normal pancreatic beta cell response, as indicated by the plasma-free insulin and C-peptide concentrations (Table I). Negative results were obtained for an assortment of autoimmune antibodies that included antinuclear factor, antimicrosomal (thyroid), antiparietal (gastric) and antismooth muscle antibodies, rheumatoid factor, and direct and indirect Coombs tests. An overnight plasma cortisol level after a dose of dexamethasone 1 mg p.o. was 1.9 μg/dl, and urinary-free cortisol was 44.4 μg/24 hr. Plasma growth hormone and prolactin levels were within normal ranges. Plasma immunoglobin concentrations were IgG 971 mg/dl, IgM 142 mg/dl, IgA 165 mg/dl, and IgE <0.04 mg/dl, all within normal limits.

Steady state plasma glucose concentrations during a standardized insulin-glucose infusion (see Methods) amounted to 234 and 273 mg/dl for patients 1 and 2, respectively (Table II). Both values are significantly higher that the normal control of 72 ± 3.9 mg/dl (average ± SEM) for the same parameter and indicate the presence of severe insulin

resistance. Steady state plasma insulin levels were similar for both patients and the control group (Table II), further supporting the implication of abnormal responsiveness to insulin in these patients. Endogenous secretion of insulin was not suppressed during the insulin-glucose infusion as indicated by the comparable steady state plasma C-peptide values in both patients and control subjects (Table II).

TABLE II

Responsiveness to Insulin

Patient	SSPG (mg/dl)	SSPI (μU/ml)	SSPC (ng/ml)
1	234	82	8.1
2*	273	91	3.2
Controls (n=34)	72 ±3.9	91 ±4.9	2.0 ±0.2

* Free plasma insulin and C-peptide levels were measured because insulin antibodies were present. SSPG, SSPI and SSPC stand for steady state plasma glucose, insulin and C-peptide, respectively.

Anti-insulin receptor antibodies were present in both patients (Fig. 1). The serum of patient 1 inhibited specific binding of ^{125}I-insulin to normal isolated monocytes to an extent of 98.6 and 98.4% at serum dilutions of 1/7 and 1/70, respectively. Globulins isolated from the serum of patient 1 also produced 66.5 and 33.1% inhibition of ^{125}I-insulin binding to specific receptors at concentrations corresponding to serum dilutions of 1/7 and 1/70, respectively (Fig. 1, upper panel). The lesser inhibition of insulin binding to receptors seen with the isolated globulins of patient 1 is probably due to incomplete recovery of serum globulins. Similar findings were observed in patient 2, in whom the degree of inhibition was 87.0 and 70.2% for the serum and 92.2 and 67.3% for the isolated globulins at equivalent serum dilutions of 1/7 and 1/70, respectively (Fig. 1, lower panel).

Characterization of the insulin receptors of circulating monocytes could only be performed on our second patient. Fig. 2 shows the markedly decreased insulin binding to peripheral monocytes isolated from patient 2 (open circles) compared to the average binding to insulin receptors from 34 normal, lean controls (closed circles). Scatchard plots obtained from the same set of binding data reveal that the binding curves of patient 2 and the normal controls are parallel, which indicates similar receptor binding affinities but with decreased number of accessible insulin receptors (Fig. 3).

Discussion

The development of diabetes mellitus concomitantly with seemingly normal pancreatic beta cell reserve and hyperinsulinemia is the result of target organ resistance to insulin. Our two patients fulfill these conditions. Furthermore, suboptimal metabolic control as evidenced by hyperglycemia and high levels of glycosylated hemoglobin was present simultaneously with daily insulin dosages of 200 units and appropriate dietary therapy. Since insulin requirements of 200 units per day or higher have been used to define severe refractoriness to this hormone (1), both patients had marked insulin resistance.

Obesity is the most common cause of insulin resistance, and both patients were overweight. However, unresponsiveness to insulin in obesity is usually mild to moderate and reverses after short-term or chronic caloric restriction (8). In both patients resistance to insulin and hyperglycemia were severe and persisted despite consistent diets of 1200 and 1400 calories a day, respectively. Also, the insulin receptor deficiency that accounts for the hormone resistance in obesity (11) is usually milder than the markedly decreased number of receptors demonstrated in the second patient. Therefore, obesity per se cannot explain the severe insulin resistance of either patient. Hormonal antagonists to insulin action were secreted in normal levels and were also normally suppressible. Circulating insulin antibodies were either undetectable (patient 1) or were present in titers too low to be consistent with the severity of the insulin resistance. Insulin serum binding capacities of 55 units/liter or higher have been correlated with daily requirements of 200 or more units of insulin and are associated with severe insulin resistance (1).

Studies on the circulating monocytes of the second patient revealed a severe deficiency in the number of insulin receptors, and in both patients serum insulin receptor antibodies could be demonstrated. In consequence, these patients appear to have the type B syndrome of insulin resistance (11). The pathogenesis of the insulin unresponsiveness in this syndrome involves mainly the blocking of insulin receptors by the antireceptor autoantibodies (32, 33), although a decrease in the binding affinity of the accessible receptor sites has also been reported on the patients' monocytes (34). However, removing the specific antibodies from the surface receptor sites of monocytes from type B patients has both increased the insulin binding and normalized the receptor binding affinity (35). Also, when fibroblasts and circulating mononuclear cells were isolated from type B patients and followed by long-term culture, cells with normal insulin binding characteristics were produced, indicating that the receptor abnormalities of these cells are not intrinsic but probably secondary to perturbation by the antireceptor antibodies (35). Further evidence is provided by reports that resistance to insulin was reversed and insulin receptor binding parameters were normalized after immunosuppressive therapy

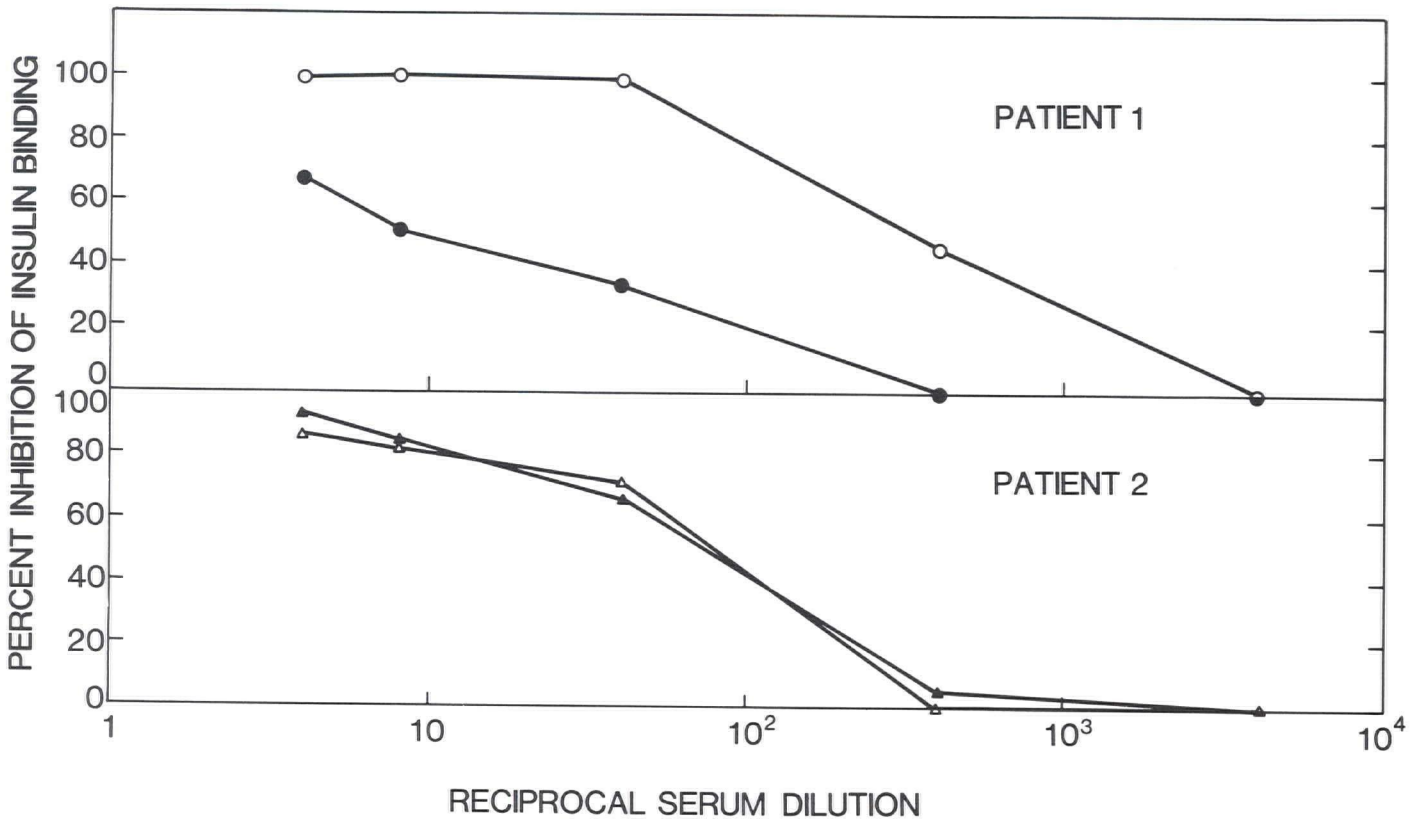

Fig. 1

Inhibition of insulin binding to specific receptors of normal human monocytes by patients' serum and serum globulins. ^{125}I-insulin ($5x10^{-11}$M) was incubated with a suspension of 40-60x10^6 mononuclear cells isolated from the blood of normal subjects. Incubations were carried out to equilibrium at 15°C for two hours in a buffer system consisting of Hepes 25mM, Tricine 25mM, NaCl 110mM, KCl 3.5mM, $MgSO_4$ 1.2mM, bovine serum albumin 1%, pH 7.6. Specific binding was defined as associated hormone displaceable by 10^{-6}M cold insulin, and the binding reaction was carried out in the presence and absence of the patients' deinsulinized serum or purified globulins at the equivalent serum dilutions indicated on the abscissa. Serum deinsulinization was carried out by acidification and adsorption of free insulin onto dextran-coated charcoal followed by pH neutralization. Open symbols represent data obtained with patients' serum and closed symbols data from experiments with isolated globulins.

(36) and multiple plasmapheresis (37) that brought about a decrease in antireceptor antibody titers. Paradoxically, these antireceptor antibodies stimulate glucose transport and metabolism in adipocytes and muscle cells (38,39) and activate pyruvate dehydrogenase and acetylcoenzyme A carboxylase from fat cells (40). These findings seem to indicate that the antireceptor antibodies are heterogeneous and comprise both blocking and activating species that differ in their specificity for various antigenic determinants on or near the insulin receptor. It is also noteworthy that spontaneous remission of insulin resistance and development of hypoglycemia have occurred in several type B patients (41,42), which could be explained by a change in the relative concentrations of blocking and activating antireceptor antibodies.

Other clinical entities caused by antireceptor autoantibodies have also been described. Graves' disease is characterized by the presence of both blocking and stimulating antibodies directed against the receptor for thyrotropin located on the thyroid plasma membranes (43), and patients with myasthenia gravis have circulating antibodies against the acetylcholine receptor of the myoneural endplate (44).

The pathogenetic relationship between acanthosis nigricans and insulin resistance is still obscure. Estrogen therapy in two type A patients has resulted in partial and complete remissions of their acanthosis nigricans, respectively, without change in either insulin resistance or the receptor abnormalities (34). A similar observation has been reported in a patient with acanthosis nigricans and insulin resistance due to a postreceptor defect (13). Insulin receptor autoantibodies and severe insulin resistance have also been described in the absence of acanthosis nigricans (45), although the patient later developed this skin disorder (AH Rubenstein, personal communication). Acanthosis nigricans was noted in our second patient long before

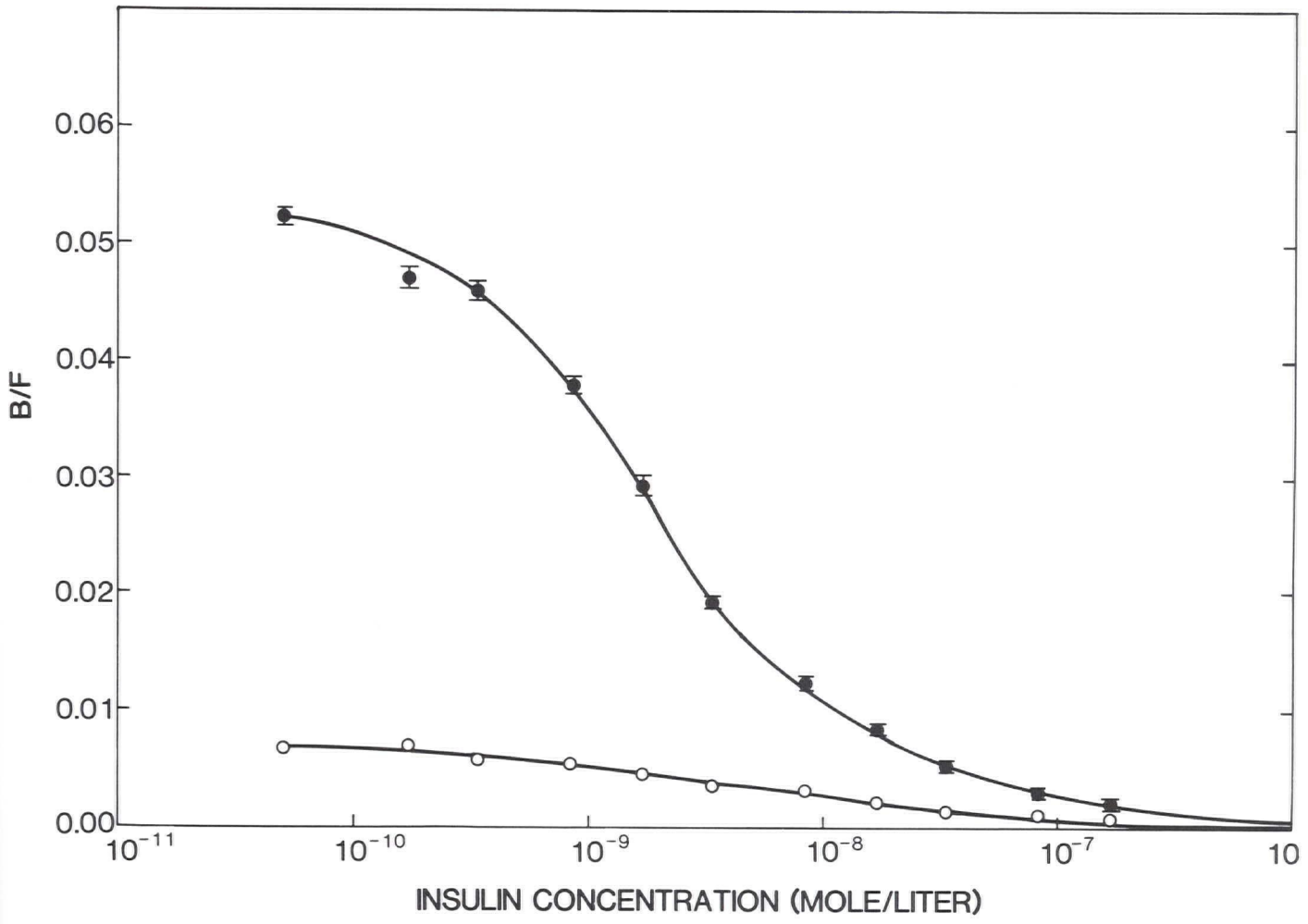

Fig.2

Displacement of ^{125}I-insulin by varying concentrations of cold insulin from monocytes of patient 2 (open circles) and normal controls (closed circles). Experimental conditions were similar to those in Fig. 1. The binding data have been normalized to a monocyte count of 10^7 cells/ml. Normal control values represent the mean of 34 measurements on different individuals placed on a 200 gm carbohydrate diet for three days before the study. Vertical bars represent the standard error of the mean.

diabetes was diagnosed, and no evidence for it existed in patient 1. These observations suggest that the pathogenesis of acanthosis nigricans and insulin resistance are independent of each other. As a corollary, it is advisable to investigate the presence of insulin receptor antibodies in patients with otherwise unexplained insulin resistance even if acanthosis nigricans is absent.

Acknowledgments

The author wishes to acknowledge the support of the Dykstra Foundation, Detroit, Michigan and the Clinical Research Unit of Henry Ford Hospital. Thanks are also due to Messrs. John Hill, Jalileh Mansour, Louise Petermann, Robert Vukmirovich, Zoe McGrath, R.N., and Karen Blessing, R.N., for their excellent technical assistance, and to Ms. Susan Boyle for her expert secretarial help.

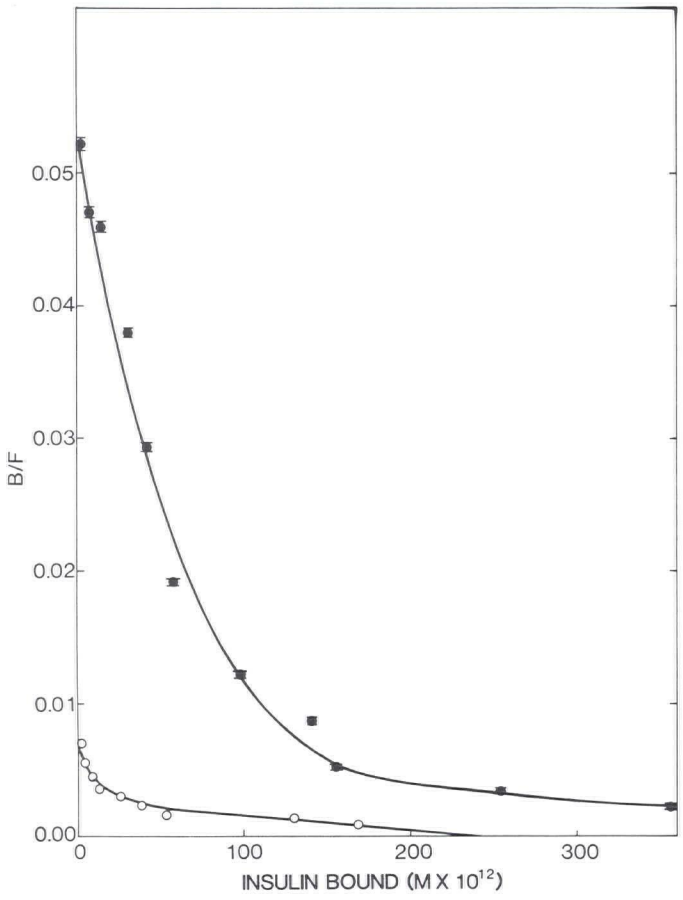

Fig. 3

Scatchard plot of the insulin binding to circulating monocytes of patient 2 (open circles) and 34 normal controls (closed circles). These data have been calculated from the same experiments as in Fig. 2. Normal control values are presented as mean ± SEM.

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