Insulin Resistance in Patients With Depression and Its Changes During the Clinical Course of Depression: Minimal Model Analysis

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A high proportion of patients with depression develop glucose intolerance accompanied by hyperinsulinemia, suggestive of reduced insulin sensitivity (insulin resistance). The aim of this study was to evaluate insulin sensitivity in patients with depression and its changes during the clinical course of depression. Twenty nondiabetic patients with depression (13 males and 7 females aged 44 ± 14 years; body mass index [BMI] 23.2 ± 2.8 kg/m^2) were prospectively studied by the frequently sampled intravenous glucose tolerance test (FSIGT) and the oral glucose tolerance test (OGTT) before and after treatment of depression, and an age-, sex-, and BMI-matched control group (n = 13) was examined once by the FSIGT. Metabolic indices measuring glucose effectiveness at basal insulin (SG) and insulin sensitivity (SI) were derived from minimal model analysis. Each patient was treated by cyclic antidepressants with an 1,800 to 2,200 kcal/d food intake and underwent no exercise therapy. SI was significantly lower in patients before treatment versus control subjects (6.0 ± 2.5 *v* 13.8 ± 8.6 × 10^{-5} $min^{-1} \cdot mol^{-1} \cdot L$, *P* < .01). After treatment of depression, a significant increase in SI (10.7 ± 7.5 × 10^{-5} $min^{-1} \cdot mol^{-1} \cdot 1$, *P* < t.01) was observed without changes in the BMI, fasting blood glucose, and SG. This was associated with a decrease in the insulin response during the OGTT and FSIGT. We conclude that patients with depression have impaired insulin sensitivity and resultant hyperinsulinemia and that these abnormalities can be resolved after recovery from depression.

PREVIOUS STUDIES have indicated that diabetes mellitus is often associated with depression[1] and suggested that depression is a factor which increases the risk of developing diabetes.[2] Patients with depression have been shown to exhibit glucose intolerance accompanied by elevated serum insulin levels after oral glucose loading,[3,4] as well as reduced glucose responsiveness to exogenous insulin during an insulin tolerance test.[5] These findings suggest the presence of reduced insulin sensitivity (insulin resistance) in patients with depression, but no studies have focused on insulin sensitivity in patients with depression with a specific and quantitative measurement of insulin sensitivity and its changes during the clinical course of depression.

We previously reported that 3 patients with depression demonstrated remarkable improvement in insulin sensitivity as estimated by the minimal model analysis[6] after recovery from depression.[7] However, the changes in insulin sensitivity during the clinical course of depression and the relation between insulin sensitivity and the severity of depression remain uncertain.

Minimal model analysis as suggested by Bergman[6] is a simple, noninvasive, and reliable method to quantify insulin sensitivity[8] and permits an investigation of glucose and insulin interactions during a frequently sampled intravenous glucose tolerance test (FSIGT). The model allows measurement of several important indices including the insulin sensitivity index (SI), and glucose effectiveness at basal (SG) and zero (GEZI) insulin. In addition, from the FSIGT, first-phase insulin secretion (AIR) and the glucose disappearance constant (Kg) can be estimated.

The aims of this study were to estimate AIR, Kg, SI, SG, and GEZI in patients with depression compared with normal subjects, and to investigate the changes in these parameters during the clinical course of depression. To this end, we performed an FSIGT with minimal model analysis and a standard oral glucose tolerance test (OGTT) in 20 patients with depression before and after treatment of depression.

SUBJECTS AND METHODS

Subjects

Twenty patients with depression were studied. There were 13 males and 7 females aged 44 ± 14 years (mean ± SD) with a body mass index (BMI) of 23.2 ± 2.8 kg/m^2 (Table 1). All had a diagnosis of depressive disorder according to DSM-IV criteria,[9] and these diagnoses included major depressive disorder (n = 12) and depressive disorder NOS (n = 8). Clinical and laboratory tests were normal, with the exception of mild hypertension in 5 patients and mild hyperlipidemia in 6 patients. None of the subjects had a history of diabetes or were receiving treatment for glucose metabolism, insulin secretion, or insulin resistance. All of them had normal fasting plasma glucose (FPG) with American Diabetes Association criteria.[10]

Thirteen age-, sex-, and BMI-matched healthy subjects served as controls. They were selected from among the clinical and laboratory staff who volunteered to participate in the study.

All subjects received a full explanation of the study and provided informed consent before participation in the study.

Experimental Protocol

Each patient underwent a FSIGT and OGTT on 2 occasions, once when they were symptomatically depressed and then again 82 ± 28 (mean ± SD) days later, following antidepressant treatment. At these times, depressive symptoms were scored using the Hamilton Rating Scale for Depression (HRSD).[11] Selective serotonin reuptake inhibitors (SSRIs) were not used in this study because they may cause a weight reduction[12,13] or an improvement in insulin sensitivity.[14,15] Tricyclic or tetracyclic antidepressants were selected for treatment of the patients. They were treated orally with 30 to 75 mg maprotiline (n = 5), 75 mg amitriptyline (n = 3), 75 mg dosulepine (n = 7), or 75 mg amoxapine

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Table 1. Clinical Characteristics of Control Subjects and Patients With Depression Before and After Treatment

Characteristic	Control	Patients		*P*	
		Before Treatment	After Treatment	C *v* Pb*	Pb *v* Pa†
No. of subjects (male:female)	13 (7:6)	20 (13:7)			
Age (yr)	46 ± 12	44 ± 14		.7	
BMI (kg/m^2)	22.6 ± 2.9	23.2 ± 2.8	23.1 ± 2.1	.6	.9
SBP (mm Hg)		130 ± 17	126 ± 14		.3
DBP (mm Hg)		72 ± 11	74 ± 9		.5
TC (mmol/L)		5.3 ± 0.7	5.1 ± 0.5		.6
TG (mmol/L)		1.3 ± 0.3	1.2 ± 0.2		.1
HRSD		16 ± 6	5 ± 5		<.0001

NOTE. Data are the mean ± SD.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides.

*For comparisons between control subjects (C) and patients before treatment (Pb), we used Student's *t* test.

†For comparisons between patients before treatment (Pb) and after treatment (Pa), we used the paired *t* test.

(n = 5) daily during the study period. Six patients were treated with an additional 25 mg clomipramine intravenous drip infusion daily for the first 5 to 15 days of the study period. The treatment regimen for each patient was clinically decided after careful assessment of the severity of depression, types of depressive symptoms, possible side effects, age, and body weight. No patients used any other medications known to affect glucose metabolism or insulin action. No formal aerobic exercise was permitted during the study periods, although normal daily activities were not restricted. Patients were advised that their diet should include 1,800 to 2,200 kcal/d, with no specific dietary restrictions.

Control subjects were studied once with a FSIGT with minimal model analysis, and the results were compared with those of the patients.

OGTT

The OGTT was started between 8:30 and 9:00 AM after an overnight fast, and baseline samples for glucose and insulin were obtained. Glucose (75 g dextrose in 150 mL solution) was administered orally, and subsequent samples were obtained at 30, 60, 90, and 120 minutes. Heparinized blood samples were kept on ice and centrifuged promptly under refrigeration, and were stored below −20°C until assay.

FSIGT

We performed the FSIGT according to the protocol suggested by Finegood et al.[16] The FSIGT was started between 8:30 and 9:00 AM after an overnight fast and after at least a 30-minute period of recumbency. Butterfly needles were inserted into an anticubital vein in each arm and kept patent by slow drip of physiologic saline. One needle was used for blood sampling only, and the other for administration of glucose and insulin. Baseline samples for glucose and insulin were obtained at −15 and −5 minutes. Glucose (50% dextrose 0.3 g/kg body weight) was administered intravenously within 2 minutes starting at time 0. Further blood samples (2.0 mL each) from the antecubital vein were obtained at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes. Insulin (Humulin R; Shionogi, Osaka, Japan; 1 U) was infused into the antecubital vein to improve the reliability of parameter identification[16,17] at time 20 minutes. Heparinized blood samples were kept on ice and centrifuged promptly under refrigeration, and were stored below −20°C until analysis.

Assays

The plasma glucose concentration was measured with an automatic analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan) using the glucose oxidase method. The plasma insulin concentration was measured by radioimmunoassay using an Insulin Riabead II kit (Dainabot, Tokyo, Japan) with an intraassay coefficient of variation of 1.9%, 1.2%, and 1.7% at 53.4, 325.8, and 1,062 pmol/L, respectively.

FSIGT With Minimal Model Analysis

The AIR was expressed as the area under the insulin curve (AUC) between 0 and 10 minutes after intravenous administration of glucose. The total glucose response ($AUC_{glucose}$) was determined as the glucose AUC from 0 to 180 minutes of the FSIGT. The trapezoid method was used to calculate the insulin AUC and glucose AUC. The Kg was computed as the slope of the linear least-square regression line to the natural logarithm of the glucose concentration versus time from 10 to 19 minutes (Kg10-19) and 19 to 30 minutes (Kg19-30) after administration of glucose. Kg10-19 was used to estimate glucose disappearance by endogenous insulin secretion, and Kg19-30 was used to estimate glucose disappearance mainly by exogenous insulin administration. SI and SG were computed by the minimal model program written by one of the authors (Y.S.) in True BASIC on a Macintosh SE (Apple Computer, Cupertino, CA). The simplex method was used for nonlinear least-square estimation of the parameters, and the Runge-Kutta algorithm was used for solving differential equations. GEZI was determined as the difference between total SG and glucose disposal mediated by the fasting insulin concentration (F-IRI): thus, GEZI = SG - SI × F - IRI.[18] The disposition index was calculated as the product of the SI and AIR.

Measurement of Symptoms of Depression

The severity of depression symptoms was scored using the HRSD. Each of the 21 items of the HRSD were scored at 0 to 2 or 0 to 4 points before and after treatment of depression, and cumulative totals of individual symptom scores were recorded. The HRSD is a standard observer rating scale for depression and has been shown to be both a reliable and valid measure of the severity of depression.[19,20]

Statistical Analysis

Data are expressed as the mean ± SD. Unless otherwise stated, Student's *t* test was used for unpaired comparisons, and the paired *t* test was used for comparison of data before and after treatment. When glucose and insulin values at each time point of the OGTT and FSIGT were compared, Fisher's protected least-significant difference test was applied after ANOVA with repeated measures. The .05 level of significance was used. Statistical analysis was performed with the software package StatView Version 5.0 (SAS Institute, Cary, NC).

RESULTS

Depressed patients were treated with antidepressants and had no change in their BMI during the treatment period. The HRSD score improved from 16 ± 6 points to 5 ± 5 points (Table 1).

Changes in the glucose and insulin response after the OGTT are shown in Fig 1. Basal glucose levels did not differ before and after recovery from depression, while at 30, 60, and 90 minutes after glucose loading, plasma glucose concentrations were significantly lower after treatment versus before treatment (Fig 1A). Insulin concentrations during the OGTT after recovery from depression were significantly lower at basal and 120 minutes versus before treatment (Fig 1B). The AUC for glucose and insulin concentrations during the OGTT was significantly higher in the depressed phase compared with the recovered phase ($P < .01$).

Glucose and insulin responses during the FSIGT are shown in Fig 2A and B. Basal glucose and insulin concentrations measured in the FSIGT were similar to those measured in the OGTT both before and after treatment of depression. The time course of glucose and insulin concentrations was significantly different before versus after treatment by ANOVA with repeated measures. After treatment, glucose and insulin levels were significantly lower at the time points between 40 and 60 minutes for glucose and between 40 and 60 minutes, 120 minutes, and 160 to 180 minutes for insulin as compared with the values before treatment.

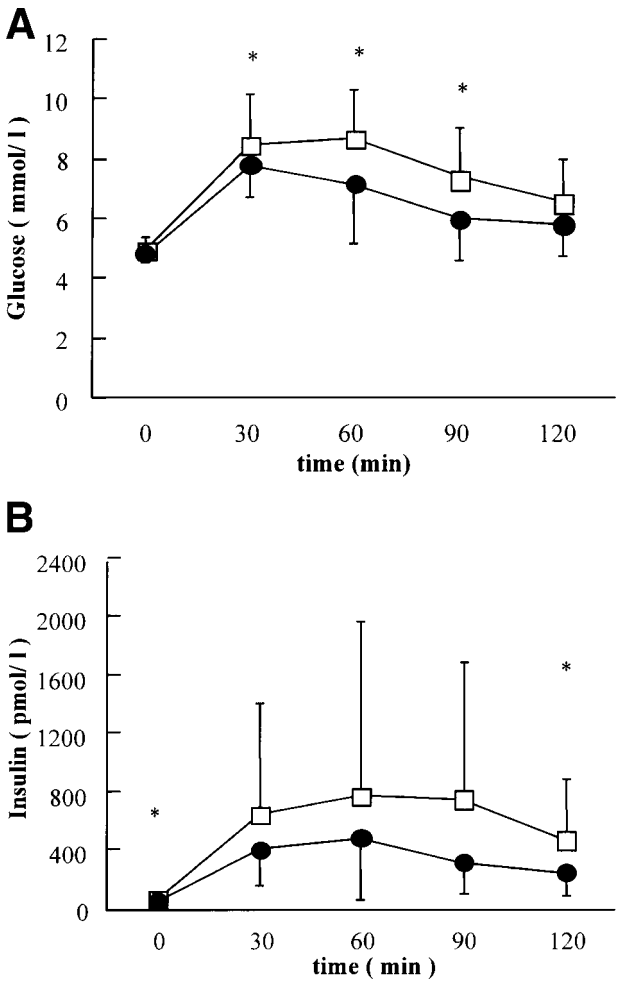

Fig 1. Glucose (A) and insulin (B) responses during the OGTT in 20 patients with depression before (□) and after (●) treatment of depression. Data are the mean ± SD. Fisher's PLSD test was applied after ANOVA with repeated measures. *Statistically significant at $P < .05$.

Changes in metabolic parameters calculated from the FSIGT are shown in Table 2. Comparison of the data before and after treatment showed no significant differences in the FPG, Kg10-19, SG, GEZI, and disposition index. However, F-IRI, AIR, $AUC_{glucose}$, Kg19-30, and SI improved significantly after treatment of depression. Individual results for each subject are shown for SI (Fig 3A) and SG (Fig 3B).

The relation between SI and the HRSD score is shown in Fig 4. Generally, depressed patients showed a lower value for SI independent of the HRSD score before treatment. After treatment of depression, SI improved to a various extent and showed a wide range of values.

DISCUSSION

Depression has a serious influence on diabetic patients, as it has a negative impact on their quality of life and overall functioning.[21,22] The recognition and treatment of depression is also important for the management of diabetes because of its unfavorable effect on glycemic control[23,24] and compliance with treatment regimens.[25] While the association between depression and diabetes is well recognized,[3-5] little is known about the underlying mechanism of the association between the two conditions. Previous studies have suggested the presence of insulin resistance in patients with depression using nonquantitative measures of insulin sensitivity.[3-5] However, the changes in insulin sensitivity in the clinical course of depression and the relationship between depression severity and insulin sensitivity remain uncertain. This is the first report on changes in insulin sensitivity and its association with depression severity during the clinical course of depression, using a specific and quantitative measure of insulin sensitivity.

After treatment of depression, SI increased significantly and the enhanced insulin secretion showed a tendency to subside. Depressed patients manifested impaired insulin sensitivity independent of depression severity, and after treatment, they demonstrated different degrees of improvement in SI (Fig 4). SG showed no remarkable change during treatment of depression. These results confirm that the impaired insulin sensitivity in patients with depression can be resolved following an improvement of depression.

Patients with depression often show a decrease in appetite and food intake, with a relative excess of carbohydrate and fat consumption.[26,27] Additionally, depressed patients generally suffer from sleep disturbance and impaired daily physical activity. It is well recognized that factors such as the BMI, dietary fat intake, sleep, or exercise may affect insulin sensitivity in humans.[28-32] In the present study, depressed patients had no diet or exercise therapy and their BMI remained constant during the observation period. The improvement in SI could not be accounted for by the BMI. However, some behavioral changes, such as an increase in daily physical activity, improvement in sleep disturbances, or changes in eating behavior following the treatment of depression, might contribute to the improvement of insulin sensitivity.

Some pharmacologic effect might be responsible for the changes in insulin sensitivity during the recovery from depres-

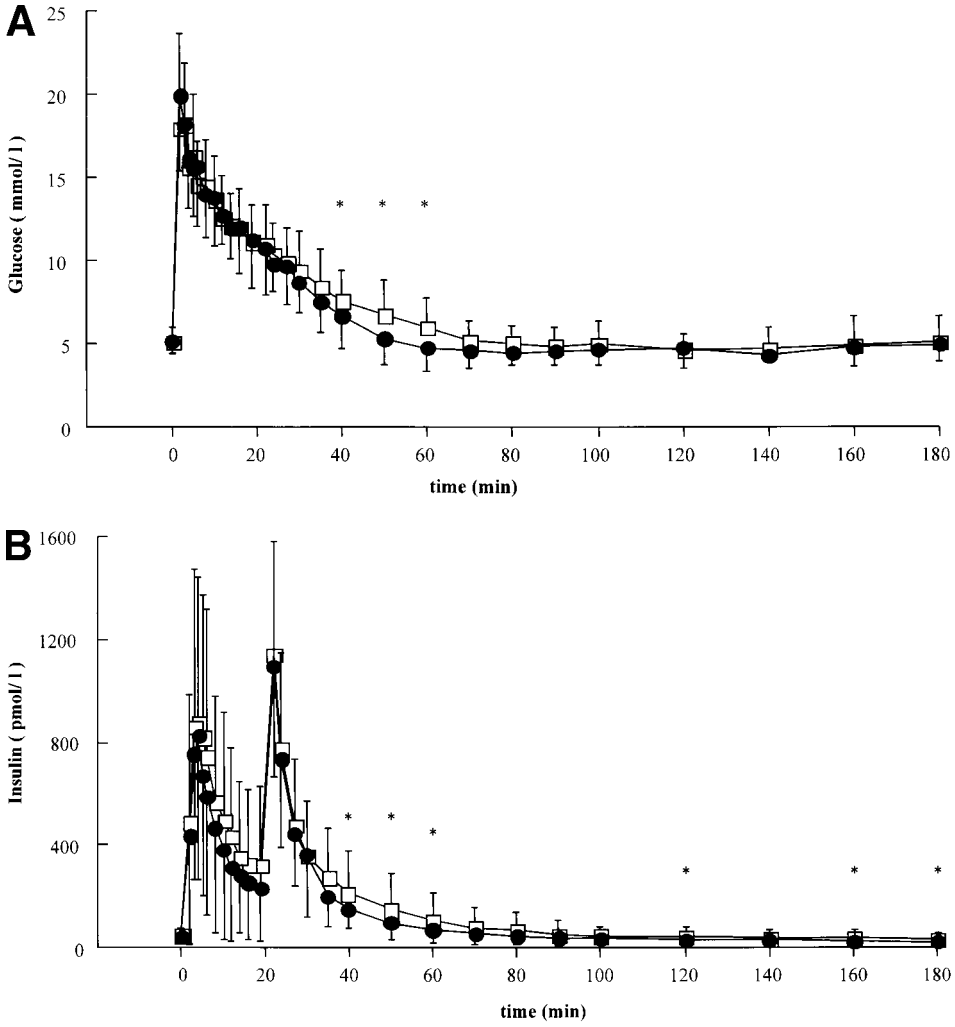

Fig 2. Glucose (A) and insulin (B) responses during the FSIGT in 20 patients with depression before (□) and after (●) treatment of depression. Data are the mean ± SD. Fisher's PLSD test was applied after ANOVA with repeated measures. *Statistically significant at $P < .05$.

sion. Although there has been no report on the direct effect of the tricyclic or tetracyclic antidepressants used in this study on insulin sensitivity, the cyclic antidepressants are known to increase appetite and body weight[33] and occasionally cause hyperglycemia in diabetic patients.[34] Recently, Lustman et al[35] reported that nortriptyline, a tricyclic antidepressant, had the direct effect of worsening glycemic control in depressed patients with diabetes, whereas the improvement in depression produced by nortriptyline had an independent beneficial effect on glycemic control in diabetic patients with depression. It seems less likely that the cyclic antidepressants had a direct effect in improving insulin sensitivity in our patients.

Table 2. Metabolic Parameters Derived From the FSIGT With Minimal Model Analysis in Control Subjects and Patients With Depression Before and After Treatment of Depression

Parameter	Controls	Patients		*P*	
		Before Treatment	After Treatment	C *v* Pb	Pb *v* Pa
FPG (mmol/L)	5.1 ± 1	4.9 ± 0.4	4.8 ± 0.3	.2	.6
F-IRI (pmol/L)	30.1 ± 18.1	50.0 ± 37.2	34.8 ± 16.8	.08	.02
AIR (pmol/L · min)	2,991 ± 2,481	6,732 ± 4,770	4,852 ± 3,997	.01	.04
$AUC_{glucose}$ (mmol/L · min)	1,101 ± 146	1,183 ± 260	1,086 ± 152	.3	.02
Kg10-19 ($\times 10^{-2}$/min)	2.2 ± 1.8	2.0 ± 1.0	2.0 ± 1.0	.2	.9
Kg19-30 ($\times 10^{-2}$/min)	2.4 ± 1.3	1.7 ± 0.8	2.5 ± 1.3	.1	.04
SI ($\times 10^{-5} \cdot min^{-1} \cdot pmol^{-1} \cdot L$)	13.8 ± 8.6	6.0 ± 2.5	10.7 ± 7.5	.0005	.004
SG ($\times 10^{-2}$/min)	2.3 ± 1.3	2.5 ± 0.8	2.5 ± 0.7	.6	.9
GEZI ($\times 10^{-2}$/min)	1.9 ± 0.9	2.2 ± 0.8	2.1 ± 0.8	.8	.7
Disposition index	0.37 ± 0.35	0.35 ± 0.27	0.43 ± 0.46	.7	.3

NOTE. Data are the mean ± SD.

*For comparisons between control subjects (C) and patients before treatment (Pb), we used Student's *t* test.

†For comparisons between patients before treatment (Pb) and after treatment (Pa), we used the paired *t* test.

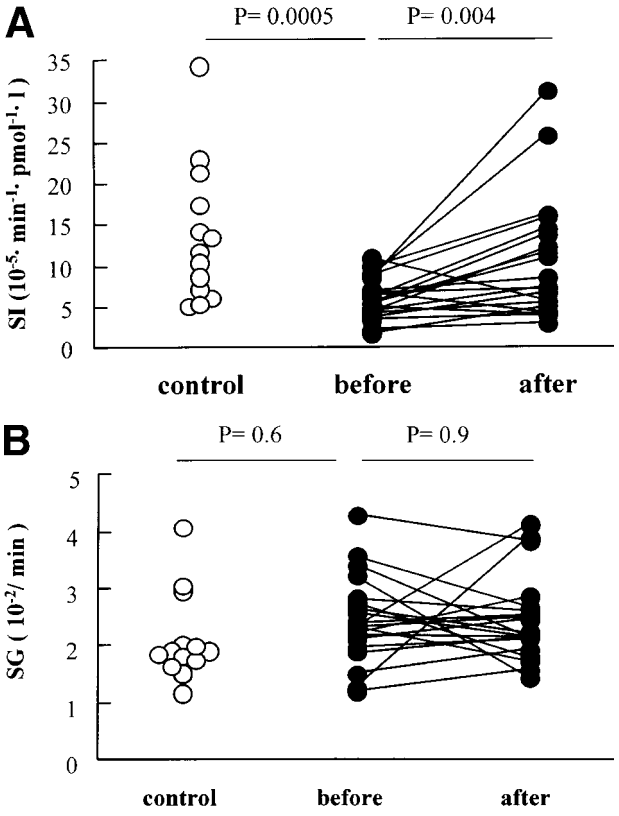

Fig 3. Individual measurements of SI (A) and SG (B) derived from minimal model analysis in control subjects and in patients with depression before and after treatment. Student's *t* test was used for unpaired comparisons, and the paired *t* test was used for paired comparisons.

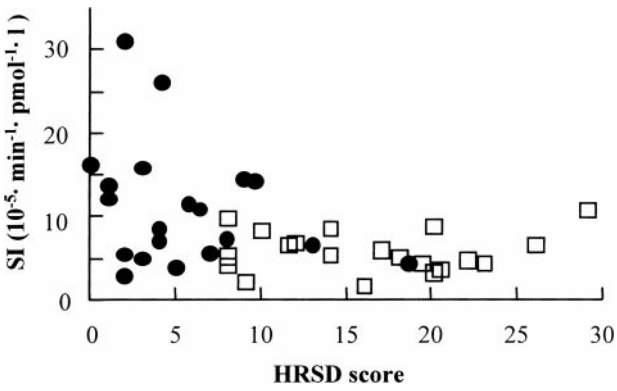

Fig 4. Relation between the SI and HRSD score before (□) and after (●) treatment of depression.

There is an extensive literature documenting the associations between abnormalities of the hypothalamic–pituitary–end-organ axes (eg, hypothalamic-pituitary-adrenocortical, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-somatotropic axes) and mood disorders.[36,37] These neuroendocrinologic abnormalities are known to cause both insulin resistance and mood disorders. For instance, depression is frequently associated with basal hypercortisolemia and/or a blunted cortisol response after a dexamethasone suppression test.[5,36] On the other hand, patients with Cushing's syndrome, which is characterized by cortisol hypersecretion, have a high rate of depression[38] together with insulin resistance.[39,40] These endocrinologic abnormalities may play a role in the association between depression and insulin resistance.

Abnormal serotonergic function in the central nervous system has been suggested to have an important role in the pathogenesis of depression.[41,42] On the other hand, the antidepressant agent fluoxetine, a SSRI, improves insulin-mediated glucose disposal as investigated by the euglycemic-hyperinsulinemic clamp technique in obese patients with type 2 diabetes mellitus, independently of its action on body weight.[14] These facts may suggest that the central serotonergic function relates to both depressive symptomatology and insulin resistance, and links these two pathogeneses.

In conclusion, our findings may suggest that some central nervous system dysregulation that causes depression might simultaneously affect peripheral insulin sensitivity, possibly via the behavioral and/or neuroendocrinologic pathway.

It is well recognized that insulin resistance and hyperinsulinemia are common features in widespread diseases such as essential hypertension, obesity, non–insulin-dependent diabetes mellitus, dyslipidemia, and arteriosclerosis.[43,44] Recent studies have suggested that depression might have a significant relationship with hypertension,[45] abdominal obesity,[46] ischemic heart disease,[47,48] and stroke.[49] On the basis of our observations, such conditions might be linked to the insulin resistance due to depression in part. It is striking that insulin resistance can be improved in accordance with the recovery from depression, suggesting that successful treatment of depression might decrease the risk of developing diabetes, hypertension, and cardiovascular disease in patients with depression.

REFERENCES

1. Gavard JA, Lustman PJ, Clouse RE: Prevalence of depression in adults with diabetes. An epidemiological evaluation. Diabetes Care 16:1167-1178, 1993

2. Eaton WW, Armenian H, Gallo J, et al: Depression and risk for onset of type II diabetes. A prospective population-based study. Diabetes Care 19:1097-1102, 1996

3. Winokur A, Maislin G, Phillips JL, et al: Insulin resistance after oral glucose tolerance testing in patients with major depression. Am J Psychiatry 145:325-330, 1988

4. Tashiro A, Hongo M, Ota R, et al: Hyper-insulin response in a patient with depression. Changes in insulin resistance during recovery from depression. Diabetes Care 20:1924-1925, 1997

5. Nathan RS, Sachar EJ, Asnis GM, et al: Relative insulin insensitivity and cortisol secretion in depressed patients. Psychiatry Res 4:291-300, 1981

6. Bergman RN: Toward physiological understanding of glucose tolerance. Minimal-model approach. Diabetes 38:1512-1527, 1989

7. Okamura F, Tashiro A, Utsumi A, et al: Insulin resistance in patients with depression and its changes in the clinical course of depression: A report on three cases using the minimal model analysis. Intern Med 38:257-260, 1999

8. Bergman RN, Prager R, Volund A, et al: Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. J Clin Invest 79:790-800, 1987

9. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (ed 4). Washington, DC, American Psychiatric Association, 1994

10. American Diabetes Association: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20:1183-1197, 1997

11. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56-61, 1960

12. Levine LR, Rosenblatt S, Bosomworth J: Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. Int J Obes 11:185-190, 1987 (suppl 3)

13. Daubresse JC, Kolanowski J, Krzentowski G, et al: Usefulness of fluoxetine in obese non–insulin-dependent diabetics: A multicenter study. Obes Res 4:391-396, 1996

14. Maheux P, Ducros F, Bourque J, et al: Fluoxetine improves insulin sensitivity in obese patients with non–insulin-dependent diabetes mellitus independently of weight loss. Int J Obes Relat Metab Disord 21:97-102, 1997

15. Potter van Loon BJ, Radder JK, Frolich M, et al: Fluoxetine increases insulin action in obese type II (non–insulin dependent) diabetic patients. Int J Obes Relat Metab Disord 16:S55-S61, 1992 (suppl 4)

16. Finegood DT, Hramiak IM, Dupre J: A modified protocol for estimation of insulin sensitivity with the minimal model of glucose kinetics in patients with insulin-dependent diabetes. J Clin Endocrinol Metab 70:1538-1549, 1990

17. Quon MJ, Cochran C, Taylor SI, et al: Direct comparison of standard and insulin modified protocols for minimal model estimation of insulin sensitivity in normal subjects. Diabetes Res 25:139-149, 1994

18. Kahn SE, Bergman RN, Schwartz MW, et al: Short-term hyperglycemia and hyperinsulinemia improve insulin action but do not alter glucose action in normal humans. Am J Physiol 262:E518-E523, 1992

19. Fava GA, Kellner R, Munari F, et al: The Hamilton Depression Rating Scale in normals and depressives. Acta Psychiatr Scand 66:26-32, 1982

20. Knesevich JW, Biggs JT, Clayton PJ, et al: Validity of the Hamilton Rating Scale for Depression. Br J Psychiatry 131:49-52, 1977

21. Kohen D, Burgess AP, Catalan J, et al: The role of anxiety and depression in quality of life and symptom reporting in people with diabetes mellitus. Qual Life Res 7:197-204, 1998

22. Jacobson AM, de Groot M, Samson JA: The effects of psychiatric disorders and symptoms on quality of life in patients with type I and type II diabetes mellitus. Qual Life Res 6:11-20, 1997

23. Mazze RS, Lucido D, Shamoon H: Psychological and social correlates of glycemic control. Diabetes Care 7:360-366, 1984

24. Lustman PJ, Griffith LS, Gavard JA, et al: Pharmacotherapy of depression may improve both mood and glucose regulation in diabetes. Diabetes Care 15:1631-1639, 1992

25. Littlefield CH, Craven JL, Rodin GM, et al: Relationship of self-efficacy and binging to adherence to diabetes regimen among adolescents. Diabetes Care 15:90-94, 1992

26. Fernstrom MH, Krowinski RL, Kupfer DJ: Appetite and food preference in depression: Effects of imipramine treatment. Biol Psychiatry 22:529-539, 1987

27. Kazes M, Danion JM, Grange D, et al: Eating behaviour and depression before and after antidepressant treatment: A prospective, naturalistic study. J Affect Disord 30:193-207, 1994

28. Lovejoy J, DiGirolamo M: Habitual dietary intake and insulin sensitivity in lean and obese adults. Am J Clin Nutr 55:1174-1179, 1992

29. Walton C, Godsland IF, Proudler AJ, et al: Effect of body mass index and fat distribution on insulin sensitivity, secretion, and clearance in nonobese healthy men. J Clin Endocrinol Metab 75:170-175, 1992

30. Ferrannini E, Vichi S, Beck-Nielsen H, et al: Insulin action and age. European Group for the Study of Insulin Resistance (EGIR). Diabetes 45:947-953, 1996

31. Van Cauter E, Blackman JD, Roland D, et al: Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. J Clin Invest 88:934-942, 1991

32. Devlin JT: Effects of exercise on insulin sensitivity in humans. Diabetes Care 15:1690-1693, 1992

33. Berken GH, Weinstein DO, Stern WC: Weight gain. A side-effect of tricyclic antidepressants. J Affect Disord 7:133-138, 1984

34. Goodnick PJ, Henry JH, Buki VM: Treatment of depression in patients with diabetes mellitus. J Clin Psychiatry 56:128-136, 1995

35. Lustman PJ, Griffith LS, Clouse RE, et al: Effects of nortriptyline on depression and glycemic control in diabetes: Results of a double-blind, placebo-controlled trial. Psychosom Med 59:241-250, 1997

36. Targum SD, Sullivan AC, Byrnes SM: Neuroendocrine interrelationships in major depressive disorder. Am J Psychiatry 139:282-286, 1982

37. Krishnan KR, Manepalli AN, Ritchie JC, et al: Growth hormone–releasing factor stimulation test in depression. Am J Psychiatry 145:90-92, 1988

38. Kelly WF: Psychiatric aspects of Cushing's syndrome. Q J Med 89:543-551, 1996

39. Page R, Boolell M, Kalfas A, et al: Insulin secretion, insulin sensitivity and glucose-mediated glucose disposal in Cushing's disease: A minimal model analysis. Clin Endocrinol (Oxf) 45:715-720, 1996

40. Nosadini R, Del Prato S, Tiengo A, et al: Insulin resistance in Cushing's syndrome. J Clin Endocrinol Metab 57:529-536, 1983

41. Meltzer H: Serotonergic dysfunction in depression. Br J Psychiatry Suppl 8:25-31, 1989

42. Coppen AJ, Doogan DP: Serotonin and its place in the pathogenesis of depression. J Clin Psychiatry 49:4-11, 1988 (suppl)

43. Reaven GM: Role of insulin resistance in human disease (syndrome X): An expanded definition. Annu Rev Med 44:121-131, 1993

44. DeFronzo RA, Ferrannini E: Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991

45. Jonas BS, Franks P, Ingram DD: Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Fam Med 6:43-49, 1997

46. Rosmond R, Bjorntorp P: Endocrine and metabolic aberrations in men with abdominal obesity in relation to anxio-depressive infirmity. Metabolism 47:1187-1193, 1998

47. Hippisley-Cox J, Fielding K, Pringle M: Depression as a risk factor for ischaemic heart disease in men: Population based case-control study. BMJ 316:1714-1719, 1998

48. Ford DE, Mead LA, Chang PP, et al: Depression is a risk factor for coronary artery disease in men: The Precursors Study. Arch Intern Med 158:1422-1426, 1998

49. Everson SA, Roberts RE, Goldberg DE, et al: Depressive symptoms and increased risk of stroke mortality over a 29-year period. Arch Intern Med 158:1133-1138, 1998