OBSERVATIONS

Improvement of Insulin Sensitivity After Adrenalectomy in Patients With Pheochromocytoma

Impaired glucose tolerance is frequent in patients with pheochromocytoma (1). A decreased insulin secretion is considered to be the main cause for pheochromocytoma-associated diabetes (2). Data from animal and circumstantial evidence from clinical studies suggest that catecholamines can induce insulin resistance. Previous studies characterized the glucose metabolism in patients with pheochromocytoma by fasting blood glucose levels (3), an intravenous insulin test (4), or an oral glucose tolerance test (OGTT) with corresponding insulin levels (1,5) before and after surgery. These studies primarily investigated the changes of insulin secretion and did not calculate the whole-body insulin sensitivity from euglycemic clamps. In animal studies, epinephrine was shown to induce insulin resistance in rat muscle (6). There is further evidence from clinical studies that insulin resistance can be induced by catecholamines via β-adrenergic stimulation (7) or epinephrine (8). Therefore, it is very likely that catecholamine excess in patients with pheochromocytoma can induce insulin resistance. Hence, we investigated the extent of insulin resistance by means of the euglycemic-hyperinsulinemic clamp technique (9) in three patients (two women and one man) with pheochromocytoma and diabetes before and 5 weeks after adrenalectomy. To exclude glucose toxicity–induced insulin resistance, clamps were performed 2 weeks after normalization of hyperglycemia.

All of the patients had a history of sustained hypertension, and one patient had a history of paroxysmal hypertension. The two women had a family history of type 2 diabetes and required insulin therapy before surgery; the man (no family history of diabetes) was treated with metformin before surgery. In each proband, whole-body glucose uptake (means ± SEM) significantly improved from 23.4 ± 4.1 before surgery to 36.2 ± 7.7 μmol · kg^{-1} · min^{-1} 5 weeks after the adrenalectomy.

The improved insulin sensitivity after surgery was confirmed in all of the subjects by a decrease in fasting hyperinsulinemia from 163 ± 19 before surgery to 102 ± 21 pmol/l after surgery. In contrast to previous studies, no inhibitory effect on fasting insulin secretion by high catecholamine levels was detected. In one patient, diabetes and hyperinsulinemia were reversed by the removal of the tumor. In the other two subjects, type 2 diabetes was known for >6 years and treated with insulin 2 and 3 years before the diagnosis of pheochromocytoma. Although diabetes was not reversible in these two patients, insulin treatment could be converted into oral antidiabetic treatment in one patient, and the daily insulin dose could be significantly reduced in the other patient. There was no change in BMIs or the concentrations of free fatty acids, triglycerides, and total, LDL, and HDL cholesterol after surgery compared with before surgery. Normalization of the 24-h urinary excretion of catecholamines after surgery was achieved in each of the patients. No patient took any drug that influenced the high-performance liquid chromatography analysis of the catecholamines.

Previous studies showed an improvement of glucose metabolism as determined by fasting (3) or 2-h OGTT plasma glucose levels (1,5) after adrenalectomy in patients with pheochromocytoma. Because these studies (1,5) concentrated only on the assessment of insulin-secretory defects in patients with pheochromocytoma, the catecholamine-induced impaired glucose tolerance was explained by the detected decrease in the insulin secretion response during the OGTT (1). Although β-receptor stimulation (catecholamines) can induce insulin resistance, as suggested by animal (6) and clinical studies (4,7,8), these studies did not investigate whether the improvement in glucose homeostasis after surgery is also the result of an improvement in insulin action.

The threshold for insulin sensitivity (i.e., a normalization of whole-body glucose uptake determined by the euglycemic clamp) was only achieved in the male patient. In this patient, the insulin treatment could be stopped. Therefore, it is likely that, in this patient only, diabetes was induced by the high catecholamine plasma concentrations. In the two female patients, insulin resistance was most likely only exacerbated by the high catecholamine levels. Furthermore, in contrast to the male

patient, the female patients had a family history of type 2 diabetes. In addition to insulin resistance, improvement of hyperinsulinemia could also be due to an insulin secretion–stimulating effect of catecholamines in these patients. Thus, in contrast to the previous findings indicating that reduced insulin secretion is the main cause for impaired glucose tolerance in pheochromocytoma (1,5). In our patients, impaired glucose metabolism was induced (in the male patient) or exacerbated (in the two female patients) by insulin resistance induced by catecholamine excess. Moreover, in contrast to these studies (1,5), even in the male patient with catecholamine-induced mildly impaired glucose tolerance, we observed a postoperative increase of insulin secretion.

In conclusion, in the three patients with pheochromocytoma and diabetes, catecholamine overproduction led to increased insulin resistance. Insulin sensitivity improved after complete adrenalectomy. The previously described inhibitory effect of catecholamine excess on fasting insulin secretion was not detected in these patients.

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References
1. Turnbull DM, Johnston DG, Alberti KG, Hall R: Hormonal and metabolic studies in a patient with phaeochromocytoma. *J Clin Endocrinol Metab* 51:930–933, 1980
2. Isles CG, Johnson JK: Phaeochromocytoma and diabetes mellitus: further evidence that alpha 2 receptors inhibit insulin release in man. *Clin Endocrinol (Oxf)* 18:37–41, 1983
3. Stenström G, Sjöström L, Smith U: Diabetes mellitus in phaeochromocytoma: fasting blood glucose levels before and after surgery in 60 patients with phaeochromocytoma. *Acta Endocrinol (Copenh)* 106:511–515, 1984
4. di Paolo S, de Pergola G, Cospite MR, Guastamacchia E, Cignarelli M, Balice A, Nardelli GM, Giorgino R: Beta-adrenoreceptors desensitization may modulate catecholamine induced insulin resistance in human phaeochromocytoma. *Diabete*

Metab 15:409–415, 1989

5. Uehara Y, Kuroiwa H, Shimizu H, Sato N, Shimomura Y, Mori M: Tumor resection attenuated the impaired tolerance of glucose in patients with asymptomatic pheochromocytoma. *J Med* 24:193–203, 1993

6. Niklasson M, Holmang A, Lonnroth P: Induction of rat muscle insulin resistance by epinephrine is accompanied by increased interstitial glucose and lactate concentrations. *Diabetologia* 41:1467–1473

7. Attvall S, Fowelin J, von Schenck H, Lager I, Smith U: Insulin resistance in type 1 (insulin-dependent) diabetes following hypoglycemia: evidence for the importance of beta-adrenergic stimulation. *Diabetologia* 30:691–697, 1987

8. Deibert DC, DeFronzo RA: Epinephrine-induced insulin resistance in man. *J Clin Invest* 65:717–721, 1980

9. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237: E214–E223, 1979

Association of Autoimmune Pancreatitis and Type 1 Diabetes

Autoimmune exocrinopathy and endocrinopathy of the pancreas

Autoimmune pancreatitis is a recently described clinical entity characterized by diffuse or focal swelling of the pancreas, irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography, hypergammaglobulinemia, eosinophilia, the presence of autoantibodies, fibrosis, and lymphocyte infiltration in the exocrine pancreas, together with a responsiveness to corticosteroid therapy (1–3). It has been suggested that carbonic anhydrase II, an antigen of duct cells of the pancreas, or lactoferrin in the pancreatic acinus may be the candidates for the target antigen, although there is the possibility of other candidates (4). It has been reported that this disease is sometimes associated with autoimmune diseases such as Sjögren's syndrome, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, and immune thrombocytopenia (5,6). On the other hand, it is well known that an autoimmune mechanism is involved in the pathogenesis of type 1A (immune-mediated) diabetes (7). Here we report, for the first time, an association of autoimmune pancreatitis and type 1A diabetes.

A 56-year-old woman was admitted to the hospital complaining of mild left hypochondralgia radiating to the back. She had no manifestations of sicca syndrome and no history of pancreatitis or alcohol consumption. Her family history was not contributory. Her BMI was 23.2 kg/m^2, and her eosinophils were increased to 528/μl. The patient's total serum bilirubin, serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamil transpeptidase, serum amylase, lipase, elastase-1, and C-reactive protein levels were normal. Serum γ-globulin was elevated to 1.63 g/dl and IgG was elevated to 2,000 mg/dl (normal range 800–1,600). The patient tested negative for antinuclear antibody.

The pancreatic exocrine and endocrine functions were as follows: The bentiromide test value was 50.9% (73.1–90.1), showing exocrine dysfunction. Fasting plasma glucose was 141 mg/dl, and plasma glucose after breakfast was 395 mg/dl. She required insulin for control. HbA$_{1c}$ was 5.6% (3.0–6.0). The patient's fasting immunoreactive insulin was 1.9 μU/ml and fasting C-peptide was 0.3 ng/ml. Urinary C-peptide excretion was 22 μg/day. The increment of serum C-peptide in response to intravenous administration of 1 mg glucagon was 0.2 ng/ml, indicating severe impairment of insulin secretion. The patient was positive for islet cell antibody (ICA). IA-2 antibody was positive at 2.7 U/ml (cutoff <0.4) mea-sured by radioimmunoassay kit (RSR, Ltd., Cardiff, Wales, U.K., provided by Cosmic Corp., Tokyo). Anti-GAD antibody was negative. Anti-microsome antibody and anti-thyroglobulin antibody were positive at 1:400 and 1:100 titer for each. The patient possessed HLA-DR4 (DRB1*04051) and DQB1 0401, the major HLA types in type 1 diabetes in Japanese people (8). Other HLA types found in this case subject were A2, B61, B67, CW7, DRB1*1201, and DQB1* 0301. IgM antibodies to cytomegalovirus, Epstein-Barr virus, rubella virus, and mumps virus (measured by enzyme-linked immunosorbent assay), and antibody to Coxsackie B4 virus (measured by complement fixation method) were all negative.

Abdominal ultrasonography showed diffuse hypoechoic swelling of the pancreas. Computed tomography (CT) with enhancement demonstrated swelling of the pancreas (Fig. 1). Endoscopic retrograde cholangiography and pancreatography showed a diffuse narrowing and irregularity of the main pancreatic duct and mild smooth stenosis of the lower common bile duct (Fig. 2).

Because autoimmune pancreatitis was strongly suggested, corticosteroid administration was initiated. Prednisolone (30 mg/day) was administered and the dose was tapered. One month after the steroid treatment was started, the swelling of the pancreas improved to normal size (Fig. 3), and the bentiromide test value improved to 71.2%. However, insulin secretion was

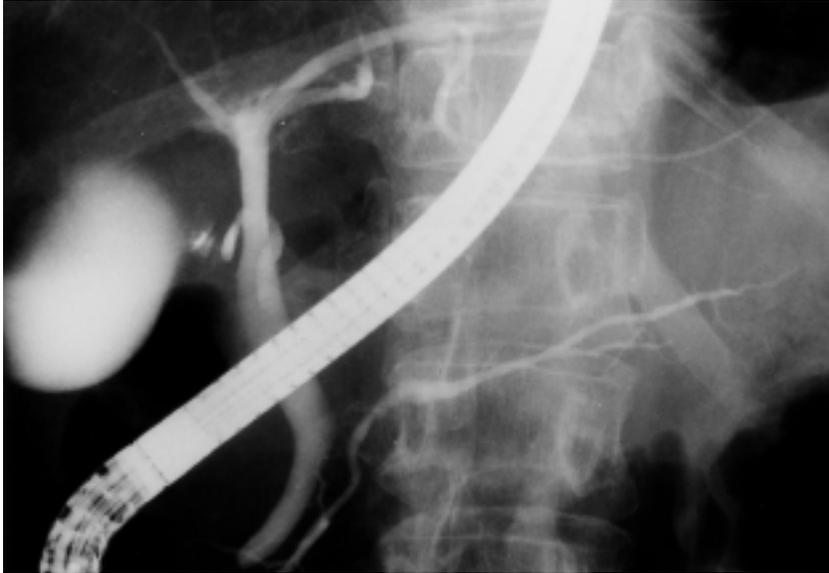**Figure 1**—*CT on admission. Diffuse swelling of the pancreas can be seen.*

Figure 2—*Endoscopic retrograde cholangiography and pancreatography on admission. Diffuse irregular narrowing of the main pancreatic duct and mild smooth stenosis of the lower common bile duct can be seen.*

susceptible HLA. Involvement of known viruses that have affinity for the pancreas was not found.

In conclusion, we reported the first case of association of autoimmune pancreatitis and type 1A diabetes; namely, autoimmune exocrinopathy and endocrinopathy of the pancreas.

These conditions may characterize a novel subtype of type 1A diabetes, although further studies are required to confirm this hypothesis.

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References
1. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N: Chronic pancreatitis caused by an autoimmune abnormality: proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 40:1561–1568, 1995
2. Ito T, Nakano I, Koyanagi S, Miyahara T, Migita Y, Ogoshi K, Sakai H, Matsunaga S,

not restored; the C-peptide response to a glucagon test after treatment was 0.1 ng/ml. The basal plasma glucagon level was 94 pg/ml, and the increment of plasma glucagon after intravenous infusion of 30 g arginine hydrochlorate in 30 min was 228 pg/ml, suggesting that α-cell function was preserved. The patient is being treated as an outpatient with 5 mg/day prednisolone and multiple insulin injections.

Ito et al. (2) reported cases of diabetes that occurred at the same time as autoimmune pancreatitis and were improved by steroid treatment. We also have experienced cases of diabetes associated with autoimmune pancreatitis that improved after steroid treatment (6). In those cases, the ICA and anti-GAD antibody were negative. In contrast, the present case subject was positive for ICA and IA-2 antibody, which are good markers of type 1A diabetes (7,9). Despite the severe impairment of insulin secretion, glucagon secretion was preserved. This finding is uncharacteristic of diabetes secondary to chronic pancreatitis, in which α-cell function is also impaired in the stage when β-cell function is severely impaired (10). Thus, this case was diagnosed as an association of type 1A diabetes and autoimmune pancreatitis. Because the patient's HbA_{1c} on admission was normal, the clinical presentation of type 1A diabetes and autoimmune pancreatitis seems simultaneous. The reason the impaired insulin secretion

was not restored while the exocrine function improved after steroid treatment may be that β-cell damage had progressed to an irreversible stage.

This association of autoimmune pancreatitis and type 1A diabetes may suggest common factors in the etiopathogenesis of both diseases, although the mechanism remains to be elucidated. Another possibility is that local disturbance of immunobalance associated with autoimmune pancreatitis triggered the immune mechanism of type 1A diabetes in the patient bearing the

Figure 3—*CT on admission after steroid treatment. The pancreas returned to normal size.*

Yasuda O, Sumii T, Nawata H: Autoimmune pancreatitis as a new clinical entity: three cases of autoimmune pancreatitis with effective steroid therapy. *Dig Dis Sci* 42:1458–1468, 1997

3. Taniguchi T, Seko S, Azuma K, Tamegai M, Nishida O, Inoue F, Okamoto M, Mizumoto T, Kobayashi H: Autoimmune pancreatitis detected as a mass in the tail of the pancreas. *J Gastroenterol Hepatol* 15:461–464, 2000

4. Okazaki K, Uchida K, Ohana M, Nakase H, Uose S, Inai M, Matsushima Y, Katakura K, Ohmori K, Chiba T: Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. *Gastroenterology* 118:573–581, 2000

5. Horiuchi A, Kawa S, Akamatsu T, Aoki Y, Mukawa K, Furuya N, Ochi Y, Kiyosawa K: Characteristic pancreatic duct appearance in autoimmune chronic pancreatitis: a case report and review of the Japanese literature. *Am J Gastroenterol* 93:260–263, 1998

6. Seko S, Taniguchi T, Nishikawa H, Azuma K, Asagoe K, Otani Y, Miyake N, Inoue F, Nishida O, Mizumoto T, Furukawa H: A case of autoimmune pancreatitis associated with immune thrombocytopenia. *Gastrointest Endosc* 42:192–197, 2000

7. Eisenbarth GS: Type 1 diabetes mellitus: a chronic autoimmune disease. *N Engl J Med* 314:1360–1368, 1986

8. Ikegami H, Ogihara T: Genetics of insulin-dependent diabetes mellitus. *Endocrine J* 43:605–613, 1996

9. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jacksoon RA, Chase HP, Eisenbarth GS: Prediction of type 1 diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 45:926–933, 1996

10. Sjoberg RJ, Kidd GS: Pancreatic diabetes mellitus. *Diabetes Care* 12:715–724, 1989

Use of Sibutramine Hydrochloride Monohydrate in the Treatment of the Painful Peripheral Neuropathy of Diabetes

When amitriptyline was first shown to help some patients with the painful peripheral neuropathy of diabetes, it was unknown exactly how the medication worked (1). Max et al. (2) then showed that the most likely mechanism involved was through the central nervous system metabolism of norepinephrine. This finding led to the successful trial of extended-release venlafaxine (3,4), an antidepressant that inhibits the uptake of norepinephrine among other centrally acting monoamines. Because type 2 diabetes is often associated with obesity and the weight-losing drug sibutramine hydrochloride monohydrate is associated with the blockage of reuptake of norepinephrine in the central nervous system (5), this agent was tried in the treatment of the painful peripheral neuropathy seen in diabetes.

A 58-year-old woman with a 10-year history of type 2 diabetes and lifelong obesity (BMI 45.5 kg/m²) presented with poorly controlled diabetes and an HbA_{1c} level of 7.9%. At the time, she was taking metformin and NPH insulin twice a day. Initially, her treatment consisted of weight loss (7 lb.) and discontinuation of insulin use, and over a period of months her HbA_{1c} level dropped to 6.6%. She then developed burning paresthesias of both distal lower extremities. A physical examination revealed that she had absent deep tendon reflexes in the Achilles' tendon and decreased sensation to pinprick and vibratory sense of the feet. She had no history of alcohol or drug abuse. She was started on 15 mg sibutramine daily. In less than 1 week, she had 90% relief of the pain in her feet. The pain recurred when she stopped taking the medicine and was promptly relieved when 10 mg per day was restarted and continued to the present time. The patient had no increase in blood pressure or pulse; however, she also experienced had no further weight loss.

These findings led to the trial of sibutramine 15 mg per day in eight other type 2 diabetic patients who had painful neuropathy. All of the patients were obese women. They had had known diabetes from 1 to 29 years and all were on various oral agents with varying degrees of control. The length of pain symptoms had been from a few weeks to 3 years.

All patients responded to the medication with a 50–100% reduction in pain (average 75%). The response occurred usually within 1 week of starting the medication. Because of the expense of the medication, all of the patients stopped the medicine with the recurrence of pain. Two patients restarted the medicine again, with prompt relief. The other six were treated with various other medications in an attempt to relieve their discomfort.

Both the Diabetes Control and Complications Trial (6) and the U. K. Prospective Diabetes Study Group (7) have shown that decreasing an individual's mean blood sugar level can decrease the onset and progression of diabetic neuropathy. Weight loss alone can also lead to a decrease in the mean blood sugar level, possibly preventing or delaying the onset of the painful peripheral neuropathy seen in some diabetic patients. Sibutramine hydrochloride monohydrate seems to be an ideal method of treatment in obese type 2 diabetic patients with painful neuropathy.

In these case reports, the medication seems to relieve the discomfort. However, because of the expense of the drug, because no third-party payer would help compensate for the medication, and because no patient was in a dedicated weight loss program, the medication was not continued in the majority of the patients and weight loss was not achieved.

This observation suggests that sibutramine hydrochloride monohydrate combined with a structured weight loss program may help relieve the pain of diabetic neuropathy and eventually achieve weight loss in the obese diabetic patient.

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References
1. Davis JL, Lewis SB, Gerich JE, Kaplan RA, Schultz TA, Wallin DB: Peripheral diabetic neuropathy treated with amitriptyline and fluphenazine. *JAMA* 238:2291–2292, 1977
2. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R: Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 326:1250–1256, 1992
3. Davis JL, Smith RL: Painful peripheral diabetic neuropathy treated with venlafaxine HCL extended release capsules (Letter). *Diabetes Care* 22:1909, 1999
4. Kunz NR, Goli V, Lei D, Rudolph R: Treating painful diabetic neuropathy with venlafaxine extended release (Abstract). *Diabetes* 49 (Suppl. 1), A165, 2000
5. Lebovitz H: Appetite suppressant agents: current problems and controversies. *Clinical Diabetes* 15:229–235, 1977
6. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the develop-

ment and progression of long term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
7. U. K. Prospective Diabetes Study Group: Intensive blood glucose control with sulfonylureas or insulin and risk of complications with type 2 diabetes (UKPDS 33). *Lancet* 352:837–854, 1998

COMMENTS AND RESPONSES

Insulin Sensitivity Indexes Calculated From Oral Glucose Tolerance Test Data

In the article by Matsuda and DeFronzo on this issue (1), the authors proposed a formula to calculate the insulin sensitivity index (ISI) from oral glucose tolerance test (OGTT) data and compared their formula with a formula previously published by us (2,3). Unfortunately, a mistake was made in reporting our formula. We described our formulas (2), which calculate the ISI for glycemia [ISI(gly)] and free fatty acids (FFAs) [ISI(ffa)], as follows: ISI(gly) = 2/[(INSp × GLYp) + 1], and ISI(ffa) = 2/[(INSp × FFAp) + 1], where INSp, GLYp, and FFAp are insulinemic, glycemic, and FFA areas, respectively, during an OGTT. Areas (only baseline, 1-h, and 2-h samplings) were expressed by taking the mean normal value as unit (i.e., by dividing the value of insulin, glycemia, and FFA areas of the study subjects by the mean normal values of these parameters), so that, in normal subjects, ISI(gly) and ISI(ffa) were always ~1, with maximal variations among patients between 0 and 2.

In contrast to our description, Matsuda and DeFronzo calculated the (INSp × GLYp) in our formula by multiplying insulin and glycemia (mean values during an OGTT, rather than areas) by each other and then dividing the result by an undefined "constant." The difference is substantial. In fact, in 72 subjects, we found that the correctly calculated ISI(gly) in normal subjects was close to 1 (as expected), and the minimal value among obese patients with impaired glucose tolerance was 0.18. According to our formula as altered by Matsuda and DeFronzo, when a low constant (25% of the mean normal insulin

value) was used, the ISI(gly) normal value was 0.08, and the minimal value among patients was 0.01, whereas by using a high constant (fourfold the mean normal value of glucose), the mean and minimal values were 1.88 and 1.61. Clearly, these narrow ranges of values and their dependence on the constant would make the test of little clinical significance. Correlation with several parameters (BMI, waist circumference, etc.) is also affected and is higher when high constants are used. But which constant is used by Matsuda and DeFronzo? I would be grateful if these authors would repeat their calculation according to the formula published by us.

Unlike our original formula, the altered formula yields results that are linked to the units used to express insulin and glucose. This effect is also true for the formula of Matsuda and DeFronzo, who expressed glucose and insulin as milligrams per deciliter and microunits per milliliter, respectively. In fact, the ISI in their normal group would change from ~3.75 to ~67.42 if glucose was expressed in millimoles per liter.

Finally, correlation between the euglycemic insulin clamp and an OGTT-derived ISI may not be meaningful, because the two tests have different significance. The former is performed under reproducible but artificial conditions (sustained hyperinsulinemia, suppression of FFA, etc.) and measures glucose utilization by tissues. The latter is performed under rather physiological conditions, with hormonal and metabolic variables unmodified, and measures the whole-body clinical parameters of insulin action (i.e., the insulin effect on blood glucose and FFA).

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References
1. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22:1462–1470, 1999
2. Belfiore F, Iannello S, Volpicelli G: Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. *Mol Genet Metab* 63:134–141, 1998
3. Belfiore F, Iannello S: Insulin resistance in

obesity: metabolic mechanisms and measurement methods. *Mol Genet Metab* 65: 121–128, 1998

Response to Belfiore

In our article (1), the constant (*C*) represents the product of the mean plasma glucose concentration multiplied by the mean plasma insulin concentration in normal healthy subjects. Thus, as described in the original article by Belfiore et al. (2), we divided the product of the mean plasma glucose and insulin concentrations in the impaired glucose tolerant and diabetic subjects by the product of the mean plasma glucose and insulin concentrations in the normal healthy subjects. To calculate the mean plasma glucose and insulin concentrations, we first calculated the area under the curve for insulin and glucose and divided by 120 min (the length of the oral glucose tolerance test [OGTT]). Therefore, whether one uses the product of the area under the plasma insulin and glucose concentration curves or the product of the mean plasma glucose and mean plasma insulin concentrations, one obtains the same values that are presented in our article. The mean insulin sensitivity value calculated in the 62 normal subjects in our article was 1.0 (range 0.4–1.6). The "normal values" cited in Belfiore's letter (3) for "low" and "high" constants have no relevance to the calculations used in our article, and it is unclear to us how or why these low and high constant values were selected.

The euglycemic insulin clamp is widely acknowledged to represent the gold standard for measuring insulin sensitivity in vivo and is based on sound physiological principles. During the procedure, plasma glucose and insulin concentrations are clamped, and the glucose infusion rate (plus any residual endogenous glucose production) equals the rate of insulin-mediated glucose disposal by all tissues in the body. In contrast, during the OGTT, both plasma glucose and insulin concentrations are simultaneously and rapidly changing, and steady-state conditions are never achieved. Consequently, it is difficult to draw any conclusions about either insulin sensitivity or insulin secretion during the OGTT. Our article represents the first attempt to derive an index of insulin sensitivity from the OGTT and to validate the derived index by comparing it with the directly measured rate of insulin-mediated glucose disposal

during a euglycemic insulin clamp performed in the same subject.

We agree with Belfiore that any test that restrains the plasma glucose and insulin concentrations from changing is nonphysiological. However, unless these variables are clamped, it is impossible to obtain a direct measure of insulin-mediated glucose disposal. It should be pointed out that in every day life most individuals ingest mixed meals. Therefore, the ingestion of 75 g glucose also can hardly be considered to be physiological. Moreover, the hormonal (insulin) and metabolic (glucose) variables during the OGTT are not unmodified, but are constantly changing, making it impossible to derive a direct measure of insulin sensitivity. Because the plasma glucose concentration increases after glucose ingestion, one also has the compounding variable of glucose-mediated glucose uptake, which is obviated by performing the insulin clamp at euglycemic levels.

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References

1. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 22:1462–1470, 1999
2. Belfiore F, Iannello S, Volpicelli G: Insulin sensitivity indices calculated from basal and OGTT induced insulin, glucose, and FFA levels. *Mol Gen Metab* 63:134–141, 1998
3. Belfiore F: Insulin sensitivity indexes calculated from oral glucose tolerance test data (Letter). *Diabetes Care* 23:1595, 2000

Regarding Depressive Symptoms and Metabolic Control in African-Americans With Type 2 Diabetes

I n the January 2000 issue of *Diabetes Care*, Gary et al. (1) reported a significant graded relationship between greater depressive symptoms and higher serum levels of cholesterol and triglycerides ($P < 0.050$) in patients with diabetes. They also reported higher serum levels of HDL cholesterol with more depressive symptoms ($P = 0.047$). Overall, the patients' diabetes was well controlled (>48% patients had HbA_{1c} levels <8.0%, the acceptable range according to American Diabetes Association recommendations).

Type 2 diabetic patients often have quantitative changes in plasma lipid profiles, which are characterized by higher triglyceride and lower HDL cholesterol levels than the average population (2,6).

Scoppola et al. (3) showed that total cholesterol, LDL cholesterol, and triglycerides decreased by 9, 8, and 12%, respectively, after blood glucose optimization, which was evident by an improved level of HbA_{1c}. In addition, Purnell et al. (4) showed that, compared with the subjects in the conventionally treated group ($n = 680$), those subjects receiving intensive diabetes therapy ($n = 667$) had a more favorable distribution of cholesterol.

It is a well-known fact that alcohol intake is associated with a significant elevation of both triglyceride and HDL cholesterol levels (2,5), as well as depression.

We wonder what the outcome of this study would have been if alcohol had been included as a confounding factor. If the patients in this study had been consuming alcohol on a regular basis, the study findings could then be explained on this basis alone.

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References

1. Gary TL, Crum RM, Cooper-Patrick L, Ford D, Brancati FL: Depressive symptoms and metabolic control in African-Americans with type 2 diabetes. *Diabetes Care* 23:23–29, 2000
2. Dias CM, Nogueira P, Rosa AV, De Sa JV, Gouvea MF, Marinho Falcao JC: Total cholesterol and high-density lipoprotein cholesterol in patients with non-insulin-dependent diabetes mellitus. *Acta Med Port* 8:619–628, 1995
3. Scoppola A, Testa G, Frontoni S, Maddaloni E, Gambardella S, Menzinger G, Lala A: Effects of insulin on cholesterol synthesis in type II diabetes patients. *Diabetes Care* 18:1362–1369, 1995
4. Purnell JQ, Marcovina SM, Hokanson JE, Kennedy H, Cleary PA, Steffes MW, Brunzell JD: Levels of lipoprotein (a), apolipoprotein B, and lipoprotein cholesterol distribution in IDDM: results from follow-up in the Diabetes Control and Complications Trial. *Diabetes* 44:1218–1226, 1995
5. Parker DR, McPhillips JB, Derby CA, Gans KM, Lasater TM, Carleton RA: High-density-lipoprotein cholesterol and types of alcoholic beverages consumed among men and women. *Am J Public Health* 86:1022–1027, 1996
6. Uusitupa M, Siitonen O, Voutilainen E, Aro A, Hersio K, Pyorala K, Penttila I, Ehnholm C: Serum lipids and lipoproteins in newly diagnosed non-insulin-dependent (type II) diabetic patients, with special reference to factors influencing HDL-cholesterol and triglycerides levels. *Diabetes Care* 9:17–22, 1986

Response to Rehman et al.

W e would like to thank Rehman et al. (1) for their thoughtful comments regarding our article (2). In general, it is well documented that older African-American women do not have a high occurrence of alcohol use (3–5). Our population was 76% female. Nevertheless, we did examine alcohol use in our baseline assessment. Only 19 individuals (10% of the population) reported drinking alcohol in the month before the visit. Of the 18 individuals who responded to the CAGE (cut down, annoyed by criticism, guilty about drinking, and eye-opener drinks) questionnaire items (6), only 7 individuals scored ≥2, indicating suspicion of alcoholism.

To assess the possibility of alcohol use as a potential confounder, we examined both the mean Center for Epidemiologic Studies Depression Scale (CES-D) depressive symptom score and the mean level of each lipid outcome, stratified by alcohol use in the past month versus no alcohol use. No statistically significant differences were shown between alcohol status and the main independent variable, CES-D depressive symptom score. Likewise, no statistically significant differences were shown for total cholesterol, HDL cholesterol, LDL cholesterol, or triglyceride levels by alcohol status.

In the linear regression models presented in the article, we examined the relationship between depressive symptoms and each lipid outcome (total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride levels) adjusted for age, sex, income, social support, and duration of diabetes. In response to the letter, we also conducted this analysis including alcohol use in the past month as a covariate. A statistically significant trend between depressive symptoms and total cholesterol ($P = 0.026$), HDL cholesterol ($P = 0.047$), and triglyceride ($P = 0.041$) levels persisted after adjustment for alcohol use. Similarly, the marginally significant relationship between depressive symptoms and LDL cholesterol was virtually unchanged after adjustment for alcohol use ($P = 0.176$).

We conclude that alcohol use was uncommon in this population, and that there was no apparent relationship between alcohol use and lipids.

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References
1. Rehman SU, Shakaib A, Rashid S: Regarding depressive symptoms and metabolic control in African-Americans with type 2 diabetes (Letter). *Diabetes Care* 23:1595, 2000
2. Gary TL, Crum RM, Cooper-Patrick L, Ford D, Brancati FL: Depressive symptoms and metabolic control in African-Americans with type 2 diabetes. *Diabetes Care* 23:23–29, 2000
3. Grant BF, Harford TC, Dawson DA, Chou PS, Dufour M, Pickering R: Prevalence of DSM-IV alcohol abuse and dependence: United States, 1992. *Alcohol Health Res World* 18:243–248, 1994
4. Caetano R, Herd D: Black drinking practices in northern California. *Am J Drug Alcohol Abuse* 10:571–587, 1984
5. Grant BF, Harford TC, Chou P, Pickering R, Dawson DA, Stinson FS, Noble J: Prevalence of DSM-III-R alcohol abuse and dependence: United States, 1988. *Alcohol Health Res World* 15:91–96, 1991
6. Ewing JA: Detecting alcoholism: the CAGE Questionnaire. *JAMA* 252:1905–1907, 1984

HbA$_{1c}$ Determination and Predicting the Clinical Status of Diabetic Patients

We read with interest the recent study from Caragher et al. (1), which cautioned using HbA$_{1c}$ values obtained by an ion capture method (IMx; Abbot Diagnostics, Abbot Park, IL) to predict the clinical status of diabetic patients (1).

Glycohemoglobin (GHb) is a marker of long-term glycemic control and has been shown to correlate with mean blood glucose concentrations. In a recent study, it was demonstrated that GHb may be a highly specific and convenient alternative to fasting blood glucose for the diagnosis and screening of diabetes (2). Methods to determine HbA$_{1c}$ results include cation-exchange high-performance liquid chromatography (HPLC), boronate affinity, electrophoresis, and immunoassays. Thus far, no universally accepted methodological gold standard for HbA$_{1c}$ determination exists. The Diabetes Control and Complications Trial designated the cation-exchange HPLC (Diamat; Bio-Rad, Richmond, CA) as the recommended comparison method. However, different commercially available methods measure different fractions of GHb, which results in varying HbA$_{1c}$ results, depending on the method used. The National Glycohemoglobin Standardization Programs' (NGSP) certified methods demonstrate less variability and better comparability to NGSP-assigned target values versus noncertified methods (3). Neither the Abbot ion capture method nor the turbidimetric immunoinhibition method (Beckman Coulter Synchron; Beckman, Brea, CA), which was used in the study by Caragher et al. (1), were included in the list of NGSP-certified methods as of June 2000 (4). Rather, the method used, which is certified to the criteria of the NGSP, is the HPLC assay (Tosoh Medics, San Francisco, CA).

If the HbA$_{1c}$ test results and the clinical impression in a diabetic patient do not match, then HbA$_{1c}$ values should be determined with secondary methods, preferably NGSP-certified assays that are based on different principles. Measurements of fructosamine and/or calculations of mean blood glucose levels (a mean of 4–5 daily home measurements for 1 week before HbA$_{1c}$ evaluation) may represent alternative methods for long-term control of diabetes in patients whose HbA$_{1c}$ results and clinical status do not correlate (5).

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References
1. Caragher TE, Dohnal JC, Lomont ME: Cautionary note regarding HbA$_{1c}$ methods predicting the clinical status of diabetic patients (Letter). *Diabetes Care* 23:867–868, 2000
2. Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, Flegal KM, Eberhardt MS, Goldstein DE: Use of GHb (HbA$_{1c}$) in screening for undiagnosed diabetes in the U.S. population. *Diabetes Care* 23:187–191, 2000
3. Little RR: Recent progress in glycohemoglobin (HbA$_{1c}$) testing (Editorial). *Diabetes Care* 23:265–266, 2000
4. National Glycohemoglobin Standardization Program (NGSP): List of NGSP certified methods. Available from http://web.missouri.edu/~diabetes/ngsp/methods.htm. Accessed 30 June 1999.
5. Schnedl WJ, Krause R, Halwachs-Baumann G, Trinker M, Lipp RW, Krejs GJ: Evaluation of HbA$_{1c}$ determination methods in patients with hemoglobinopathies. *Diabetes Care* 23:339–344, 2000

Erratum

Watson JM, Jenkins EJE, Hamilton P, Lunt MJ, Kerr D: Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 23:455–459, 2000

The authors of the above paper have discovered that the wrong numbers were plotted when compiling Fig. 1 of the above article. The corrected figure appears below:
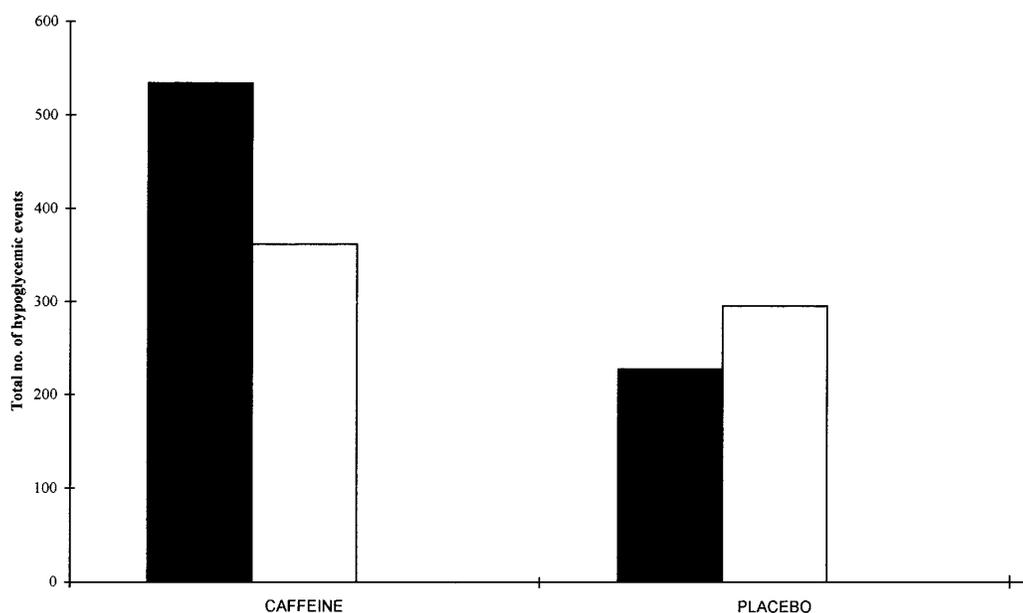

Figure 1—*Symptomatic hypoglycemic evens. P < 0.03 vs. placebo. □, measured; ■, symptomatic.*