

OBSERVATIONS

Missense Mutation of Pro387Leu in Protein Tyrosine Phosphatase-1B (PTP-1B) Is Not Associated With Type 2 Diabetes in a Chinese Han Population

Type 2 diabetes is both a phenotypically and genotypically heterogeneous disease. It is caused by defective insulin secretion and action. Protein tyrosine phosphatases (PTPases) play important roles in insulin cascade signal transduction and have been suggested to be related to insulin resistance (1,2). PTP-1B, a member of the PTP family, is expressed widely in many tissues, acting as a negative regulator in the insulin receptor signal transduction pathway (3–5). The PTP-1B gene is located on the long arm of human chromosome 20, in the region of q13.1–q13.2, which has been linked to quantitative trait loci of obesity and insulin (6,7). A recent study by Echwald S.M. et al. (8) demonstrated that a Pro387Leu variation of the PTP-1B gene, which resulted in the impairment of the serine phosphorylation of the PTP-1B peptide (in vitro experiment), was associated with type 2 diabetes in a Danish Caucasian population with a genotype relative risk of 3.7 (CI 1.26–10.93, $P = 0.02$). Since studies involving the association between the genetic variations and type 2 diabetes are often controversial and inconsistent in different ethnic populations, we tested the association between the Pro387Leu variation of PTP-1B gene with type 2 diabetes in a Chinese Han population for the first time.

The Pro387Leu variation of PTP-1B gene was detected using PCR and restriction fragment–length polymorphism in 589 subjects chosen from the Han population living in southern China, including 329 type 2 diabetic patients (men/women 143/186, age 59.4 ± 9.9 years, BMI 23.9 ± 3.5 kg/m²) and 238 control subjects (men/

women 100/138, age 57.5 ± 8.3 years, BMI 23.8 ± 3.1 kg/m²). The control subjects underwent a 75-g oral glucose tolerance test and were diagnosed with normal glucose tolerance (NGT) in accordance with the 1997 American Diabetes Association criteria. The study was approved by the ethnics committee of our institution. All the subjects gave informed consent.

In our study, only two subjects heterozygous for the mutation were found in the NGT control group, with genotype and allele frequencies of 0.008 and 0.004, respectively. We found another two heterozygotes in the diabetic patient group; the genotype and allele frequencies were 0.006 and 0.003, respectively. The differences did not reach statistical significance between groups ($P > 0.05$ for both). The distribution was consistent with Hardy-Weinberg equilibrium. We then examined the impacts of the mutation on metabolic and anthropometric parameters in both groups. Among NGT control subjects, there were no significant differences in age, fasting plasma glucose (FPG), or lipid profile between the two subgroups with or without the Leu387 mutation ($P > 0.05$), while BMI was significantly higher in subjects with the Leu387 allele (23.74 ± 3.05 vs. 28.55 ± 2.19 kg/m², $P = 0.027$). In the diabetic patient group, no differences were observed in age, BMI, FPG, HbA_{1c}, C-peptide, or lipid profile ($P > 0.05$). Since the mutation rate was quite low in the examined Chinese Han population and at the same time there were 31 subjects with a BMI > 27 kg/m² in the subgroup without the Leu387 mutation, the difference found in BMI between the mutation carriers and noncarriers in the control group was likely attributed to individual variance rather than the true difference caused by the presence of the mutation.

In conclusion, our data indicated that the mutation of Pro387Leu in PTP-1B gene was present in the Chinese Han population examined, but this variation was not associated with type 2 diabetes.

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Retinopathy Is Associated With Cardiovascular and All-Cause Mortality in Both Diabetic and Nondiabetic Subjects

The Hoorn Study

Diabetic retinopathy has been associated with increased cardiovascular and all-cause mortality risks among diabetic populations (1). The exact mechanism of this association, however, still remains unclear (1). Recently, we reported (2) that hypertension, dyslipidemia, and obesity are associated with retinopathy in diabetic and nondiabetic individuals. Conceivably, these associations with cardiovascular risk factors, which explain the occurrence of retinopathy in a nondiabetic population, may also explain the association of retinopathy and mortality. Therefore, the purpose of this population-based, prospective cohort study was to describe the association of retinopathy with cardiovascular and all-cause mortality in diabetic and nondiabetic individuals. Further investigation was directed toward the contribution of cardiovascular risk factors and risk factors of retinopathy to the association of retinopathy and mortality risk. The study population consisted of an age-, sex-, and glucose tolerance-stratified random sample of the Hoorn Study ($n = 631$), a study of diabetes and diabetes complications. At baseline, the years 1989–1990, extensive physical and ophthalmological examinations were performed (2). Follow-up on mortality until January 2002 was available (median duration 10.7 years; range 0.5–12.2). Cox proportional hazards analyses were conducted to assess mortality risks and independent contributions of cardiovascular risk factors to the association of retinopathy with mortality. Retinopathy was detected in 85 (44 nondiabetic and 41 diabetic) subjects (13.6%), 88% of whom had nonproliferative retinopathy. During the follow-up period, 157 (25.1%) participants died, 62 (9.9%) of whom had a cardiovascular cause of death. The cardiovascular mortality risks for subjects with retinopathy adjusted for age and sex were 1.75 (0.60–

5.08) and 2.20 (1.03–4.70) in nondiabetic and diabetic subjects, respectively. The all-cause mortality risks were 1.43 (0.74–2.79) and 2.05 (1.23–3.44) in nondiabetic and diabetic subjects, respectively. After adjustment for diabetes and diabetes duration, the mortality risks in diabetic subjects were 1.67 (0.72–3.86) for cardiovascular mortality and 1.61 (0.92–2.81) for all-cause mortality. BMI, prior cardiovascular disease, and triglycerides explained smaller portions of the association in diabetic subjects, whereas the mortality risk was only lowered by glycated hemoglobin in nondiabetic subjects. Adjustment for other cardiovascular risk factors, such as hypertension, smoking, and homocysteine, did not considerably change the estimates. Finally, after adjustment for all explanatory risk factors in diabetic and nondiabetic subjects together, a 1.4-fold (0.7–2.8) higher risk for cardiovascular mortality and a 1.4-fold (0.9–2.1) higher risk for all-cause mortality in subjects with retinopathy remained unexplained. The contribution of several cardiovascular risk factors to the increased risk of (cardiovascular) mortality might suggest shared pathophysiological mechanisms in microvascular and macrovascular disorders. Other mechanisms that could possibly contribute to the unexplained 40% increased mortality risk include inflammation, endothelial dysfunction, or advanced glycation end products.

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The Antilipidemic Effects of Ezetimibe in Patients With Diabetes

The Adult Treatment Panel (ATP)-III guidelines list diabetes as a coronary heart disease (CHD) risk equivalent (1). Therefore, the LDL cholesterol goal of <100 mg/dl for patients with diabetes is equivalent to that of patients with known CHD (1,2). Hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy is recommended as first-line treatment in diabetic patients with elevated LDL cholesterol levels (2,3). Despite maximum statin doses, not all patients are able to reach this goal. In addition, some patients experience drug-induced side effects when statin doses are titrated upwards in an attempt to reach that goal. In such cases, lipid-lowering combination therapy may be warranted because doubling the statin dose has been shown to only incrementally improve LDL cholesterol reduction, whereas the use of lipid-lowering medications with different mechanisms of action have demonstrated synergistic effects (4).

Ezetimibe (Zetia; Merck/Schering-Plough Pharmaceuticals, North Wales, PA) is the first in a novel class of antihyperlipidemic agents called 2-azetidionones, which act as a selective cholesterol absorption inhibitor. Ezetimibe is indicated for the treatment of primary hypercholesterolemia, alone or in combination with statin therapy (5). Compared with placebo, ezetimibe as monotherapy decreases LDL cholesterol levels by 16–19% (6–8). When it is added to statin therapy, ezetimibe demonstrates a significant 15–

20% additional mean percent reduction in LDL cholesterol levels compared with statin use alone (9–11). To date, the safety and efficacy of ezetimibe in a diabetic population has not been reported. The objective of this report was to retrospectively determine the effectiveness and safety of ezetimibe in patients with diabetes at a private endocrinology practice.

The study population consisted of patients with diabetes who were prescribed Zetia, had no medication changes between baseline and follow-up visits, had fasting values obtained at baseline and follow-up, and received ezetimibe for a minimum of 6 weeks. The 23 identified patients were elderly (63.2 ± 12.4 years of age), were obese (95.8 ± 24.9 kg), and had long-standing diabetes (16.3 ± 12.2 years), but had excellent control of glucose levels (HbA_{1c} $6.9 \pm 1.1\%$) and blood pressure (115.9 ± 9.3 and 69.1 ± 4.1 mmHg for systolic and diastolic, respectively). Of the 23 patients, 2 had type 1 diabetes. At baseline, 74% (17 of 23) of patients were receiving statin therapy (for a minimum of 6 months), including 3 patients who received combination therapy with micronized fenofibrate, gemfibrozil, and sustained-release niacin, respectively. Two additional patients were receiving sustained-release niacin and micronized fenofibrate monotherapy, respectively. The remaining four patients received no antilipidemic medication at baseline.

The average time of follow-up was 83 days. With the addition of ezetimibe, there was a statistically significant 21% mean reduction in total cholesterol (219.6 ± 44.5 to 174.3 ± 39.9 mg/dl; $P < 0.001$) and a 34% average decrease in LDL cholesterol levels (129.3 ± 36.2 to 85.9 ± 27.2 mg/dl, $P < 0.001$). There were no significant changes in triglycerides ($P = 0.215$), HDL cholesterol ($P = 0.06$), aspartate aminotransferase ($P = 0.444$), or alanine aminotransferase ($P = 0.319$) values. Seventy percent of patients (16 of 23) had an LDL cholesterol level < 100 mg/dl.

Ezetimibe represents a safe and effective treatment for patients with diabetes who are not at their LDL cholesterol goals. Clinicians should consider ezetimibe as a reasonable addition to statin therapy for diabetic patients unable to tolerate statins at high doses or for patients who fail to reach therapeutic end points on maximum-dose statin therapy.

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Severe Diabetic Ketoacidosis Associated With Acute Myocardial Necrosis

We describe a case of a 28-year-old woman who was admitted to our hospital with severe diabetic ketoacidosis. She was known to have had type 1 diabetes for 10 years. During the previous 2 days, she had gone to a party, drank a considerable amount of alcohol, and did not administer her regular dose of insulin.

On admission, she was semicomatose and tachypnoic, her blood pressure was 90/70 mmHg, and her heart rate 80 bpm. Laboratory tests showed severe metabolic acidosis (pH 6.92, bicarbonate 2.2 mmol/l, pCO₂ 1.49 kPa), very high blood glucose (75 mmol/l), hyponatremia (104.3 mmol/l), hypochloremia (70 mmol/l), severe hyperkalemia (8.5 mmol/l), and elevated blood urea (20.3 mmol/l) and creatinine (317 μmol/l). Blood ethanol level was 0.2 g/l. Screening for possible intoxication, including cocaine, opiates, and amphetamines, was negative. Electrocardiogram (ECG) showed sinus rhythm with wide QRS complexes and diffuse nonspecific ST changes.

The patient was treated with continuous intravenous saline and insulin infusion. After 12 h, her blood glucose decreased to 17.5 mmol/l (pH 7.23, bicarbonate 12.0 mmol/l, potassium 5.12 mmol/l, and sodium 127.8 mmol/l).

Blood urea decreased to 14.6 mmol/l and creatinine to 154 μ mol/l. ECG was also normalized. After 36 h, the patient experienced transient stabbing chest pain, which was partially relieved by the change of body position. Complex ventricular arrhythmias, including short runs of ventricular tachycardia, were noticed. Repeat ECG revealed mild ST elevations in leads II, III, and aVF with negative T-waves in leads V2–V4. Echocardiography revealed somewhat depressed left ventricular systolic function (LVEF 45%) with hypokinesis of the posterior and inferior walls. Serum troponin I increased to 343 ng/ml (normal value \leq 0.4 ng/ml). On day 3 she was pain free but still had frequent premature ventricular beats. Troponin gradually decreased to 178 ng/ml. ECG showed ST segment normalization with flattening of T-waves in leads II, III, and aVF. Repeat echocardiography on day 5 showed reversal of posterior/inferior wall hypokinesis and normalization of left ventricular systolic function. The patient had an uneventful recovery. Coronary angiography on day 13 revealed normal coronary arteries with no evidence of coronary artery disease.

Different electrocardiographic patterns, including acute pseudoinfarction, have already been described in patients with ketoacidosis and hyperkalemia (1,2). None of these patients, however, had evidence of myocardial necrosis, as seen in our case. Despite very high levels of cardiac specific troponin I, echocardiography demonstrated rapid reversibility of wall motion abnormalities that corresponded to ECG changes. This is in contrast to previous observations showing no compromise but even increased myocardial contractility during diabetic ketoacidosis (3). The mechanism of myocardial necrosis in our patient is unclear. It might have been a late consequence of severe acid-base and electrolyte disturbances that might have triggered coronary spasms leading to ischemic myocardial necrosis. The coincidence of infectious myocarditis is less likely, but cannot be excluded.

In conclusion, severe diabetic ketoacidosis might be associated with myocardial necrosis of unknown mechanism leading to transient wall motion abnormalities and ventricular arrhythmias.

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A Novel Approach to Preventing Diabetic Ketoacidosis in a Patient Treated With an Insulin Pump

A 56-year-old man with brittle type 1 diabetes and unaware of the effects of hypoglycemia was started on a continuous subcutaneous insulin infusion (CSII) in April 2000. After 12 months, he achieved excellent glycemic control, and his HbA_{1c} values averaged 6.5%. During this time, however, the patient required admission to the hospital on four separate occasions for diabetic ketoacidosis despite frequent self-monitored blood glucose (SMBG) (six to eight times per day) and frequent catheter insertion site changes. The patient insisted that he administered subcutaneous injections, as directed, when there was any question of pump dysfunction. Medical teams noted that the patient developed diabetic ketoacidosis very rapidly on several occasions. During one admission, he reported an SMBG value of 99 mg/dl at 10:00 A.M. Within 95 min, the patient was brought to the emergency room with a glucose level of 510 mg/dl

and an anion gap of 35 mmol/l. Because of the frequent episodes of diabetic ketoacidosis, the patient's insulin therapy was switched from CSII to multiple daily insulin injections. However, the patient preferred CSII therapy for the quality-of-life benefits provided by the insulin pump, particularly the greater flexibility in meal planning, fewer subcutaneous injections, and less frequent hypoglycemic episodes. To accommodate the patient's wishes and prevent diabetic ketoacidosis, we devised the following treatment strategy. Sixty percent of basal insulin was provided by a daily injection of glargine insulin, and his bolus requirements were provided by the insulin pump. The basal rate of the pump was programmed for 0.2 units/h to prevent the insulin from crystallizing within the catheter. After 18 months, the patient has experienced no further episodes of diabetic ketoacidosis and has maintained acceptable glycemic control with HbA_{1c} values averaging 7.1%.

With CSII treatment, our patient had frequent occurrences of diabetic ketoacidosis, which is a morbid and potentially lethal consequence of the failure to deliver adequate amounts of insulin. When basal insulin infusion rates are interrupted in patients treated with CSII, the subcutaneous reserves of short-acting insulin are insufficient to prevent the metabolic processes that lead to hyperglycemia and ketogenesis (1). Glargine insulin is an alternative to CSII therapy for mimicking physiological basal insulin secretion. Glargine insulin kinetics demonstrate relatively consistent insulin levels for \geq 24 h after a single subcutaneous injection (2,3). In our patient, glargine insulin limited the ketosis and the associated complications that occurred with temporary infusion interruptions with the CSII. By combining daily glargine insulin injections with short-acting insulin boluses from an insulin pump, our patient had no episodes of diabetic ketoacidosis and maintained the lifestyle benefits provided by the insulin pump.

We must note that ketoacidosis rates have diminished in patients treated with CSII. Currently, the rates of diabetic ketoacidosis are similar in patients treated with CSII or multiple daily injections (4). However, our strategy may benefit some patients who have recurrent diabetic ketoacidosis on insulin pump therapy.

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Successful Treatment of Insulin Allergy in a Type 1 Diabetic Patient by Means of Constant Subcutaneous Pump Infusion of Insulin

A 21-year-old white woman (BMI 21.2 kg/m²) was admitted for management of uncontrolled diabetes with cutaneous allergies to insulin. Past medical history was marked by several al-

lergies, including coconuts and penicillin with laryngeal edema.

Type 1 diabetes was diagnosed 4 years previously and treated by three daily injections of semisynthetic human insulin (48 units/day). Four months later, the patient developed a local allergic reaction, a nettle rash without systemic manifestation that involved all injection sites. This reaction began <5 min after each injection despite H1 antihistamine treatment and subsided after 3–4 h, suggesting a type 1 IgE-mediated hypersensitivity reaction. She had a significant eosinophilia at 800.10⁶/l (normal 0–500). Prick skin testing was negative but intradermal tests with animal or human insulin, NPH or regular, and protamine were both positive without dilution. Unfortunately, rapid-acting analogs of insulin were not tested, but the patient developed a cutaneous reaction after a premeal injection of lispro (Eli Lilly), which is a recombinant analog of insulin that may be less antigenic because it does not aggregate to form polymers (1,2). Poor compliance resulted in intermittent insulin administration and poor metabolic control. HbA_{1c} was 13.5% (normal <6%) at entry.

Gradual desensitization with low doses of insulin was not appropriate because of the subject's strict insulin requirements. Based on the few literature reports available (3–5), we initiated a treatment with continuous subcutaneous insulin using lispro insulin at a basal rate of 1.6 units/h. We chose to use an external insulin pump infusion as a low-dose provider for both desensitization and treatment of diabetes. Boluses were replaced with temporarily increased basal rates (2 units/h) over 3 h starting 1 h before meals, which were based on low-glycemic index foods (6), to avoid potential allergy reactivation by the necessarily large premeal doses of insulin. The Quickset infusion set (MiniMed) was used because there was no need for additional adhesive. The usual antihistamine oral treatment (cetirizine) was maintained.

Since the beginning of constant lispro infusion, we have not observed any local reaction at the insertion site of the catheter or elsewhere. The patient's glycemic profile improved significantly. HbA_{1c}, which was initially at 13.5%, was reduced to 8.2% after 3 months and remained between 7.5 and 8% during follow-up. The average capillary blood glucose values over the last month were 5.66 ± 1.65

mmol/l premeal and 8.25 ± 1.10 mmol/l 2-h postmeal. She reported less than two minor hypoglycemic episodes every week, and two severe episodes occurred because of physical activity. A hyperglycemic episode without ketosis that followed transient corticosteroid therapy to treat an allergic reaction to a wasp sting was successfully treated with temporarily increased basal rates (3.5 units/h) of insulin.

Although our patient developed an allergy to the insulin molecule itself, she was successfully treated using continuous subcutaneous infusion of lispro insulin with only an external insulin pump. One year later, although intradermal tests remained positive, particularly with rapid-acting insulin analogs, we could stop antihistamine treatment and introduce premeal boluses (<8 units) without reactivating cutaneous allergies.

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Glycyrrhizin and Serum Testosterone Concentrations in Male Patients With Type 2 Diabetes

Extracts of licorice root are widely used in many countries as flavoring agents, breath fresheners, and candy. Licorice consumption had been reported to decrease serum testosterone concentrations (1). An explanation for this result was that glycyrrhizic acid, the active component of licorice, interfered with 17 β -hydroxysteroid dehydrogenase, which catalyzes the conversion of androstenedione to testosterone. We were very interested in the effects of glycyrrhizic acid to decrease serum testosterone concentrations. Glycyrrhizin, which is extracted from the roots of the plant *Glycyrrhiza glabra* (licorice), is widely used for the treatment of chronic hepatitis in Japan and reportedly reduces the progression of liver disease to hepatocellular carcinoma. The efficacy of glycyrrhizin treatment is currently under investigation in Europe (2). There are few data available on the effects of glycyrrhizin on serum testosterone concentrations (3). We have recently reported that reduced serum testosterone concentrations could cause insulin resistance (4) and atherosclerosis (5) in male patients with type 2 diabetes. Therefore, we attempted to determine the effects of glycyrrhizin on serum testosterone concentrations in male patients with type 2 diabetes and chronic hepatitis.

This study included 18 male patients with type 2 diabetes and chronic hepatitis who were given weekly glycyrrhizin, which contained 240–525 mg glycyrrhizic acid, for >1 year and 21 male patients not given glycyrrhizin. We measured serum concentrations of total and free testosterone (normal range 2.7–10.7 ng/ml and 14–40 pg/ml, respectively) and performed carotid ultrasonography (5), which is used increasingly in clinical re-

search concerning pathophysiology of atherosclerosis, in those patients.

Clinical characteristics of patients treated with ($n = 18$) and without ($n = 21$) glycyrrhizin are as follows: mean age (66.9 ± 7.1 vs. 66.8 ± 6.7 years), duration of diabetes (13.7 ± 7.3 vs. 12.6 ± 10.3 years), BMI (23.0 ± 2.3 vs. 22.7 ± 1.8 kg/m²), levels of HbA_{1c} (7.4 ± 1.5 vs. $7.0 \pm 0.9\%$), presence of hypertension (77.8 vs. 66.7%), presence of hyperlipidemia (33.4 vs. 38.1%), and history of cigarette smoking (61.1 vs. 57.1%) were not significantly different between groups. Serum concentrations of total and free testosterone were significantly lower in patients given glycyrrhizin than those in patients not given glycyrrhizin (4.3 ± 2.2 vs. 5.9 ± 1.7 ng/ml, $P = 0.0113$; 6.7 ± 3.8 vs. 11.1 ± 3.8 pg/ml, $P = 0.0009$, respectively). Mean intima-media thickness and plaque score by carotid ultrasonography were significantly greater in patients given glycyrrhizin than in patients not given glycyrrhizin (1.12 ± 0.29 vs. 0.89 ± 0.23 mm, $P = 0.0385$; 6.8 ± 3.1 vs. 3.7 ± 3.3 , $P = 0.0326$, respectively). Glycyrrhizin treatment was an independent risk factor ($\beta = 0.464$, $P = 0.0433$) for atherosclerosis (plaque score) after adjustment for age, hypertension, hyperlipidemia, smoking history, and glycemic control (HbA_{1c}).

Despite a major limitation of small sample size, this study suggests that glycyrrhizin decreased serum testosterone concentrations in male patients with type 2 diabetes and chronic hepatitis. Reduced serum testosterone concentrations may cause insulin resistance and atherosclerosis, as well as sexual dysfunction and decreased libido in men. Special attention should be directed at serum testosterone concentrations in male patients with type 2 diabetes and chronic hepatitis treated with glycyrrhizin.

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ACE Insertion/Deletion Genotypes and Angiotensin II Receptor Blockade in Diabetic Nephropathy

Is there a light at the end of the tunnel?

Pharmacogenetics is the study of genetic influence on response to drugs. This is an area of increasing attention due to the possibilities of improving overall treatment effects in patients through individual strategies. Mogensen (1) addresses this subject and diabetic renal disease in relation to our study. In the study in question (2), we masked and prospectively investigated the renoprotective effects of angiotensin II receptor blockade (ARB) in hypertensive type 1 diabetic patients with diabetic nephropathy homozygous for the insertion (I) or deletion (D) allele of the ACE/ID polymorphism during 36 months of fol-

low-up (2,3). We demonstrated that ARB by losartan confers similar beneficial renoprotective effects in patients with II and DD genotypes (2,3). Mogensen points out a contradiction between our present study (2) and our previous observational follow-up study of the influence of the ACE/ID polymorphism on the long-term efficacy of ACE inhibition in type 1 diabetic patients with diabetic nephropathy (4). The previous observational follow-up study demonstrated that DD patients have an accelerated rate of decline of the glomerular filtration rate during 7 years of ACE inhibition compared with patients with the I allele (4). We want to point out that the studies were carried out using two distinctly different types of drugs for blockade of the renin-angiotensin-aldosterone system, thus the results should not be expected to be identical. The present study using ARB was designed in an attempt to overcome the impeding interaction between ACE/ID genotypes and ACE inhibition by blocking the renin-angiotensin-aldosterone system at the receptor site (2,3). Therefore, demonstration of equal renoprotection in patients with DD or II ACE genotypes during ARB treatment is indeed distinct from our first study of ACE inhibition (4) and provides new and important information by identifying homozygous DD patients as a group that may receive specific benefits from ARB treatment. In addition, our present study is the first prospective pharmacogenetic study in diabetic nephropathy (2). The results indicate that there is a new light ahead in the treatment of diabetic nephropathy, but further pharmacogenetic studies should be carried out to identify patients who will benefit from treatment with particular drugs.

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S.A. has received research support from Merck. H.-H.P. holds stock in Novo Nordisk, has received honoraria from Merck and Sanofi-synthelabo, and has received grants from Merck, Astra, and Sanofi-synthelabo.

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Early Diagnosis of Primary Biliary Cirrhosis in Type 1 Diabetes

The possible role of eosinophilia

Type 1 diabetes is often associated with other autoimmune diseases (1), including primary biliary cirrhosis (2). Furthermore, type 1 diabetes and primary biliary cirrhosis may share similar pathogenetic pathways (3). In type 1 diabetic patients, the identification of markers for associated autoimmune diseases may permit earlier diagnosis and more effective treatment.

A 46-year-old man with type 1 diabetes (age of onset 26 years) was admitted into our hospital due to poor glycemic control (HbA_{1c} 11.3%) with severe daily hypoglycemia and significant hyperglycemic spikes. At admission, routine blood tests showed mild eosinophilia (6.7%, 482.4/mmc versus normal 1–4%, 72–282/mmc) and markedly elevated values for γ -glutamyl transpeptidase (γ GT) (203 units/l versus normal, 8–61) and alkaline phosphatase (571 units/l versus normal, 91–258). Aspartate, alanine aminotransferase, and bilirubin values were normal. Alkaline phosphatase gradually increased during hospitalization (from 571 to 683

units/l), whereas γ GT did not change significantly. Mild eosinophilia (5.9%, 403.9/mmc) occurred ~18 months before hospitalization, but all common causes of eosinophilia were excluded. Twelve months before hospitalization, γ GT and alkaline phosphatase values were normal. The patient did not show any history of jaundice, pruritus, or dyspepsia. During hospitalization, any causes of hepatobiliary disease, including viral infections, were accurately excluded. Moreover, common causes of eosinophilia were also excluded. Screening for autoimmunity showed normal values for the common panel of autoantibodies (antinuclear, anti-thyroid peroxidase, anti-thyroglobulin, and anti-cardiolipin) except for anti-mitochondrial antibodies (titer 1:40).

Abdominal ultrasonography did not reveal any abnormal findings. Extrahepatic biliary tracts were not dilated. Ultrasound-guided liver biopsy was then performed. Histological findings showed flogistic infiltration of the portal tract and hepatic lobules. Moreover, there was portal tract fibrosis with focal infiltration of lobules, including a picture of intrahepatic biliary duct disease. This picture was consistent with stage 2 primary biliary cirrhosis according to Scheuer classification (4). Ursodesoxicholic acid treatment was begun, and since then cholestasis values have decreased and glycemic control has improved.

The present case shows an association between type 1 diabetes and asymptomatic primary biliary cirrhosis. One year before hospitalization, the patient did not show abnormal markers for cholestasis, but 18 months beforehand, he did show mild eosinophilia. In the last decade, evidence for an association between mild eosinophilia and primary biliary cirrhosis has constantly increased. Moreover, according to most recent studies, mild eosinophilia seems to be an indicator of early disease stages and is considered a strong predictor of good response to ursodesoxicholic acid treatment and of better prognostic outcomes (5).

To the best of our knowledge, this is the first case of mild eosinophilia associated with primary biliary cirrhosis in type 1 diabetic patients. This case suggests that in type 1 diabetic patients, isolated mild eosinophilia should be carefully regarded when common causes of eosinophilia have been excluded. Indeed, when con-

sidering the possible association between type 1 diabetes and primary biliary cirrhosis (1–3) in type 1 diabetic patients with unexplained eosinophilia, γ GT, alkaline phosphatase, and anti-mitochondrial antibodies should be evaluated to discern which subjects are at risk for primary biliary cirrhosis. In patients with positive anti-mitochondrial antibodies but normal γ GT and alkaline phosphatase values, the latter should be strictly monitored. Patients with anti-mitochondrial antibodies and elevated γ GT and alkaline phosphatase values should undergo a liver biopsy. In this way, mild eosinophilia may be considered a marker of asymptomatic primary biliary cirrhosis at earlier stages, when biochemical and clinical responses to ursodesoxicholic acid treatment can lead to better results. In addition, an early and effective treatment of primary biliary cirrhosis may permit better diabetes control.

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Plasma Levels of Adiponectin Are Associated With Insulin Resistance and Serum Levels of Triglyceride in Japanese Metabolically Obese, Normal-Weight Men With Normal Glucose Tolerance

Adiponectin is expressed in and secreted from visceral fat, and its plasma level has been reported to correlate with insulin resistance and triglyceride metabolism in nondiabetic subjects (1,2). However, these relationships have not been evaluated in Japanese metabolically obese normal-weight (BMI <25 kg/m² and visceral fat areas [evaluated by abdominal CT scanning] \geq 100 cm²) men with normal glucose tolerance (NGT) (3–5).

The present study comprised 16 metabolically obese normal-weight men (aged 35.6 ± 1.8 [mean \pm SE] years, BMI 23.8 ± 0.3 kg/m², visceral fat areas 130.8 ± 5.2 cm²) and 15 age-matched normal men (BMI <25 and visceral fat areas <100 cm²) (aged 33.6 ± 1.8 years, BMI 20.9 ± 0.3 kg/m², visceral fat areas 56.5 ± 5.1 cm²) with NGT.

The plasma levels of adiponectin were measured using a radioimmunoassay kit (Linco Research, St. Charles, MO).

Comparisons between metabolically obese normal-weight and normal subjects were done using the Mann-Whitney *U* test, and correlations were evaluated by Spearman's rank correlation.

There were no significant differences in plasma levels of adiponectin between metabolically obese normal-weight (10.2 ± 1.3 ng/ml) and normal subjects (12.0 ± 0.8 ng/ml). The BMI ($P < 0.01$)

and serum levels of triglyceride (1.67 ± 0.14 vs. 0.92 ± 0.09 mmol/l, $P < 0.01$) were significantly increased in metabolically obese normal-weight subjects compared with normal subjects. The glucose infusion rate (index of insulin resistance during the euglycemic-hyperinsulinemic clamp study) in metabolically obese normal-weight subjects (53.9 ± 3.4 μ mol \cdot kg⁻¹ \cdot min⁻¹; $P < 0.01$) were significantly decreased compared with normal subjects (65.8 ± 2.7 μ mol \cdot kg⁻¹ \cdot min⁻¹) (4,6).

The plasma levels of adiponectin were significantly correlated with glucose infusion rate ($r = 0.509$, $P < 0.05$), serum levels of triglyceride ($r = -0.730$, $P < 0.01$), and the visceral fat areas ($r = -0.597$, $P < 0.05$) in metabolically obese normal-weight subjects.

There were not significant correlations between plasma levels of adiponectin and glucose infusion rate ($r = 0.146$, $P = 0.584$), serum levels of triglyceride ($r = -0.446$, $P = 0.095$), or visceral fat areas ($r = -0.214$, $P = 0.423$) in normal subjects.

Visceral fat is an important determinant factor of the plasma level of adiponectin, which is known to exert an insulin-sensitizing effect (2,7). Unexpectedly, similar plasma levels of adiponectin and different glucose infusion rates were observed in metabolically obese normal-weight and normal subjects. The small number of patients may be the explanation for this unexpected result. Further study should be carried out in a larger population of Japanese metabolically obese normal-weight subjects.

Significant correlation between plasma levels of adiponectin and glucose infusion rate was observed in metabolically obese normal-weight subjects. Plasma adiponectin levels may play an important role in the development of insulin resistance in Japanese metabolically obese normal-weight subjects.

The plasma levels of adiponectin were significantly correlated with the serum levels of triglyceride in metabolically obese normal-weight subjects. Cnop et al. (2) demonstrated that association of adiponectin with increased visceral fat may shift the fate of apolipoprotein B away from degradation toward secretion from the liver, resulting in elevated triglyceride concentrations. This phenomenon might have occurred in our Japanese metaboli-

cally obese normal-weight subjects with NGT.

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Apolipoprotein B Is an Independent Risk Factor for Microalbuminuria in Taiwanese Patients With Type 2 Diabetes

Microalbuminuria, a predictor for overt nephropathy and early cardiovascular mortality, is always associated with hypertension, hyperglycemia, and dyslipidemia (1). In the study of Tai et al. (2), performed in Taiwanese type 2 diabetic patients, albumin excretion rate was significantly associated with hypertension but not with glycemic control. To further examine the association between lipid profile and microalbuminuria in Taiwanese type 2 diabetic subjects, a total of 260 nonsmoking patients (117 men, 143 women; mean age \pm SD, 60.7 \pm 11.0 years) with normal renal function and not using antihypertensive or lipid-lowering agents were cross-sectionally recruited. Normoalbuminuria ($n = 152$) and microalbuminuria ($n = 108$) were defined as urinary albumin-to-creatinine ratios (ACRs) <30 and $30\text{--}299 \mu\text{g}/\text{mg}$, respectively. Lipid parameters included serum total cholesterol, triglycerides, HDL and LDL cholesterol, apolipoprotein A1, and apolipoprotein B (ApoB). Potential confounders (age, sex, BMI, duration of diabetes, insulin therapy, systolic and diastolic blood pressure, and HbA_{1c}) were adjusted for in multivariate analyses. Mann-Whitney *U* test, Spearman correlation coefficients, and logistic regression were used.

The results showed that among the lipid profile, only total cholesterol and ApoB were significantly ($P < 0.05$) different between patients with microalbuminuria and those with normoalbuminuria (208.5 \pm 40.9 vs. 197.5 \pm 38.6 mg/dl for total cholesterol and 123.1 \pm 37.9 vs. 106.4 \pm 29.0 mg/dl for ApoB). For cor-

relation coefficients, only ApoB was significantly correlated with ACR ($\gamma = 0.166$); total cholesterol showed borderline significance ($\gamma = 0.113$, $0.05 < P < 0.1$). Multivariate-adjusted odds ratios (ORs) (95% CI) for microalbuminuria were significant only for ApoB (1.016 [1.007–1.024]) and total cholesterol (1.007 [1.000–1.014]), but total cholesterol was nonsignificant with additional adjustment for ApoB. While the lipid parameters were treated as binary variables with cut points at medians and using the lower halves as reference groups, only ApoB (cut point: 108 mg/dl) showed significant multivariate-adjusted OR for microalbuminuria (2.209 [1.303–3.746]).

Atherogenic lipoproteins can infiltrate into the glomerular endothelium and mesangial cells, initiating a cascade of events similar to atherosclerosis (3). Samuelsson et al. (4) reported that ApoB was associated with a declining glomerular filtration rate in patients with chronic renal disease and that renal dyslipidemia was predominantly associated with the accumulation of ApoB-containing lipoproteins in both sclerotic and nonsclerotic glomeruli (5). The observation of the present study in Taiwanese type 2 diabetic patients suggests that ApoB-containing lipoproteins could also initiate early glomerular injury leading to incipient diabetic nephropathy with microalbuminuria.

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Carotid Intima-Media Thickness in Patients With Type 2 Diabetes

The significance of microalbuminuria and different risk factors for atherosclerosis

Microalbuminuria is a well-established risk factor for atherosclerosis in patients with type 2 diabetes (1,2). In this cross-sectional study, we examined the effect of microalbuminuria on the intima-media thickness (IMT) of the carotid arteries, an index of early atherosclerosis (3), in patients with type 2 diabetes.

We studied a total of 120 subjects with type 2 diabetes (60 men and 60 women, aged 61.4 ± 6.8 years, duration of diabetes 10.4 ± 7.7 years, and HbA_{1c} $7.9 \pm 1.7\%$ [mean \pm SD]) randomly selected from the outpatient diabetes clinic. Microalbuminuria was diagnosed when albumin excretion (measured by radioimmunoassay) was >20 and <200 $\mu\text{g/ml}$ in two of three overnight, timed urine collections. Subjects were divided into two groups based on the presence of microalbuminuria.

All carotid B-mode real-time ultrasound measurements were performed by the same experienced physician, who was blinded to the patient's urine albumin status. Measurements of the IMT were performed in both the right and left common carotid arteries (CCAs) and internal carotid arteries (ICAs), as previously described (4).

Forty-six (38.3%) subjects had mi-

croalbuminuria. There were no significant differences between the study groups in terms of sex, age, blood pressure, BMI, waist-to-hip ratio, duration of diabetes, HbA_{1c} , type of antidiabetic treatment, smoking habit, fasting plasma glucose, insulin, triglycerides or HDL cholesterol, and the use of statins and ACE inhibitors. Plasma total and LDL cholesterol levels were higher in the microalbuminuric group ($P < 0.02$). The IMT/CCA values were higher in the microalbuminuric group compared with the normoalbuminuric group (0.99 ± 0.14 vs. 0.89 ± 0.15 mm, respectively; $P = 0.001$), but this was not the case concerning the IMT/ICA values (0.94 ± 0.14 vs. 0.93 ± 0.16 mm, respectively; $P = 0.69$).

Multivariate analysis, after adjustment for a number of confounding factors, such as age, sex, blood pressure, BMI, waist-to-hip ratio, duration of diabetes, HbA_{1c} , type of antidiabetic treatment, smoking status, plasma lipids, and the use of ACE inhibitors and statins, demonstrated that only the presence and degree of microalbuminuria were independently associated with IMT/CCA ($B = 0.01$, $SE[B] = 0.003$, $P < 0.0001$ and $B = 0.0001$, $SE[B] = 0.00001$, $P = 0.02$, respectively). In addition, it is noteworthy that microalbuminuric patients treated with ACE inhibitors tended to have lower IMT/CCA values than patients not treated with this class of medication ($P = 0.06$), whereas no such difference was found with the use of statins. The lack of association between microalbuminuria and the IMT/ICA value is explained by the fact that ICAs at the bifurcation are more sensitive to local atherosclerosis and do not necessarily reflect the status of the arterial tree. In nondiabetic subjects, the IMT/CCA shows a graded association with various cardiovascular risk factors and thus can be used as an indicator for the presence of atherosclerosis in other arteries (3).

It is concluded that microalbuminuric subjects with type 2 diabetes have higher IMT/CCA values than normoalbuminuric subjects and that the presence as well as the degree of microalbuminuria are independent predictors of IMT/CCA.

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COMMENTS AND RESPONSES

Association Between Elevated Testosterone and Development of Microalbuminuria During Puberty in Female Subjects With Type 1 Diabetes

Response to Amin et al.

We read with great interest the recent article by Amin et al. (1), reporting that differences in IGF-1 and androgen concentrations and disruption of glycemic control accom-

many years before the time of admission as some of the “background diseases” are consequent upon having problems with glucose regulation?

Table 2 clearly shows that patients were most insulin sensitive on admission and following discharge, least sensitive with corresponding changes in β -cell function, and that fasting plasma glucose levels did not vary throughout the study, which would indicate that treatment with typical antipsychotic medication may have contributed to their findings. However, if on admission, patients were divided into “low and high” categories according to their CGI scores, significant differences began to emerge. The “low and high” scores were either ≤ 6 or > 6 (the maximum being 7), respectively. Therefore, the authors compared the most extremely ill with all of the other patients. The cutoff figures were picked arbitrarily with no scientific reasons given for doing so. Furthermore, we were not told how many patients fit into each category. From a statistical perspective, the correlation coefficient for CGI and insulin was $r = 0.37$ and for CGI and fasting blood glucose was 0.47; the respective r^2 values are 0.22 and 0.14, implying that 71% of the variance cannot be explained by these findings. Namely, that “acute psychotic stress” was not primarily responsible for their results. Indeed, we are told later in the RESULTS section that there was a negative correlation between insulin sensitivity and “psychotic stress” on admission, but we are not given any r value or indeed any indication of the numbers of patients in each group, making it impossible to judge what real significance these findings have.

The authors state in the CONCLUSIONS that prestudy medications cannot explain their findings because atypical antipsychotics were not used. However, typical antipsychotics have been implicated in the abnormal glucose regulation seen in schizophrenia, as the authors themselves state. In addition, we are not told how long patients were free of their medications before admission, as certain intramuscular preparations can have effects for many months after their last administration. Finally, the importance of chronic stress as a potential pathogenetic mechanism in the development of type 2 diabetes in schizophrenia is evident; however, the results presented by Shiloah et al. (1)

do not provide any evidence for acute stress causing such glucose dysregulation.

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The Effect of Weight Loss on Endothelial Functions in Obesity

Response to Sciacqua et al.

We read with interest the article by Sciacqua et al. (1) showing improvement of endothelial function in healthy obese subjects (no sex specified) after short-term (12–16 weeks) weight loss. By adopting a low-calorie diet associated with exercise, only two-thirds of the subjects enrolled in the study were able to achieve a reduction of at least 10% of initial weight (due to a high drop-out rate). In these subjects, maximal vasodilator response to the highest dose of acetylcholine increased from 211 to 358% of baseline, indicating improved endothelium-dependent vasodilation. The choice of obese subjects without known additional risk factors was the right one to make, thus avoiding the many possible confounders affecting endothelial function.

However, we disagree with the conclusions of the authors that “this is the first study to prospectively evaluate the effects of weight loss and physical activity on endothelium-dependent vasodilation of obese normotensive subjects,” as our study of a multidisciplinary program, including low-calorie Mediterranean-type diet, exercise, and behavioral and nutri-

tional counseling in obese women, was published earlier (2). In that study, we performed the first long-term prospective evaluation of the effect of weight loss on endothelial functions and circulating markers of vascular inflammation in 56 obese but otherwise healthy women (2). After 12 months, the women lost at least 10% of their initial weight (-9.8 ± 1.5 kg [range 7.5–13]) and increased their physical activity from 46 ± 12 to 131 ± 29 min/week. All of this was associated with improved endothelial functions as assessed by the hemodynamic (blood pressure decrease) and rheologic (platelet aggregation response to ADP) responses to L-arginine (3 g i.v.), the natural precursor of nitric oxide (3). Moreover, the raised circulating concentrations of proinflammatory cytokines (interleukin-6 and tumor necrosis factor- α) and intracellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1, respectively) that the obese women had at baseline were significantly reduced after weight loss.

The pathogenesis of endothelial dysfunction in obesity remains uncertain; the relative roles of insulin resistance, circulating nonesterified fatty acids, or adipocyte-associated cytokines are being delineated. For example, both nonesterified fatty acids (4) and interleukin-6 or tumor necrosis factor- α (5) can induce vascular dysfunction and insulin resistance. In obese individuals, circulating nonesterified fatty acids and proinflammatory cytokines are increased, which may explain, at least in part, their increased cardiovascular risk. We have also shown that a long-term (2 years) multidisciplinary program aimed to reduce body weight through lifestyle changes in obese women was associated with reduction of insulin resistance and increased adiponectin concentrations (6). Because adiponectin possesses anti-inflammatory properties and improves glucose tolerance (7), hypo adiponectinemia may contribute to the low-grade inflammation and the insulin resistance that characterize human obesity. Thus, the increased cardiovascular risk of obese people may be seen as the result, at least in part, of increased inflammatory stimuli and decreased anti-inflammatory mechanisms.

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