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.

Steen Andersen, md[1]
Peter Jacobsen, md[1]
Hans-Henrik Parving, md, dmsc[1,2]

From the [1]Steno Diabetes Center, Gentofte, Denmark; and the [2]Faculty of Health Science, University of Aarhus, Aarhus, Denmark.

Address correspondence to Steen Andersen, Steno Diabetes Center, Niels Steensens Vej 2, DK-2820 Gentofte, Denmark. E-mail: stan@steno.dk.

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.

References

1. Mogensen CE: Genetics and diabetic renal disease: still a big black hole (Editorial). *Diabetes Care* 26:1631–1632, 2003
2. Andersen S, Tarnow L, Cambien F, Rossing P, Juhl TR, Deinum J, Parving HH: Long-term renoprotective effects of losartan in diabetic nephropathy: interaction with ACE insertion/deletion genotype? *Diabetes Care* 26:1501–1506, 2003
3. Andersen S, Tarnow L, Cambien F, Rossing P, Juhl TR, Deinum J, Parving HH: Renoprotective effects of losartan in diabetic nephropathy: interaction with ACE insertion/deletion genotype? *Kidney Int* 62:192–198, 2002
4. Parving HH, Jacobsen P, Tarnow L, Rossing P, Lecerf L, Poirier O, Cambien F: Effect of deletion polymorphism of angiotensin converting enzyme gene on progression of diabetic nephropathy during inhibition of angiotensin converting enzyme: observational follow up study. *BMJ* 313:591–594, 1996

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 (γGT) (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 γGT 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, γGT 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, antithyroglobulin, 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, γGT, 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 γGT and alkaline phosphatase values, the latter should be strictly monitored. Patients with anti-mitochondrial antibodies and elevated γGT 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.

Carmine Gazzaruso, md
Stefano Giordanetti, md
Pasquale De Cata, md
Guido Poggi, md
Pietro Fratino, md

From the Internal Medicine Unit, Metabolic Diseases Clinic, IRCCS Maugeri Foundation Hospital, Pavia, Italy.

Address correspondence to Carmine Gazzaruso, MD, IRCCS Maugeri Foundation Hospital, Internal Medicine Unit–Metabolic Diseases Clinic, Via Ferrata 8, 27100 Pavia, Italy. E-mail: cgazzaruso@fsm.it.

References

1. Hanukoglu A, Mizrachi A, Dalal I, Admoni O, Rakover Y, Bistritzer Z, Levine A, Somech E, Lehmann D, Tuval M, Boaz M, Golander A: Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives: a multicenter study. *Diabetes Care* 26:1235–1240, 2003
2. Prince MA, Vialettes B, Zevaco-Mattei C, Vague P: Clinical characteristics and etiological markers in insulin-dependent diabetes associated with an organ-specific autoimmune disease. *Acta Diabetol Lat* 20: 221–229, 1983
3. Mason AL, Xu L, Guo L, Munoz S, Jaspan JB, Bryer-Ash M, Cao Y, Sander DM, Shoenfeld Y, Ahmed A, Van de Water J, Gershwin ME, Garry RF: Detection of retroviral antibodies in primary biliary cirrhosis and other idiopathic biliary disorders. *Lancet* 351:1620–1624, 1998
4. Scheuer PJ: Ludwig Symposium on biliary disorders, part II: pathologic features and evolution of primary biliary cirrhosis and primary sclerosing cholangitis. *Mayo Clin Proc* 73:179–183, 1998
5. Yamazaki K, Nakadate I, Suzuki K, Sato S, Masuda T: Eosinophilia in primary biliary cirrhosis. *Am J Gastroenterol* 91:516–522, 1996

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/m^2 and visceral fat areas [evaluated by abdominal CT scanning] ≥ 100 cm^2) men with normal glucose tolerance (NGT) (3–5).

The present study comprised 16 metabolically obese normal-weight men (aged 35.6 ± 1.8 [mean ± SE] years, BMI 23.8 ± 0.3 kg/m^2, visceral fat areas 130.8 ± 5.2 cm^2) and 15 age-matched normal men (BMI <25 and visceral fat areas <100 cm^2) (aged 33.6 ± 1.8 years, BMI 20.9 ± 0.3 kg/m^2, visceral fat areas 56.5 ± 5.1 cm^2) 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 μmol · kg^{-1} · min^{-1}; $P < 0.01$) were significantly decreased compared with normal subjects (65.8 ± 2.7 μmol · kg^{-1} · 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-