

OBSERVATIONS

Metabolic Control and Adherence to American Diabetes Association Practice Guidelines in a Pharmacist-Managed Diabetes Clinic

The provision of diabetes care has shifted from the specialist to the generalist in primary care practice. Evidence suggests utilization of nonphysician providers in conjunction with physician-directed protocols improves glycemic control (1). The purpose of this study was to evaluate the impact of a pharmacist-managed diabetes clinic (PMC) on glycemic control and adherence to American Diabetes Association (ADA) standards of medical care in a collaborative physician-pharmacist practice. This was a retrospective analysis comparing patients referred to the PMC for diabetes management with a randomly selected group of patients with diabetes, managed exclusively by their primary care physicians. Only patients with a minimum of 3 months of laboratory data and two visits to the pharmacist or physicians were included.

Pharmacist-managed clinic patients (16 women, 12 men) were 51.8 ± 14.7 years of age and had a BMI of 35.4 ± 9.2 kg/m² (mean \pm SD). The physician-managed group (16 women, 13 men) were 56.4 ± 13.8 years of age and had a BMI of 33.5 ± 9.2 kg/m². Over 90% of patients in each group were African-American and had type 2 diabetes. Average duration of diabetes was not significantly different between groups.

Baseline HbA_{1c} values were significantly higher in PMC patients compared with the physician-managed group (10.3 ± 2.1 vs. $8.2 \pm 2.8\%$, respectively; $P = 0.008$). The PMC patients had significant improvements in glycemic control; HbA_{1c} levels decreased from 10.3 ± 2.1 to $7.9 \pm 1.8\%$ ($P < 0.0001$) and RPG concentrations from 12.94 ± 5.80 to 8.09 ± 3.10 mmol/l ($P = 0.002$). Patients in the physician-managed group had

nonsignificant reductions in HbA_{1c} levels (8.2 ± 2.8 to $6.8 \pm 1.8\%$, $P = 0.065$) and RPG concentrations (11.88 ± 4.40 to 10.44 ± 4.73 mmol/l; $P = 0.49$). More PMC patients were placed on aggressive combination antihyperglycemic medications compared with the physician-managed group (61 vs. 21%; $P = 0.003$). Blood pressure, body weight, and lipid parameters did not change significantly within or between groups.

Adherence to ADA guidelines was significantly greater in PMC patients compared with patients managed by their physicians. HbA_{1c} measurements were obtained in 85.7 and 62.1% ($P = 0.04$), albumin-to-creatinine determinations in 89.3 and 35.7% ($P = 0.0001$), FLP assessment in 92.9 and 65.5% ($P = 0.021$), and foot examination 82.1 and 6.9% ($P = 0.0001$) of patients in PMC compared with physician-managed group, respectively. Referrals for dietary instruction, podiatry care, and evaluation of diabetic retinopathy were made significantly more often in PMC compared with physician-managed patients, (57.1 vs. 10.3%, $P = 0.02$; 85.7 vs. 34.4%, $P = 0.0001$; and 85.7 vs. 55.2%, $P = 0.02$, respectively). Rates for aspirin use and annual influenza vaccinations were similar between groups.

In agreement with previous studies, pharmacist-managed diabetes programs have been shown to improve glycemic control (2,3). This is the first study to evaluate guideline adherence in a PMC. Compliance with these guidelines in primary care practices is reportedly suboptimal (4). Adherence rates in this study are superior to those reported in primary care practices and similar to those described in multidisciplinary programs (1,4). Adherence to guidelines and provision of quality healthcare require continuous long-term education and monitoring of patients. An environment in which a physician-extender is continuously working with a physician on site can provide this type of care. Further studies should examine the cost-effectiveness of collaborative physician-pharmacist practice models.

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References

1. Aubert RE, Herman WH, Waters J, Moore W, Sutton D, Peterson BL, Bailey CM, Koplan JP: Nurse case management to improve glycemic control in diabetic patients in a Health Maintenance Organization. *Ann Intern Med* 129:605–612, 1998
2. Jaber LA, Halapy H, Fernet M, Tummala-palli S, Diwakaran H: Evaluation of a pharmaceutical care model on diabetes management. *Ann Pharmacother* 30:238–243, 1996
3. Coast-Senior EA, Kroner BA, Kelley CL, Trilli LE: Management of patients with type 2 diabetes mellitus by pharmacists in primary care clinics. *Ann Pharmacother* 32:636–641, 1998
4. Ho M, Marger M, Beart J, Yip I, Shekelle P: Is the quality of diabetes care better in a diabetes clinic or in a general medicine clinic? *Diabetes Care* 20:472–475, 1997

Twenty-Four Hour Action of Insulin Glargine (Lantus) May Be too Short for Once-Daily Dosing: A case report

The insulin analog insulin glargine has a pharmacodynamic profile described as peakless and of longer duration than human NPH insulin (1). This allows for convenient once-daily dosing for coverage of basal insulin needs. We recently had the opportunity to examine whether this is the case in the following patient.

T.L. is a 53-year-old man with a history of type 1 diabetes for the past 16 years. Before hospitalization, he had a history of widely variable blood glucose levels, from 50 to 400 mg/dl, while using a 4-injection regimen of premeal insulin lispro and ultralente at dinner. He has no

known diabetic complications. Before admission, he had a history of heavy ethanol abuse, with a daily intake of 48–72 oz wine or beer per day. On the day of admission, the patient developed left arm weakness and progressive loss of consciousness. A computed tomography scan revealed a massive intracerebral bleed. Admission laboratory data revealed glucose of 292 mg/dl, a bicarbonate of 15 mEq/l, an anion gap of 18, trace urine ketones, and a blood pH of 7.34. After treatment of compensated diabetic ketoacidosis, the patient was maintained on an intravenous insulin infusion between 1 and 2 units/h. On the fifth hospital day, enteral feedings via a feeding tube were initiated. The enteral formula provided 2 kcal/ml, with a composition consisting of 43% carbohydrate, 17% protein, and 40% fat. The feeding rate was successfully increased and maintained at 35 ml (70 calories) per hour without residual stomach accumulation. Total nutrition intake was 1,680 kcal/day. On the sixth hospital day, the patient was given a 30-unit dose of insulin glargine at 9:00 P.M. and was weaned off of the insulin infusion over the next 4 h. For the next 11 days, the patient continued to receive continuous enteral feeding. He remained on respiratory support and received no other calories by either oral or parenteral route. From day 6 to day 12, he received insulin glargine as a single dose, given at 9:00 P.M. In addition to basal insulin coverage, as described above, glucose excursions >200 mg/dl were treated with supplemental subcutaneous lispro insulin. Marked hyperglycemia was noted at 10:00 P.M. after this single-dose regimen and required supplemental lispro insulin coverage on 4 of the 6 days. For purposes of comparison, days 7–12 are defined as period 1. For days 13–18, or period 2, the glargine dose was converted to a split dose given at 9:00 A.M. and 9:00 P.M. On day 13, the patient's enteral tube feeding was electively discontinued from 11:00 A.M. to 2:00 P.M. for a procedure. At 2:00 P.M., hypoglycemia occurred (blood glucose 41 mg/dl). Two subsequent glargine doses were held and then restarted at 10 units every 12 h. The mean glucose levels were not significantly different between the two treatment periods during time points 2:00 A.M., 6:00 A.M., 10:00 A.M., 2:00 P.M., and 6:00 P.M. However, the mean glucose level was significantly higher at 10:00 P.M. during period 1 than at 10:00 P.M. during period 2

(mean glucose 226 ± 37 vs. 132 ± 27 mg/dl, respectively, $P < 0.005$ by two-tailed t test). This data point represents 1-h postdosing, or 25 h after receiving the previous dose.

The data suggest that, in this patient, insulin glargine has a 24-h action profile. However, the slow onset of action for the subsequent nighttime dose may have produced a window of relative insulinopenia, resulting in higher blood glucose levels at night. This problem was corrected by giving glargine as a split dose every 12 h. We suggest that for patients receiving a constant inflow of carbohydrates, once-daily dosing of insulin glargine may not provide effective 24-h coverage. In addition, the present case underscores the need to provide intravenous dextrose to glargine-treated patients receiving continuous enteral feeding in the event that the enteral feeding is discontinued. We suggest that more studies are needed to determine whether once-daily dosing of insulin glargine provides effective basal insulin coverage for all insulinopenic patients in various clinical settings or whether a subset of patients may require twice-daily dosing.

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The authors thank John Pezzullo, PhD, for his advice on statistical analysis.

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References

1. Lantus (insulin glargine) [package insert]. Bridgewater, NJ, Aventis, 2001

C-Reactive Protein and Insulin Resistance in Subjects With Thalassemia Minor and a Family History of Diabetes

Insulin resistance is common in hemoglobinopathy including thalassemias. Excessive iron deposition in the liver is associated with a high prevalence of glu-

ucose intolerance in patients with hemoglobinopathy requiring repeated blood transfusion (1). In Hong Kong, up to 8.5% of pregnant women have thalassemia trait (2), which is a minor form of thalassemia and does not require blood transfusion. Furthermore, nearly 50% of patients with type 2 diabetes <35 years of age have a family history of diabetes (3). Both conditions share the common feature of insulin resistance. We postulate that there may be a clustering of these disorders in susceptible individuals. We therefore conducted a case-control study of subjects with normal glucose tolerance to examine the relationship among thalassemias, liver function tests, and index of insulin sensitivity (homeostasis model assessment of insulin resistance [$HOMA_{IR}$]).

From a cohort of 835 siblings of young-onset type 2 diabetic patients, 17 normal glucose-tolerant subjects with thalassemia minor and a family history of diabetes were identified. Age-, sex-, and BMI-matched normal glucose-tolerant individuals without thalassemia from the same cohort were selected for comparison. Plasma glucose and serum insulin during the oral glucose tolerance test (OGTT), high sensitive C-reactive protein (hsCRP), plasma lipid concentrations, and indexes of liver function, as well as anthropometric parameters, were measured.

Normal glucose-tolerant individuals with thalassemia minor had higher fasting insulin concentrations (49 [31–65] vs. 29 [20–41] pmol/l, $P = 0.003$; geometric mean [interquartile range]) and lower HDL cholesterol (1.15 ± 0.31 vs. 1.42 ± 0.39 , $P = 0.03$) than control subjects. Thalassemia minor subjects were more insulin resistant ($HOMA_{IR}$: 10.6 [6.3–14.6] vs. 6.1 [4.1–9.1], $P = 0.004$), had an exaggerated insulin response during the OGTT (insulin area under the curve at 120 min: 52,496 [34,670–91,468] vs. 26,275 [21,377–35,793] pmol \cdot l⁻¹ \cdot min⁻¹, $P = 0.007$), and higher hsCRP levels (1.06 [0.60–2.25] vs. 0.44 [0.20–0.83] mg/l, $P = 0.009$) compared with subjects without thalassemia. $HOMA_{IR}$ correlated with γ -glutamyl transpeptidase ($r = 0.595$, $P < 0.001$) and alanine aminotransferase ($r = 0.536$, $P = 0.026$) in subjects with thalassemia minor only.

Individuals with thalassemia minor had insulin resistance, increased inflammatory marker, and low HDL cholesterol

levels. Normal glucose tolerance was maintained in these individuals by hypersecretion of insulin. The fasting hyperinsulinemia and exaggerated insulin response during the OGTT imply that both the liver and muscle are resistant to insulin action. The strong correlation between hepatic enzymes and HOMA_{IR} as well as elevated hsCRP in subjects with thalassemia suggests that low-grade hepatic inflammation is closely correlated with insulin resistance. An increased iron turnover from low-grade hemolysis of microcytic erythrocytes may lead to hepatic damage and increased oxidative stress, both of which can contribute to insulin resistance (4). Intriguingly, hepatic iron overload is associated with some features of the metabolic syndrome (5). Our results suggest that the burden of thalassemia minor on glucose homeostasis cannot be fully explained by overweight or a family history of diabetes. We propose that the presence of thalassemia minor may have a direct effect on glucose homeostasis in individuals with a positive family history of diabetes, although the exact mechanism requires further exploration.

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Acknowledgments—This project was supported by the Hong Kong Research Grant Committee, the Chinese University Strategic Grant, the Hong Kong Government Innovation and Technology Fund, and an educational grant from Servier International.

The authors are most grateful for the contribution of Prof. J.A.J.H. Critchley, who died in a tragic auto accident. We thank Cherry Chiu and Stanley Ho for their technical support as well as all medical and nursing staff at the Diabetes Management and Education Center for their contribution.

References

1. Merkel PA, Simonson DC, Amiel SA, Plewe G, Sherwin RS, Pearson HA, Tamborlane WV: Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. *N Engl J Med* 318:809–814, 1988
2. Sin SY, Ghosh A, Tang LC, Chan V: Ten years' experience of antenatal mean corpuscular volume screening and prenatal diagnosis for thalassaemias in Hong Kong. *J Obstet Gynaecol Res* 26:203–208, 2000
3. Ko GTC, Chan JCN, Yeung VTF, Chow CC, Li JKY, Lau MSW, Mackay IR, Rowley MJ, Zimmet P, Cockram CS: Antibodies to glutamic acid decarboxylase in young Chinese diabetic patients. *Ann Clin Biochem* 35:761–767, 1998
4. Maddux BA, See W, Lawrence JC, Jr., Goldfine AL, Goldfine ID, Evans JL: Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by micromolar concentrations of alpha-lipoic acid. *Diabetes* 50:404–410, 2001
5. Mandler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, Le Gall JY, Brissot P, David V, Deugnier Y: Insulin resistance-associated hepatic iron overload. *Gastroenterology* 117:1155–1163, 1999

GAD65 Antibody Epitope Patterns of Type 1.5 Diabetic Patients Are Consistent With Slow-Onset Autoimmune Diabetes

Type 1.5 diabetes (1) is characterized by rapid loss of β -cell function, failure of oral agents, and acquirement of insulin requirement (2,3). These patients have islet cell antibodies (ICAs), GAD65 autoantibodies (GAD65Abs) (4–6), or both, indicating an underlying autoimmune pathogenesis. Therefore, the question of whether type 1.5 diabetes represents a separate clinical disease or a slowly progressive form of type 1 diabetes has been raised (7,8). The aim of the present study was to investigate whether GAD65Ab epitopes in type 1.5 diabetic patients differ from those found in type 1 diabetic patients and other GAD65Ab-positive phenotypes.

Type 1.5 diabetic patients ($n = 34$) were identified as GAD65Ab-positive type 2 diabetic patients as part of a screening program in the greater Seattle area. The patients were classified with type 2 diabetes according to the 1997 ADA criteria (9) and had to meet all of the following criteria: 1) age ≥ 30 years at diagnosis of diabetes, 2) no history of ketonuria or ketoacidosis, and 3) not requiring insulin treatment at diagnosis. All patients had been diagnosed with diabetes within 12 months of blood sampling. The GAD65Ab epitope pattern was compared with the following three groups of GAD65Ab-positive subjects described in detail elsewhere (10,11), all of whom were reanalyzed for the present investigation: type 1 diabetic patients ($n = 200$), first-degree relatives ($n = 41$), and healthy subjects ($n = 28$). The studies were approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden; the Umeå University, Sweden; and the University of Washington Human Subjects Committee. All individuals gave their informed consent to participate in the study.

The GAD65Ab epitope pattern in the four groups of GAD65Ab-positive subjects was analyzed by a previously described radioimmunoassay (12,13) using recombinant ³⁵S-GAD65/67 fusion proteins. Human GAD65, rat GAD67, and fusion GAD cDNA molecules N-, M+C, M, and C used in the present study were described previously (11,14,15).

The NH₂-terminus of GAD65 was recognized by 20% (7 of 34) of the type 1.5 diabetic patients compared with 5% (10 of 200) in type 1 diabetic patients ($P = 0.03$). No significant difference in binding was observed compared with healthy individuals (11%, 4 of 41) and first-degree relatives (12%, 3 of 28). These data suggested that GAD65Ab reacting with the NH₂-terminal epitope were common in these patients. As previously reported (11), the highest frequency of samples with GAD65Ab binding only to the M-, C-, and/or M+C fusion protein was found in type 1 diabetic patients (90%), whereas first-degree relatives (67%; $P = 0.0016$), healthy individuals (75%; $P = 0.02$), and type 1.5 diabetic patients (65%; $P = 0.0003$) showed significantly lower frequencies of GAD65Ab specific to those parts of GAD65.

We conclude that GAD65Ab binding

body, low serum C-peptide level (0.4 ng/ml at 6 min after intravenous injection of 1 mg glucagon) and 24-h urine C-peptide level ($<3.0 \mu\text{g/day}$), he was diagnosed as having fulminant type 1 diabetes, and intensive insulin therapy was started (total 50 units/day at discharge).

Regarding HLA typing, A24, which is considered to be related to total β -cell destruction (4), was detected (other HLA types: A26, B54, B60, Cw1, Cw4, and DR4). Moreover, a high level of serum IP-10 (285 pg/ml, mean 38.2 pg/ml in healthy subjects) was observed, and GAD-reactive γ -interferon-producing CD4+ cells were detected in peripheral blood (10 of 50,000 CD4+ cells). Thereafter, the titer of serum GAD 65 antibody was followed, and a significant increase was found (1.7 units/ml at 1 month, 39.4 units/ml at 12 months, and 48.9 units/ml at 18 months after the onset of diabetes), indicating that autoimmunity was definitely involved. The HbA_{1c} level of this patient is now controlled at 7.2% by 49 units/day insulin, although his serum C-peptide level is below the detectable limit ($<0.2 \text{ ng/ml}$).

Although it has previously been reported that $\sim 15\%$ of cases of "classical" type 1 diabetes without islet-associated autoantibody had become positive for islet-associated autoantibody at 1 year after the onset of diabetes (5), it is unknown whether cases of so-called "fulminant" type 1 diabetes, which was originally reported as nonautoimmune type (no islet-associated autoantibody at onset of diabetes) (2), also later become positive for islet-associated autoantibody. This case of fulminant type 1 diabetes showed not only cellular immunity against islets but also clear "seroconversion" of GAD 65 antibody during the disease course. Therefore, we propose that fulminant type 1 diabetes should not be diagnosed as idiopathic type simply as a result of islet-associated autoantibody negativity at onset. Careful periodic measurement of islet-associated autoantibodies such as GAD 65 autoantibody should be performed in fulminant type 1 diabetes as well as assessment of cellular immunity against islet-associated antigen for proper classification of type 1 diabetes.

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References

1. Shimada A, Morimoto J, Kodama K, Oikawa Y, Irie J, Nakagawa Y, Narumi S, Saruta T: T-cell-mediated autoimmunity may be involved in fulminant type 1 diabetes (Letter). *Diabetes Care* 25:635–636, 2002
2. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y: A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. *N Engl J Med* 342:301–307, 2000
3. Shimada A, Morimoto J, Kodama K, Suzuki R, Oikawa Y, Funae O, Kasuga A, Saruta T, Narumi S: Elevated serum IP-10 levels observed in type 1 diabetes. *Diabetes Care* 24:510–515, 2001
4. Nakanishi K, Kobayashi T, Murase T, Nakatsuji T, Inoko H, Tsuji K, Kosaka K: Association of HLA-A24 with complete beta-cell destruction in IDDM. *Diabetes* 42:1086–1093, 1993
5. Landin-Olsson M, Arnqvist H, Blohme G, Littorin B, Lithner F, Nystrom L, Schersten B, Sundkvist G, Wibell L, Ostman J, Lernmark A: Appearance of islet cell autoantibodies after clinical diagnosis of diabetes mellitus. *Autoimmunity* 29: 57–63, 1999

Werner Syndrome in a Korean Man

A 34-year-old Korean man living in Tokyo was referred to us in January 1999 for control of his diabetes during cataract surgery. He told us that both disorders had first appeared when he was 22, along with hyperlipidemia. He had acute pancreatitis at 24, and acute appendicitis with peritonitis at 27. He was admitted to a hospital in 1998 for ileus. He has three siblings, the youngest of whom, a sister, had cataracts at 22, and her hair was streaked with gray. His father was diabetic and died at 52 from liver cancer. His mother has angina pectoris—she is 58. His father was from Masan and his

mother from Pusan, both cities in southern Korea. They were not related and no relatives were known to have a medical disorder similar to that of our patient. Inclusion of Japanese ancestry was denied at least over several generations.

A physical examination showed that our patient's height was 162.8 cm, and body weight was 54.8 kg. His hair was gray and he had sclerotic skin, a high-pitched voice, and bilateral cataracts. He said he had erectile dysfunction.

His fasting plasma glucose level was 5.4 mmol/l and HbA_{1c} level was 6.2%. Total cholesterol level was 7.24 mmol/l and triglyceride level was 12.0 mmol/l. Liver chemistry and abdominal echogram showed a fatty liver. Gastrointestinal endoscopy was done because of epigastric pain, indicating a superficial gastritis. Electrocardiogram with double Master load revealed a normal exercise tolerance. He was suspected of having Werner syndrome based on his premature aging phenotypes and his family history.

Gene analysis was done after obtaining informed consent, but the three major mutations (mutations 1, 4, and 6), which account for $\sim 90\%$ of Japanese patients with Werner syndrome, were not detected (1). However, Western blot analysis using the patient's transformed lymphocytes revealed a defect in the production of WRN RecQ helicase, the WRN gene product (2). This indicated the possibility of the truncated protein derived from the mutated WRN gene.

Of the cases of Werner syndrome worldwide, 75% are found in Japanese patients (3). Interestingly, there have been no Koreans reported in the Japanese registry, which is a list of $\sim 1,000$ patients with Werner syndrome, in spite of the racial and geographical adjacency to Japan. The rarity of Werner syndrome in Korean individuals might be partially explained by the small amount of consanguineous marriages influenced by traditional Confucianism. Also, the major WRN gene mutations found in Japanese patients may have arisen after they separated from their common ancestry with Koreans. This Korean patient may be a solitary case.

However, the genetic difference in this case from those reported and studied in Japan contributes to the understanding of the disease, as such differences have in studies of the syndrome's subtypes in Caucasians.

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References

1. Matsumoto T, Tsuchihashi Z, Ito C, Fujita K, Goto M, Furuichi Y: Genetic diagnosis of Werner's Syndrome, a premature aging disease, by mutant allele specific amplification (MASA) and oligomer ligation assay (OLA). *J Anti-Aging Med* 1:131-140, 1998
2. Goto M: Hierarchical deterioration of body systems in Werner's Syndrome: implications for normal aging. *Mech Ageing Dev* 98:239-254, 1997
3. Shiratori M, Sakamoto S, Suzuki N, Tokutake Y, Kawabe Y, Enomoto T, Sugimoto M, Goto M, Matsumoto T, Furuichi Y: Detection by epitope-defined monoclonal antibodies of Werner DNA helicases in the nucleoplasm and their upregulation by cell transformation and immortalization. *J Cell Biol* 144:1-9, 1999

Obesity Is a Critical Risk Factor for Worsening of Glucose Tolerance in a Family With the Mutant Insulin Receptor

It is generally accepted that insulin resistance precedes the development of type 2 diabetes, but the precise mechanism that links insulin resistance to overt diabetes is not well understood. Genetic defects of the insulin receptor, although the prevalence is low, are regarded as one of the specific causes of diabetes (1). However, few studies have reported long-term observations of subjects with the insulin receptor mutation (2). Here, we describe a family with the abnormal insulin

receptor who was followed-up for ~20 years.

The proband is a 34-year-old Japanese woman. At 16 years of age, she noticed acanthosis nigricans in her axillae and groin. Her BMI was 19.0 kg/m². Fasting glucose was normal, but fasting insulin concentration was as high as 240 pmol/l. Anti-insulin and anti-insulin receptor antibodies were negative. The 100-g oral glucose challenge revealed normal glucose tolerance, with peak insulin level of 4,476 pmol/l. Intravenous administration of 0.1 units/kg regular insulin only decreased her glucose level to 64% of the basal value. The number of insulin receptors on her erythrocytes was normal, and subsequent molecular analysis revealed the heterozygous deletion of Leu⁹⁹⁹ in the β -subunit of the insulin receptor, resulting in the decrease in autophosphorylation stimulated by insulin (3). Acanthosis nigricans began to fade beginning at 18 years of age, and she bore two children uneventfully. At 34 years of age, she was still nonobese, with BMI 19.7 kg/m². Fasting glucose was normal, although hypoglycemia of 2.39 mmol/l, together with cold sweat and palpitation, was noted after lunch. Because prolonged fasting of 24 h did not cause hypoglycemia, the diagnosis of reactive hypoglycemia was made. Fasting insulin concentration was 128 pmol/l. Her oral glucose tolerance was again normal, and insulinogenic index, a marker of early-phase insulin secretion (4), was as high as 9.8 (normal population values 0.7-1.3). The intravenous insulin injection successfully decreased her glucose level to 42% of the basal value, with normal responses of counter-regulatory hormones.

The heterozygous deletion of Leu⁹⁹⁹ in the β -subunit of the insulin receptor was also demonstrated in her mother and elder and younger brothers (3). Her mother was obese, with BMI 30.0 kg/m², and was diagnosed as having diabetes at 44 years of age. Her fasting insulin was as high as 222 pmol/l. The insulinogenic index of 1.1 was within normal population values but was regarded as decreased considering the underlying mutation. Her elder brother was normal glucose tolerant at 18 years of age (BMI 23.0 kg/m²) but became impaired glucose tolerant at 26 years of age (BMI 25.0 kg/m²). Fasting insulin simultaneously increased from 216 to 366 pmol/l, while the insulinogenic index decreased from 8.5 to 1.6. At

36 years of age, he had developed overt diabetes, with BMI 30.0 kg/m², and was treated with oral hypoglycemic agents. Her younger brother's fasting insulin was as high as 396 and 144 pmol/l at 12 and 20 years of age, respectively, but he was not available for follow-up.

The glucose tolerance of the lean proband remained normal during the 20-year observation period, and insulin resistance seemed to be rather ameliorated. In contrast, all the other family members with the same insulin receptor mutation who developed diabetes were obese. Thus, obesity appears to be required to develop overt diabetes for the family members of the abnormal insulin receptor. Because the diabetic members had reduced capacity to secrete insulin after oral glucose load, as estimated by the low insulinogenic index, obesity may play a pivotal role in the decompensation of β -cell function. Insufficient β -cell compensation for insulin resistance is generally considered to play an important role in the development of diabetes (5). In particular, there are several lines of evidence that β -cell dysfunction results from an increase in inherited insulin resistance (6,7) and increased abdominal adiposity (8). Obesity may increase the risk of diabetes not only by simply increasing insulin resistance but also by causing β -cell dysfunction under certain circumstances.

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References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997
2. Longo N, Wang Y, Pasquali M: Progress-

- sive decline in insulin levels in Rabson-Mendenhall syndrome. *J Clin Endocrinol Metab* 84:2623–2629, 1999
- Awata T, Matsumoto C, Momomura K, Takahashi Y, Odawara M, Kasuga M, Kadowaki T, Iwamoto Y: A 3-basepair in-frame deletion (Leu⁹⁹⁹) in exon 17 of the insulin receptor gene in a family with insulin resistance. *J Clin Endocrinol Metab* 79:1840–1894, 1994
 - Kosaka K, Hagura R, Kuzuya T: Insulin responses in equivocal and definite diabetes, with special reference to subjects who had mild glucose intolerance but later developed definite diabetes. *Diabetes* 26:944–952, 1977
 - Kahn SE: The importance of β -cell failure in the development and progression of type 2 diabetes. *J Clin Endocrinol Metab* 86:4047–4058, 2001
 - Larsson H, Ahren B: Insulin resistant subjects lack islet adaptation to short-term dexamethasone-induced reduction in insulin sensitivity. *Diabetologia* 42:936–943, 1999
 - Elbein SC, Wegner K, Kahn SE: Reduced β -cell compensation to the insulin resistance associated with obesity in members of Caucasian familial type 2 diabetic kindreds. *Diabetes Care* 23:221–227, 2000
 - Hanley AJG, McKeown-Eyssen G, Harris SB, Hegele RA, Wolever TMS, Kwan J, Zinman B: Cross-sectional and prospective associations between abdominal adiposity and proinsulin concentration. *J Clin Endocrinol Metab* 87:77–83, 2002

High Rate of *Helicobacter pylori* Re-Infection in Patients Affected by Type 1 Diabetes

Patients affected by type 1 diabetes appear to be more prone to infection than healthy subjects (1).

Recently, it has been shown that *Helicobacter pylori* (*H. pylori*) infection is common in type 1 diabetes (2) and that the use of a standard antibiotic therapy obtains a significantly lower eradication rate than in non-insulin-dependent diabetic subjects (3,4). Our aim was to assess the incidence of *H. pylori* re-infection after a successful therapy in type 1 diabetic patients. A total of 74 subjects previously infected by *H. pylori* were enrolled, including 34 type 1 diabetic subjects (16 women and 18 men, 42 ± 9 years of age) and 40 nondiabetic control subjects (17

women and 23 men, 44 ± 8 years of age). Control subjects were matched for age and sex.

None of the type 1 diabetic patients had symptoms of gastroparesis, and none was treated with domperidone. All subjects previously treated for *H. pylori* infection and successfully eradicated, as assessed both by ¹³C-urea breath test (UBT) and histology (two biopsies in antrum, body, and fundus), were re-evaluated with UBT 12 months after eradication. Re-infected patients were also submitted to endoscopy to confirm the presence of the bacterium. Daily insulin requirement and HbA_{1c} (percent total hemoglobin) expressions of glycemic metabolic control were evaluated.

We found a significantly higher incidence of *H. pylori* re-infection in type 1 diabetic patients compared with nondiabetic control subjects. In particular, 13 of 34 (38%) type 1 diabetic patients compared with 2 of 40 (5%) control subjects were re-infected with *H. pylori* 1 year after successful eradication ($P < 0.001$).

Among type 1 diabetic patients, re-infection occurrence was not affected by sex, type 1 diabetes duration, or mean age. No differences in baseline values of daily insulin requirement and HbA_{1c} were observed between re-infected and not-infected diabetic patients (43 ± 8 vs. 38 ± 9 units and 7 ± 0.7 vs. $7 \pm 0.8\%$, respectively). However, 12 months after eradication, significantly higher insulin requirement and HbA_{1c} were observed in re-infected patients compared with uninfected diabetic patients (43 ± 8 vs. 35 ± 8 units, $P < 0.05$; and 7.25 ± 1 vs. $6.8 \pm 0.8\%$, $P < 0.02$). Interestingly, when compared with the enrollment value, patients who remained uninfected by *H. pylori* after 12 months from eradication showed a reduction trend of daily insulin requirement (38 ± 9 vs. 35 ± 8 units, $P < 0.08$).

This study shows that the incidence of *H. pylori* recurrence 12 months after a successful eradication is significantly higher in type 1 diabetic subjects compared with control subjects. Some mechanism could be hypothesized for the higher rate of re-infection observed in diabetic subjects, perhaps an increased susceptibility of the host to the infection as a result of reduced lymphocyte activity and neutrophil dysfunction with failure of chemotaxis.

Better metabolic control in diabetic

patients in whom *H. pylori* has been eradicated compared with re-infected subjects was observed, suggesting a trend of ameliorated metabolic control after *H. pylori* eradication. More studies are requested to investigate the mechanisms underlying the increased susceptibility of *H. pylori* re-infection in type 1 diabetic patients and the role of the bacterium in glycemic control. Vaccine development seems to be one possible effective long-term strategy for this subset of patients.

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Acknowledgments—This study was partly supported by a grant from Associazione Ricerca Medicina, Bologna, Italy.

References

- Larkin JG, Frier BM, Ireland JT: Diabetes mellitus and infection. *Postgrad Med J* 61:233–237, 1985
- Oldenburg B, Diepersloot RJA, Hoekstra JBL: High seroprevalence of *Helicobacter pylori* in diabetes mellitus patients. *Digest Dis Sci* 41:446–458, 1996
- Gasbarrini A, Ojetti V, Pitocco D, Franceschi F, Candelli M, Torre ES, Gabrielli M, Cammarota G, Armuzzi A, Pola R, Pola P, Ghirlanda G, Gasbarrini G: Insulin-dependent diabetes mellitus affects eradication rate of *Helicobacter pylori* infection. *Eur J Gastr Hepatol* 11:713–716, 1999
- Gasbarrini A, Ojetti V, Pitocco D, Armuzzi A, Silveri NG, Pola P, Ghirlanda G, Gasbarrini G: Efficacy of different *Helicobacter pylori* eradication regimens in patients affected by insulin-dependent diabetes mellitus. *Scand J Gastroenterol* 35:260–263, 2000

Nutritional Management of Diabetes in Northern Tanzania

There is little information on the diets of African diabetic subjects (1), but any nutritional recommendation should be based on the patient's eating habits (2). In 1999, we investigated 59 diabetic outpatients (30 women and 29 men) at the Kilimanjaro Christian Medical Center in Moshi, Tanzania. Rural and urban areas were represented by 25 and 34 patients, respectively. Six patients had type 1 and 53 had type 2 diabetes. All were assessed using a food-frequency questionnaire.

The patients consumed plantains, highly extracted maize flour ("sembe"), white bread (wheat flour), and polished rice. Major vegetables were amaranth leaves, cabbage, spinach, and carrots. Kidney beans, cow peas, soy beans, and groundnuts were the main pulses, and orange, papaya, and banana the most reported fruits.

Unlike reports from other studies in Tanzania (3,4), beef was remarkably often consumed, followed by milk, fish and eggs. Of our study population, 92% consumed milk regularly, and >30% reported to frequently include fish in their diet.

Commonly, fat intake is low in Tanzania: 12.5% of energy comes from fat as reported by Mazengo et al. (3). However, nearly all patients surveyed used oils or fats for the preparation of meals—mostly sunflower oil (>80%).

In Tanzania, the total intake of carbohydrates accounts for 74–79% of energy (3). The proportion of starchy foods in meals can be reduced by increasing portion sizes of pulses, vegetables and fruits, as the latter foods were usually consumed in small amounts only. However, some patients may have difficulty with the small supply of pulses, vegetables, or fruits. The portion of monounsaturated fatty acids could be increased by including groundnuts and groundnut oil and by replacing meat by fish.

Most patients had BMI >25 kg/m², indicating energy intakes above the requirements. The first priority for diabetic meal planning is to meet individual energy requirements and to balance the intake of carbohydrates with insulin

activity. Of the patients, 64% reported consuming four to six meals, but the majority had less than five meals daily (68%). Individual nutritional advice for meal composition and timing seems to be necessary because of inflexible medical treatment. Weight reduction in overweight and obese patients as well as an intake of five to six meals at fixed times outline the first steps to improve metabolic control through nutrition in northern Tanzania. But nutrition education needs sufficient time for counseling and a sound knowledge basis.

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References

1. Swai ABM, McLarty DG: *The Management of Diabetes Mellitus*. WHO Collaborating Centre for Diabetes Mellitus, Muhimbili Medical Centre, University of Dar es Salaam, Tanzania. Published with the assistance of Novo Nordisk A/S, 1992
2. Naidu R: Dietary management of diabetes in Africa. *Diabetes Int* 10:5–8, 2000
3. Mazengo MC, Simell O, Lukmanji Z, Shirima R, Karveti RL: Food consumption in rural and urban Tanzania. *Acta Trop* 68:313–326, 1997
4. Tanner M, Lukmanji Z: Food consumption patterns in a rural Tanzanian community (Kikwawila village, Kilombero district, Morogoro region) during lean and post-harvest season. *Acta Trop* 44:229–244, 1987

Cigarette Smoking Affects Tubulointerstitial Lesions in Type 2 Diabetes

Several investigators have renewed interest in the role of tubulointerstitial injury in the progression of diabetic nephropathy (1,2). It was recently

reported that the kidney is an important target organ for damage caused by smoking (3,4). Cigarette smoking increases carboxy-hemoglobin concentration, platelet aggregability, and fibrinogen concentration, all of which may cause tissue hypoxia and contribute to vascular damage. Smoking also has a direct deleterious effect on the proximal tubule (5). Cigarette smoking is known to promote the progression of diabetic nephropathy in clinical study (6), but its effect on tubulointerstitial injury has not been established.

We evaluated glomerular and tubulointerstitial structural findings on renal biopsy specimens taken from type 2 diabetic patients and determined the relationship between smoking and renal architecture. A total of 48 patients (32 men and 16 women) with type 2 diabetes underwent renal biopsy. Information on smoking was obtained with a self-administered questionnaire. Smoking index, defined as pack-years, was estimated by multiplying the number of packs of cigarettes smoked per day by the number of years of smoking. The severity of glomerular lesions on biopsy specimen was estimated by quantitative morphometric studies using a color image processor (SPICCA-II; Olympus, Tokyo) that measured glomerular area (GA) and mesangial ratio (MR). The MR was defined as the ratio of periodic acid Schiff-positive area to GA. The severity of glomerular lesions was divided into three grades: G1, MR <15%; G2, MR 15–25%; and G3, MR >25%. The severity of tubulointerstitial lesions (TILs) was also determined by a semiquantitative estimate of the space occupied by infiltrate or fibrosis using the following grading: T1, damaged area <10%; T2, damaged area 10–30%; and T3, damaged area >30%. Overall renal injury was categorized as group 1 (minor lesions; G1 and T1), group 2 (glomerular diffuse lesions without TILs greater than or equal to G2 and T1), and group 3 (mixed type; greater than or equal to G2 and T2). Additionally, the severity of arteriopathy was graded on a 4-point scale of 0 to 3+. A single reader evaluating the biopsies was unaware of patient smoking status. This study was performed in accordance with the Helsinki Declaration, and written informed consent was obtained from each participant.

A total of 15 (31%) patients were classified as group 1, 22 (46%) as group 2,

and 11 (23%) as group 3. The mean duration of diabetes was significantly longer in group 3 (14.2 ± 6.6 years, $P < 0.05$) and also tended to be longer in group 2 (9.8 ± 5.6 years) than in group 1 (6.5 ± 3.7 years). Urinary protein excretion was significantly higher in group 3 ($1,881 \pm 651$ mg/day, $P < 0.05$) than in group 1 (536 ± 128 mg/day) and group 2 (729 ± 214 mg/day). Creatinine clearance, calculated using the Cockcroft-Gault formula (7), was significantly lower in group 3 (46 ± 14 ml/min, $P < 0.01$) than in group 1 (86 ± 24 ml/min) and group 2 (74 ± 26 ml/min). The MR was significantly higher in group 2 ($21.8 \pm 2.5\%$, $P < 0.01$) and group 3 ($20.9 \pm 7.8\%$, $P < 0.01$) than in group 1 ($12.9 \pm 5.3\%$), and the severity of TILs was significantly higher in group 3 ($26.4 \pm 5.1\%$, $P < 0.01$) than in both group 1 ($7.3 \pm 2.3\%$) and group 2 ($7.7 \pm 5.5\%$). Scores of arteriopathy were significantly higher in group 2 (1.82 ± 1.01 , $P < 0.05$) and group 3 (2.17 ± 0.83 , $P < 0.01$) than in group 1 (1.07 ± 0.74). Smoking index was significantly higher in group 3 (29.6 ± 6.6 , $P < 0.05$) than in both group 1 (16.8 ± 3.9) and group 2 (18.1 ± 4.5). Stepwise multiple regression analysis was used to identify independent factors of tubulointerstitial findings among the following variables: age, duration of diabetes, urinary protein excretion, creatinine clearance values, grades of arteriopathy, and smoking index. Smoking index ($\beta = 0.306$, $P = 0.004$), creatinine clearance ($\beta = -0.376$, $P = 0.042$), and arteriopathy ($\beta = 0.340$, $P = 0.049$) were independently associated with the severity of TILs ($R^2 = 0.636$, $P < 0.001$).

These findings indicate an association between smoking habit and tubulointerstitial injury in diabetic nephropathy.

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References

1. Gilbert RE, Cooper ME: The tubulointerstitium in progressive diabetic kidney disease. *Kidney Int* 56:1627-1637, 1999
2. D'Amico G: Tubulointerstitium as predictor of progression of glomerular diseases.

Nephron 83:289-295, 1999

3. Orth SR, Ritz E, Schrier RW: The renal risks of smoking. *Kidney Int* 51:1669-1677, 1997
4. Gambaro G, Verlato F, Budakovic A, Casara D, Saladini G, Del Prete D, Bertaglia G, Masiero M, Checchetto S, Baggio B: Renal impairment in chronic cigarette smokers. *J Am Soc Nephrol* 9:562-567, 1998
5. Hultberg B, Isaksson A, Brattstrom L, Israelsson B: Elevated urinary excretion of beta-hexosaminidase in smokers. *Eur J Clin Chem Clin Biochem* 30:131-133, 1992
6. Sawicki PT, Didjurgeit U, Muhlhauser I, Bender R, Heineman L, Berger M: Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 17:126-131, 1994
7. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-41, 1976

Diabetes and Air Pollution

The prevalence of diabetes has risen substantially in the past decade. This increase has been linked to an "epidemic" of obesity (1). However, environmental toxins, most notably dioxins, have also been suggested as contributing factors.

Because direct exposure data, in the form of measured levels of toxicants in blood, etc., are not yet available from large populations, total air toxicants from the most recent Toxics Release Inventory (TRI) were used to evaluate the relationship between the prevalence of diabetes and environmental toxicants.

Data from the 2000 Behavioral Risk Factor Surveillance System (BRFSS) were used to determine diabetes prevalence, by state (1). These data are based on self-reports obtained from 184,450 randomly dialed participants. State total air releases for all industries from the 1999 TRI were downloaded from the U.S. Environmental Protection Agency Web site (www.epa.gov). The total prevalence of diabetes in the 2000 BRFSS was $7.3 \pm 0.12\%$ (mean \pm SE)—a 49% increase from 1990 (1). Alaska had the lowest rate, 4.4%, while Mississippi had the highest, 8.8%. Race and educational level were important risk factors, with 11.1% of blacks and 12.9% of those with less than a high school education reporting diabetes.

Total reported TRI air emissions in 1999 were 2,036,510,557 lbs. Ohio industries had the highest emissions, 147,395,113 lbs, while industries in Vermont released 153,161 lbs of toxicants. Approximately 650 chemicals released by a wide variety of industries are included in the TRI. Since the reporting thresholds are high (generally 10,000 lbs) and not all industries are covered, substantial amounts of toxic chemicals are released in addition to those included in the TRI data. Dioxins and persistent bioaccumulating toxins will be included in future TRI data. (TRI data for 2001 were released in May 2000.) The dioxin reporting threshold is 0.1 g (64 FR 58666). Reporting thresholds for other persistent bioaccumulating toxins, such as pesticides, are set between 10 and 100 lbs, depending on the chemical (64 FR 58666).

A linear regression analysis (Systat, Evanston, IL) revealed a significant relationship between TRI air releases, by states, and the prevalence of diabetes ($r = 0.54$, $P = 0.000057$). Although there is a large gap between air emissions and exposure, and even though the correlation between air emissions and the prevalence of diabetes does not prove a cause-and-effect relationship, the significance of the relationship demands attention.

Several studies have suggested that exposure to dioxins may be related to the development of diabetes or altered insulin metabolism (2-4). Dioxins are formed during the combustion of plastics, particularly in municipal and medical waste incinerators (5). Dioxins are concentrated in body fat; thus, obese individuals are likely to have an increased dioxin body burden. While dioxins are among the most toxic of all known chemicals, they are not yet included in TRI data or the Center for Disease Control's National Report on Human Exposure to Environmental Chemicals.

I hope that this demonstration of a highly significant correlation between the prevalence of diabetes and the release of toxicants into the air will stimulate additional research in this area and lead to improvements in health.

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References

1. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP: The continuing epidemics of obesity and diabetes in the United States. *JAMA* 286:1195–1200, 2001
2. Michalek JE, Akhtar FZ, Kiel JL: Serum dioxin, insulin, fasting glucose, and sex hormone-binding: globulin in veterans of Operation Ranch Hand. *Clin Endocrinol Metab* 84:1540–1543, 1999
3. Vena J, Boffetta P, Becher H, Benn T, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T, Littorin M, Lyngé E, Mathews JD, Neuberger M, Pearce N, Pesatori AC, Saracci R, Steenland K, Kogevinas M: Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide: and chlorophenol production workers and sprayers. *Environ Health Perspectives* 106 (Suppl.2): 645–653, 1998
4. Pesatori AC, Zocchetti C, Guercilena S, Consonni D, Turrini D, Bertazzi PA: Dioxin exposure and non-malignant health effects: a mortality study. *Occup & Environ Med* 55:126–131, 1998
5. Exposure Analysis and Risk Characterization Group, National Center for Environmental Assessment: *The Inventory Of Sources Of Dioxin In The United States*. Washington, D.C., U.S. Environmental Protection Agency, 1998

Is ACE Inhibitor the Best First-Line Agent for Diabetes With Hypertension?

I have some questions about the opinions presented by Niskanen et al. in the December 2001 issue of *Diabetes Care* (1).

Study analysis

Was “after the fact” subanalysis designed with enough power to see the proposed difference? The subanalysis of 572 patients compared with the 10,985 patients in the Captopril Prevention Project (CAPPP) might not seem as robust as the original study. Even in the original powered-analysis study, the treatment regimens did not differ in terms of prevention of the primary end point (fatal cardiovas-

cular events; stroke, fatal and nonfatal; myocardial infarction, fatal and nonfatal; all fatal events; all cardiac events; and diabetes). Even the risk of stroke was lower with conventional therapy than with captopril therapy.

Insulin sensitivity

The CAPPP claims that captopril has a positive effect in insulin sensitivity, although this claim is not supported by other studies, including double-blinded and placebo-controlled studies.

Treatment combinations

“Conventional antihypertensive” treatment was defined as “diuretics and/or β -blocker.” Were β -blockers or diuretics administered first, and then were second agents added? Or vice versa? Even in the captopril group, patients received a diuretic if their blood pressure was not under control. The calcium antagonist also was allowed to be added to both treatment groups. The study results did not report the finalized treatment combinations.

Not supported by U.K. Prospective Diabetes Study

The U.K. Prospective Diabetes Study also compared antihypertensive treatment with an ACE inhibitor to that with a β -blocker. Neither drug was superior to the other in any outcome measured, including diabetes-related deaths, myocardial infarction, and all microvascular end points.

I recognize that diabetes, being a comorbidity disease, may require three or more drugs to achieve the specified target levels of blood pressure control. The established practice of choosing an ACE inhibitor as one of the first-line agents in most patients with diabetes is reasonable. And, for patients with microalbuminemia or clinical nephropathy, both ACE inhibitors and angiotensin receptor blockers should be used for the prevention and progression of nephropathy. We should still remember that diuretic- and β -blocker-based therapies also are supported by evidence from other studies of diabetic individuals with hypertension.

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References

1. Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A: Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/ β -blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care* 24:2091–2096, 2001

ACE Inhibitor as One of Several Possible First-Line Agents Is Reasonable for Diabetic Patients With Hypertension

We appreciate the overall constructive criticisms given by Dr. Egger (1) and we respond as follows: The Captopril Prevention Project (CAPPP) Study was the first intervention trial in hypertensive patients to compare an ACE inhibitor-based therapy with conventional antihypertensive therapy, based on diuretics and/or β -blockers, regarding the effects on cardiovascular morbidity and mortality (2). As correctly pointed out by Dr. Egger, in the whole CAPPP study population, both diabetic and nondiabetic subjects combined, no difference was found between regimens in preventing the primary end point (i.e., the combination of fatal as well as nonfatal myocardial infarction and stroke and other cardiovascular deaths). In the whole CAPPP population, the risk of stroke was lower with conventional therapy than with captopril therapy, but this was not the case in the diabetic patients. We are just as puzzled by the result in the full cohort as are others, since this result is not supported by other studies. The contributory factors may have been a higher frequency of history of strokes and transient ischemic attacks at baseline in the captopril group, and this group also had an achieved blood pressure that was 2 mmHg higher as compared with the conventionally treated group (2). The development of diabetes was one of the

predefined secondary end points of this study. Contrary to what Dr. Egger states, the captopril group ($n = 337$) had lower incidences of new-onset diabetes than the conventionally treated group ($n = 380$) (relative risk 0.86, $P = 0.039$), and this was especially marked in those who were previously untreated (relative risk 0.67, $P = 0.030$) (2).

We do appreciate Dr. Egger's overall concern about the power of the study. The results in the diabetic patient cohort are, like most other studies in this field, derived from a subanalysis from the larger CAPPP project with all its caveats. This aspect was evident in the title of our article. We fully agree with Dr. Egger that the results of this and any other single subanalysis should be interpreted with caution.

Regarding insulin sensitivity, we agree that the studies on ACE inhibition and whole-body glucose uptake during euglycemic clamp technique measurements have been contradictory. Due to space constraints, detailed speculations about the potential mechanisms were beyond the scope of our article. There are also a number of other possible metabolic disturbances in diabetic patients that are influenced beneficially by ACE inhibitor treatment, as we briefly mentioned in our article. However, regarding the effects of renin-angiotensin-aldosterone system inhibition on glucose and insulin metabolism, one should acknowledge that in the CAPPP Study (3), like in the HOPE Study (4) and the just recently published Losartan Intervention Study For End Point Reduction (LIFE) (5,6), drugs affecting renin-angiotensin-aldosterone system have shown significant long-term reduction in the incidence of new-onset diabetes, although the detailed mechanisms remain obscure.

As to treatment combinations, it is important to emphasize that we are actually comparing regimens based on various drugs, and this also holds for the design of other studies like the U.K. Prospective Diabetes Study (UKPDS) (7,8). In the conventional group of the CAPPP Study, the choice of starting treatment with either a diuretic or β -blocker was left to the investigator, since this was the accepted first-line antihypertensive therapy at the time when the CAPPP Study was initiated.

It is true that to some extent the findings may be at deviance with those found in the UKPDS (7), which showed no ad-

vantage for captopril over atenolol in reducing the risk of macrovascular and microvascular diabetic complications. As discussed above, these divergent findings may partly be explained by the fact that the blood pressure treatment goal was lower in the UKPDS ($<150/<85$ mmHg) than in the CAPPP Study (diastolic blood pressure <90 mmHg). Thus, blood pressure lowering may be more important than the choice of antihypertensive agent, although captopril was better tolerated (8).

Further, the diabetic patients recruited in the UKPDS had generally milder disturbances in glucose metabolism, and patients with symptomatic cardiovascular disease were not included in the UKPDS; therefore, these patients were likely to be at lower risk than the diabetic patients in the CAPPP Study. The LIFE Study (5) as well as the subanalysis of the LIFE diabetic population (6) ($n = 1,195$) showed that an angiotensin II receptor antagonist-based (losartan) regimen was markedly superior in preventing cardiovascular end points in diabetic patients than a β -blocker-based (atenolol) regimen. Even total mortality was reduced $\sim 40\%$ in the losartan group as compared with the atenolol group. However, the diabetic substudy in LIFE was not powered to be a mortality study, but the results were striking. The results of the LIFE Study are in line with the results of the CAPPP diabetic subpopulation analysis.

As to the concluding remarks by Dr. Egger, we totally agree. Multiple drugs are required in diabetic patients and choosing an ACE inhibitor as one of several possible first-line agents is reasonable, especially in those with renal impairment. Further and more importantly, all five classes of agents, diuretics, β -blockers, calcium antagonists, ACE inhibitors, and AT1-receptor antagonists, have presently been shown to reduce cardiovascular events in diabetic patients.

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L.H. and J.L. have received honoraria from Bristol-Myers Squibb.

References

1. Egger T: Is ACE inhibitor the best first-line agent for diabetes with hypertension? (Letter) *Diabetes Care* 25:1488, 2002
2. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmäki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Mörlin C, Björck JD, for the Captopril Prevention Project (CAPPP) Study Group: Effect of angiotensin-converting-enzyme inhibition compared with conventional morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 353:611–616, 1999
3. Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A, for the Captopril Prevention Project (CAPPP) Study Group: Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/ β -blocker based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care* 24:2091–2096, 2001
4. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–259, 2000
5. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, for the LIFE Study Group: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in the hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359:995–1003, 2002
6. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snappin S, for the LIFE Study Group: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For End Point Reduction in the Hypertension Study (LIFE): a randomised trial against atenolol. *Lancet* 359:1004–1010, 2002
7. UK Prospective Diabetes Study Group: Tight blood pressure and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 317:703–713, 1998
8. UK Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 317:713–720, 1998

Response to Schmitz

In an otherwise enticing article by Schmitz et al. (1) in the February 2002 issue of *Diabetes Care*, the authors make several assertions that are difficult to support by the data presented in the article.

The authors discuss “early-phase” insulin secretion numerous times throughout their article and seem to consider this term the same as “acute phase” insulin secretion (CONCLUSIONS, paragraph two, line 13: “[. . .] early-phase insulin release is one of the first defects to appear as type 2 diabetes develops”). Based on this assumption, they conclude that the study drug did indeed improve “early-phase” insulin secretion (presumably within 10 min after administration, by their definition) (CONCLUSIONS, paragraph 2, line 9) but there are no data presented in their article to support this contention.

As best as I could tell, Schmitz et al. measured blood samples 43 times over 24 h, but the intervals of measurement are not given. Even if they measured insulin levels at 1-min intervals after oral glucose administration, would this be equivalent to insulin secretion after intravenously administered glucose? Perhaps I am missing something here, but are these two terms interchangeable (acute-phase insulin release and early-phase insulin secretion)?

I would greatly appreciate it if the authors could clarify this point for me.

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Response to Block

I thank Dr. Block (1) for the interest in our article (2) and the editor for the opportunity to clarify the point raised. As stated several times in our article (RESULTS, Table 2, CONCLUSIONS), we define the early-phase period (i.e., where insulin secretory rates were calculated) as the initial 30 min of the prandial phase. The calculation of insulin secretion was as noted based on measurements of insulin and C-peptide, utilizing the classic combined model. Samples were drawn every 10 min during this part of the prandial period.

The cardinal issue in our article is the

effect of the insulin secretagogue repaglinide on the meal-induced insulin secretion, which is influenced by several nutrients, release of incretin hormones, etc. In CONCLUSIONS we discuss twice the intravenous glucose-induced early-phase insulin release (presumably what Dr. Block refers to as acute-phase insulin release) to notice another important aspect of type 2 diabetes pathophysiology. In the same paragraph, meal-induced insulin release was discussed as it appears from the references. We felt that the message was clear and it was easy for the general reader to distinguish between these two issues.

The allegation of the authors trying to equate meal-induced insulin secretion to intravenously glucose-induced early-phase insulin secretion warrants a comment. Oral insulin secretagogues are developed to reduce glycemia during daily life conditions (e.g., meals), but of course in the interest of gaining insight into mode of action, it may be of relevance to explore their effects on unphysiological insulin challenges (e.g., intravenous glucose). The immediate insulin secretion elicited by the latter stimulus is now demonstrated to be related to a pool of insulin vesicles docked at the plasma membrane, whereas the early-phase insulin secretion after meal ingestion is probably ascribable to a combination of release from this pool and initially undocked vesicles.

So, to some extent, it may be two sides of the same coin. Both a reduced meal-induced and intravenously glucose-induced early-phase insulin secretion are abnormalities often present in healthy prediabetic individuals (3,4). Clearly the two modes of stimulating the β -cell are only partially comparable. Nevertheless, our study deals with clinical pharmacology and insulin and glucose dynamics during daily life conditions of type 2 diabetic individuals after administration of an insulin secretagogue. In this context, we did not find it of relevance to compare this daily life condition in terms of insulin release with an (unphysiological) intravenous glucose challenge. One almost gets the impression from Dr. Block's comment that restoration of intravenously glucose-induced insulin secretion is even more pivotal than restoring the daily-life, meal-induced, early-phase insulin secretion.

Moreover, it is important to state that our study drug (repaglinide) convincingly improved insulin secretion during the initial 30 min of the prandial periods,

but we never reported that this took place within 10 min after administration. I kindly ask Dr. Block to read our article again to solve this misinterpretation.

Finally, I thank Dr. Block for giving us the opportunity to emphasize the importance of defining insulin secretion (e.g., early-phase, very early-phase, acute-phase, first-phase insulin secretion to a given challenge) very carefully.

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References

1. Block M: Response to Schmitz et al. (Letter). *Diabetes Care* 25:1490, 2002
2. Schmitz O, Lund S, Andersen PH, Jonler M, Porksen N: Optimizing insulin secretagogue therapy in patients with type 2 diabetes: a randomized double-blind study with repaglinide. *Diabetes Care* 25:342–346, 2002
3. Knowles NG, Landchild MA, Fujimoto WY, Kahn SE: Insulin and amylin release are both diminished in first-degree relatives of subjects with type 2 diabetes. *Diabetes Care* 25:292–295, 2002
4. Nyholm B, Walker M, Gravholt CH, Shearing PA, Sturis J, Alberti KGMM, Holst JJ, Schmitz O: Twenty-four-hour insulin secretion rates, circulating concentrations of fuel substrates and gut incretin hormones in healthy offspring of type 2 (non-insulin-dependent) diabetic parents: evidence of several aberrations. *Diabetologia* 42:1314–1323, 1999

COMMENTS AND RESPONSES

On Combination Therapy of Diabetes With Metformin and Dipeptidyl Peptidase IV Inhibitors

Recently, data were presented showing that metformin increased plasma active glucagon-like peptide (GLP)-1_[7–36NH₂] concentrations in obese nondiabetic male patients (1), and it was suggested that metformin was a di-

eral insulin sensitivity, through unidentified molecular mechanisms in the liver and skeletal muscle. However, it has been observed that metformin could enhance glucose-induced insulin secretion in some experimental conditions (2), although the relevance of this effect for the antihyperglycemic action of metformin is questionable. Furthermore, glucagon-like peptide (GLP)-1 has been shown to increase insulin sensitivity and non-insulin-mediated glucose disposal (3,4), suggesting that DPP-IV inhibitors, which increase GLP-1 levels, could be expected to improve insulin sensitivity as well as insulin secretion.

Our study (5) has shown that the increase of GLP-1 levels after an oral glucose load determined by metformin, consistent with previous reports, is not due to drug-induced differences in glycemia or insulinemia; in fact, this effect can also be observed in isoglycemic and isoinsulinemic conditions, i.e., during a hyperinsulinemic-euglycemic clamp. The contribution of enhancement of secretion and inhibition of degradation to the increase of GLP-1 levels during metformin therapy needs to be elucidated through further specifically designed studies, as was clearly stated in our study. The measurement of total GLP-1, as suggested by Hinke et al., would be of little use in this respect; in fact, total GLP-1 should obviously be expected to be increased, even in the case of metformin inhibiting degradation without stimulating secretion. In vitro or ex vivo experimental models, such as isolated intestinal L-cells or perfused ileum, would be more informative

for the study of the effects of metformin on GLP-1 secretion.

We also agree with Hinke et al. that, theoretically, the combination of DPP-IV inhibitors (acting mainly via the increase of early postprandial insulin secretion) and metformin (acting mainly through the enhancement of insulin sensitivity and suppression of hepatic glucose output) could be useful in the treatment of type 2 diabetes. However, the choice of therapeutic combinations should be based on evidence derived from clinical studies rather than on theoretical consideration. Demuth et al. (6) reported that the Probiobdrug DPP-IV inhibitor P32/98 has a significant hypoglycemic effect in type 2 diabetic patients treated with sulfonylureas, but it does not reduce blood glucose in those already treated with metformin. We agree with Hinke et al. that other DPP-IV inhibitors could have a more favorable profile of action when given in combination with metformin, but we advise greater caution in designing future therapeutic scenarios when so little sound clinical evidence is available.

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E.M. has received consulting fees from Molteni Pharmaceuticals and Merck Pharma Italia. C.M.R. is

a member of an advisory board for Novo Nordisk and has received grant support from Molteni Pharmaceuticals.



References

1. Hinke SA, McIntosh CHS, Hoffmann T, Kühn-Wache K, Wagner L, Bär J, Manhart S, Wermann M, Pederson RA, Demuth H-U: On combination therapy of diabetes with metformin and DP IV inhibitors. *Diabetes Care* 25:1490–1491, 2002
2. Lupi R, Del Guerra S, Fierabracci V, Marselli L, Novelli M, Patanè G, Boggi U, Mosca F, Piro S, Del Prato S, Marchetti P: Lipotoxicity in human pancreatic islets and the protective effect of metformin. *Diabetes* 51 (Suppl. 1):S134–S137, 2002
3. D'Alessio DA, Kahn SE, Leusner CR, Ensink JW: Glucagon-like peptide-1 enhances glucose tolerance both by stimulation of insulin release and by increasing insulin-dependent glucose disposal. *J Clin Invest* 95:2263–2266, 1994
4. Meneilly GS, McIntosh CH, Pederson RA, Habener JF, Gingerich R, Egan JM, Finegood DT, Elahi D: Effect of glucagon-like peptide 1 on non-insulin-mediated glucose uptake in the elderly patient with diabetes. *Diabetes Care* 24:1951–1956, 2001
5. Mannucci E, Ognibene A, Cremasco F, Bardini G, Mencucci A, Pierazzuoli E, Ciani S, Messeri G, Rotella CM: Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. *Diabetes Care* 24:489–494, 2001
6. Demuth HU, Hoffmann T, Lund K, McIntosh CHS, Pederson RA, Fuecker K, Fischer S, Hanefeld M: Single dose treatment of diabetic patients by the DP IV inhibitor P32/98 (Abstract). *Diabetes* 40 (Suppl. 1):A102, 2000