tight glycemic control, in the treatment of patients with macroalbuminuria from diabetic nephropathy.

In the first case, a 58-year-old woman with type 1 diabetes that was diagnosed when she was 17 years old was found to have 1,260 mg/day of protein in the urine. Her history was pertinent for diabetic retinopathy, neuropathy, and for recurrent congestive heart failure. Medications included digoxin, furosemide, Cozaar, and aspirin, as well as NPH and regular insulin twice daily. The HbA_{1c} was 7.7% (4.1–6.1). The treatment regimen was changed to the insulin pump, and therapy with pentoxifylline (400 mg t.i.d.) was begun. Because of gastrointestinal side effects from the pentoxifylline, the dosage was reduced to 400 mg twice per day, which was tolerated. Three months later, the 24-h urine protein was 284 mg/day, and 6 months after that, 237 mg/day. The HbA_{1c} fluctuated between 7.2 and 7.5% during that time. All other medications were continued as before.

In the second case, a 74-year-old man with type 1 diabetes that was diagnosed when he was 42 years old had been noted at age 70 years to have 312 mg/day of protein in the urine. Therapy with 10 mg/day lisinopril was begun. After 18 months, a 24-h urine sample revealed 3,643 mg/day of protein. Therapy with pentoxifylline (400 mg t.i.d.) was begun. Also at that time, the insulin regimen was changed from three injections per day to use of the insulin pump. After 6 months, a 24-h urine sample revealed 1,836 mg of protein. When tested 6 months later, the urinary protein was 1,056 mg/day, and after an additional 6 months, it was 490 mg/day. Lisinopril therapy was continued during this time. HbA_{1c} levels fluctuated between 7.2 and 8.3% (4.1–6.1) during this time, compared with values between 9.0 and 9.3% before introduction of the insulin pump.

In the third case, an 84-year old female who had type 2 diabetes with diabetic retinopathy and peripheral neuropathy was found to have 3,967 mg/day of urinary protein. Her history was pertinent for hypertension and congestive heart failure, for which she was treated with captopril (25 mg t.i.d.) and furosemide (40 mg b.i.d.). Her diabetes was managed with Humulin N and Humulin R in the morning, Humulin R at supper, and Humulin N at bedtime. Pentoxifylline was begun for the proteinuria at a dosage of 400 mg t.i.d. After 4 months, the 24-h urinary protein had been reduced to 733 mg/day, and 1 year later, the urinary protein was 787 mg/day. During this time, HbA_{1c} ranged between 5.8 and 6.5% (4.1–6.1).

These cases illustrate that pentoxifylline, in conjunction with intensive therapy for diabetes, may be particularly useful in reducing significant proteinuria. All three patients maintained stable serum creatinine levels in the range of 1.0–1.5 mg/dl. Tight glycemic control was maintained in all patients, and in the second case, there was a significant improvement in HbA_{1c} after insulin pump therapy was introduced. Two patients were taking concomitant ACEIs, and the third was on an angiotensin-receptor blocker (ARB). ARBs have been shown in an animal model to attenuate diabetic nephropathy (7). Further studies to elucidate the mechanism of improved macroalbuminuria by pentoxifylline in conjunction with tight glycemic control in the treatment of diabetic nephropathy should be considered. This treatment appears to be beneficial in forestalling the typically relentless downhill course of diabetic nephropathy.

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Correct Homeostasis Model Assessment (HOMA) Evaluation Uses the Computer Program

We read with interest the correspondence between Drs. van Haeften (1) and Matsumoto et al. (2) in a recent issue of *Diabetes Care* about the correct formula for insulin resistance calculated by homeostasis model assessment (HOMA). The HOMA model (3) is a structural computer model of the glucose-insulin feedback system in the homeostatic (overnight-fasted) state. The model consists of a number of nonlinear empirical equations describing the functions of organs and tissues involved in glucose regulation. These are solved numerically to predict glucose, insulin, and C-peptide concentrations in the fasting steady state for any combination of pancreatic β-cell function and insulin sensitivity (or resistance). These predictions allow the deduction of β-cell function (%β) and insulin sensitivity (%S) from pairs of fasting glucose and insulin (or C-peptide) measurements. The nonlinearity of the model precludes an exact algebraic solution, but estimations are possible either graphically or by using simple mathematical approximations, as presented in Matthews et al. (3): R (which is the inverse of %S) = (insulin × glucose)/22.5 and %β = 20 × insulin/(glucose − 3.5). The apparent redundancy of the expression in question was due to the removal of terms from an original, more complex, expression. Two developments have taken place since 1985.

First, the physiological basis of the model has been developed, both in terms of insulin secretion (4) and glucose metabolism (5), and further modifications have included a model of proinsulin secretion,

allowing HOMA to be used with either immunoreactive insulin or specific insulin assays, and a model of renal glucose losses, allowing its use in more hyperglycemic states. These modifications provide a more accurate representation of physiology and successfully predict the homeostatic responses to an intravenous glucose infusion. The use of the current HOMA model performs well in comparison with several tests of insulin sensitivity, including the intravenous glucose tolerance test, and with minimal model analysis and the short insulin tolerance test of Bonora (6) and tests of β-cell function (7), including the hyperglycemic clamp (8), the oral glucose tolerance test (9), and the frequently sampled intravenous glucose tolerance test (FSIVGTT) (7).

Second, the model has been incorporated in a simple MS-DOS–based computer program that allows rapid determination of %β and %S from measured values. This program is available free of charge for academic use from one of the authors (J.C.L.). Although the simple equations (3) give a qualitatively useful approximation of the model predictions, we recommend that HOMA calculations use the computer model in preference, in view of its more precise physiological basis and the validation data that are available and in the process of being published.

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Diabetic Instability and Celiac Disease

A frequent association to keep in mind

Celiac disease (CD) is caused by damage to differentiated villus epithelial cells in response to the ingestion of dietary gluten. The rate of IDDM and CD association is generally estimated to be 1–7% (1). Some clues suggest that these two conditions are linked by a common physiopathology. The first phase of insulin response is altered in islet cell antibody (ICA)-negative children with CD observed in the prediabetic state (2). In addition, some of these children with CD developed IDDM during a follow-up of 10 years (2). Furthermore, CD and IDDM are supported by an identical genetic background (class II HLA DR3 and HLA DQ2 genotypes) (1,3,4). Finally, similar mechanisms of β-cell and enterocyte cell damage mediated by tumor necrosis factor and γ-interferon are observed (4).

The recent routine accessibility of IgA endomysial antibody detection (the most sensitive and specific noninvasive screening test of CD) (1,5) showed that CD and IDDM are more frequently associated than previously reported. The usual symptoms of CD are diarrhea and a chronic malabsorption syndrome. Furthermore, the altered digestive absorption of meals worsened the metabolic control of diabetes, leading to diabetic instability. We report a case of poorly controlled IDDM caused by a severe CD free of any specific symptom.

A 47-year-old IDDM woman was referred for poor diabetic control. Her uncomplicated IDDM was diagnosed at 30 years of age. An intensive insulin therapy maintained diabetes near normoglycemia until 1 year before admission. In the last year, a loss of 1 kg of body weight (BMI 25 kg/m^2) was associated with frequent and unpredictable hypoglycemic or hyperglycemic periods. The daily calorie intake was unchanged, and no eating disorder was noted. Psychiatric pathology and factitious disease were excluded. The search for intercurrent illness was negative. Diarrhea was not present. Clinical examination was normal except for periumbilical subcutaneous lipodystrophies. Their exclusion as insulin injection sites did not improve metabolic parameters. No biological signs of malabsorption were found. Because of the presence of dyspeptic symptoms, we performed an upper digestive track fibroscopy that excluded diabetic gastroparesis. Systematic bowel biopsies showed complete mucosal atrophy typical of severe CD. IgA endomysial antibodies were positive (by indirect immunofluorescence assay). An improvement of metabolic control was observed 6 months after gluten-free diet introduction, and control bowel biopsies showed the disappearance of mucosal atrophy.

Our case was intriguing because of the lack of the usual biological and clinical features of CD. The disappearance of diabetic instability after the introduction of a specific gluten-free diet confirms the responsibility of CD in the bad metabolic control.

Diabetes instability is a severe disease that can endanger a patient's life. Because CD is a curable cause of bad metabolic control more often associated with IDDM than usually admitted, we suggest that all subjects with diabetic instability should be actively screened for CD, even if no spe-