OBSERVATIONS

B-Type Natriuretic Peptide in Type 2 Diabetes

The influence of chronic renal failure and food

Cardiac ventricles release B-type natriuretic peptide (BNP) in response to volume expansion and pressure overload; therefore, BNP concentration may be used as a biochemical marker of cardiac failure (1). BNP levels are high in diabetic subjects with left ventricular dysfunction (2). Because the diagnosis of cardiac failure may be an emergency (3), it is important to know whether the timing of BNP measurement (before or after a meal) affects the result. The effect of renal failure is also an important practical issue, since 25–40% of diabetic subjects have diabetic nephropathy. This study was designed to describe the changes elicited by chronic renal failure (CRF) and meal consumption on BNP levels in diabetic patients.

Thirty diabetic patients were divided into two groups: 15 patients without CRF (group 1: glomerular filtration rate [GFR]) by Cockcroft's formula >60 ml/min) and 15 patients with CRF (group 2: GFR <60 ml/min). No patient presented significant cardiac history based on clinical examination, electrocardiograph recording, and chest radiography. Four blood samples were collected before and 1, 2, and 3 h (T0 to T3) after a standardized meal (72 g carbohydrates, 21 g lipids, and 32 g proteins) to measure plasma BNP concentrations (IRMA Shionoria-BNP, Schering Cis Bio). Mean BNP levels (±SD) for the two groups were compared using the Mann-Whitney *U* test. Values for repeated data before and after lunch were compared by ANOVA.

Sex, age, BMI, type of diabetes, HbA_{1c}, and blood pressure were similar in the two groups. GFR was lower in group 2 (group 1: 92 ± 20, group 2: 36 ± 15 ml/min; $P < 0.001$). No significant difference was found between BNP concentrations before and after lunch in both groups (group 1: T = 12.3 ± 23.1, T1 = 11.7 ± 21.9, T2 = 12.3 ± 21.9, T3 = 12.5 ± 23.2 pg/ml; group 2: T = 34.9 ± 37.9, T1 = 34.7 ± 38.9, T2 = 35.9 ± 36.7, T3 = 35.7 ± 39.4 pg/ml). The BNP concentrations were higher in group 2 ($P < 0.05$ for each time). When the two groups were analyzed together, BNP concentrations were negatively correlated with GFR ($r = -0.56$, $P < 0.005$).

Natriuretic peptides play many physiological roles; therefore, determining whether feeding affects BNP concentrations is a practical problem. Plasma α-atrial natriuretic peptide concentrations are increased by feeding in nondiabetic subjects (4). We show here that feeding does not affect plasma BNP levels in diabetic patients; blood samples can be drawn at any time for BNP measurement.

In nondiabetic patients, BNP distinguishes patients with a left ventricular hypertrophy and CRF (5). In our study, plasma BNP concentrations were higher in diabetic patients with CRF before and after feeding. Plasma BNP may therefore be used to monitor the cardiac function in diabetic subjects with CRF, but its reduced clearance participating in its increased concentrations needs to be taken into account.

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Cholestatic Hepatitis Associated With Repaglinide

Repaglinide is a fast, short-acting meglitinide analog antidiabetic drug approved for the treatment of type 2 diabetes. Hypoglycemia is a major adverse effect of this drug (1). In rare cases, elevated liver enzymes have been noted (2). We report a patient who developed cholestatic hepatitis while taking repaglinide.

A 72-year-old man had a 2-year history of type 2 diabetes that was initially controlled by diet. He had normal liver function. Two months before presentation, he began taking repaglinide (1 mg/day), and 1 month before presentation, the daily dose was increased to 2 mg. The patient presented because of a 2-week history of itching and jaundice and was admitted to the hospital. He had no toxic habits and denied the use of any other drugs or herbal remedies.

The patient's physical examination was unremarkable except for jaundice. Aspartate aminotransferase was 83 units/l (normal <37), alanine aminotransferase 183 units/l (normal <40), alkaline phosphatase 307 units/l (normal <136), γ-glutamyltransferase 303 units/l (normal <85), and total bilirubin 12.2 mg/dl with direct bilirubin 9.4 mg/dl. Serum creatinine was 1.3 mg/dl. Serology ruled out viral causes, and screening for autoantibodies was negative. Imaging testing, including a magnetic resonance cholangiography, showed no pathological findings. A liver biopsy showed

expanded portal areas with mild proliferation of bile ducts and a moderate inflammatory infiltrate (mainly lymphocytes and some eosinophils) with ballooning of hepatocytes. Repaglinide was discontinued, and laboratory findings were normal within a month.

To our knowledge, this is the first published report of cholestatic hepatitis related to repaglinide. The putative role of repaglinide in this case of acute cholestasis is strongly supported by its temporal eligibility, the careful exclusion of alternative causes, the histological features, and the rapid improvement after drug withdrawal. The presence of some eosinophils in the liver inflammatory infiltrate suggest that an immune mechanism might be operating.

Idiosyncratic hepatic reactions are often associated with partial dose dependence and a relationship to drug metabolism (3). Repaglinide clearance is dependent on liver enzyme activity and secondarily on hepatic blood flow. These two factors are impaired at a variable extent among elderly individuals (4). Furthermore, 8% of a dose is excreted in the urine (1). This patient had an estimate of the creatinine clearance of 46.59 ml/min (Cockcroft and Gault formula). Studies carried out in patients with mild to moderate kidney impairment (30–80 ml/min) have shown higher values for drug concentration over time in both single and multiple dosing compared with those in healthy subjects (1).

The product datasheet states that dose adjustments are unnecessary in geriatric patients, while a dose titration is recommended in patients with hepatic or renal impairment. Indeed, the reduced liver enzyme activity, along with the steady decline in renal function with normal aging that can be further compromised with the presence of underlying chronic conditions such as diabetes (4), indicates that caution should be observed when repaglinide is prescribed to elderly patients. Therefore, we believe that a reduced dose should also be encouraged, and that clinicians should be aware of the potential for hepatotoxicity of repaglinide.

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Cerebral Edema Without Ketoacidosis or Hyperosmolar Coma in a 16-Year-Old Boy

Cerebral edema is a rare, but life-threatening, complication of diabetic ketoacidosis usually occurring during its treatment. There is no documentation of the occurrence of cerebral edema outside the setting of diabetic ketoacidosis (1).

We report a 16-year-old boy who walked into our clinic complaining of limited joint mobility (involving hands, elbows, and knees), poor linear growth, and diminished vision for 2 years. On direct questioning, osmotic symptoms were present for 2 years. There was no personal or family history suggestive of connective tissue disorder. The patient was alert and oriented and able to explain his medical history . He was 147.5 cm tall (height age 12 years and 4 months by Indian standards), weighed 29 kg (BMI 13.1 kg/m^2), and was in Tanner stage 2 of puberty. Pulse rate was 88 bpm and blood pressure 110/80 mmHg. There were no signs of dehydration or acidosis. The patient's skin was dry, thickened, and waxy. The prayer sign was present, along with flexion deformity of the elbow and knee joints. There were no signs of joint inflammation, and he had bilateral posterior subcapsular cataracts. Systemic examination was normal, and no organomegaly was seen. Random blood glucose was 329 mg %, and urine ketones were large. Hemogram, serum sodiumand potassium, albumin, transaminases, and creatinine were normal. HbA_{1c} was 21.4% (normal 4–6%). An abdominal ultrasonography did not reveal any pancreatic calcification. GAD antibody was negative, and the A3243G mitochondrial mutation was absent.

The patient was admitted and received regular insulin subcutaneously at 12:00 P.M. and regular with intermediate-acting insulin at 8:00 P.M. before dinner. Blood glucose was 319 mg % before dinner, 221 mg % at 2 :00 A.M., and 195 mg % at 7:00 A.M. the next morning. Urine ketones were negative at all of these times. After the patient had taken morning insulin and breakfast at 8:00 A.M., he vomited twice and became significantly drowsy. His pulse was 68 bpm, respiratory rate 22 bpm, and blood pressure 130/100 mmHg. His pupils, tendon reflexes, and plantars remained normal. Venous blood pH was 7.38, and cerebral edema was suspected. The patient's sensorium normalized within 30 min of intravenous mannitol. His pulse reverted to 86 bpm and blood pressure to 120/80 mmHg. A similar trend of alteration of sensorium and vital signs after 6 h prompted mannitol therapy every 8 h for 24 h, after which his course was unremarkable. On follow-up, 9 months after discharge, the patient's HbA_{1c} was 9.2%, and he has microalbuminuria (125 μg/min) and requires insulin for blood glucose control.

To the best of our knowledge, this is the first reported case of cerebral edema outside the setting of diabetic ketoacidosis or hyperosmolar coma. It also highlights a remarkable degree of advanced glycation end product formation (2), as evidenced by very high HbA_{1c}, limited

joint mobility (3), and cataracts at diagnosis. Though the connection, if any, between this high degree of advanced glycation end product formation and cerebral edema is unclear, a long duration of hyperglycemia in a child may serve to provide a high index of suspicion for cerebral edema while starting insulin therapy.

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Adipocytokines as a Novel Target for the Anti-inflammatory Effect of Atorvastatin in Patients With Type 2 Diabetes

Recently, Shetty et al. (1) reported a positive correlation of resistin with C-reactive protein (CRP) in a cross-sectional study of patients with type 1 or type 2 diabetes and patients in a prediabetic state. Collectively, however, little is known about the role of proinflammatory adipocytokines. The adipocyte-secreted hormones leptin and resistin have recently been regarded as proinflammatory cytokines positively associated with CRP in healthy subjects (2) and patients with diabetes (1). Shetty et al. therefore investigated whether atorvastatin may mediate part of its beneficial effects by altering resistin levels. They did find a 20% reduction of plasma resistin after statin treatment. Due to a concomitant decrease in the placebo group, however, this reduction was not statistically significant (1).

In this study, we report that atorvastatin significantly reduced plasma levels of resistin and leptin in patients with type 2 diabetes. In contrast to the Shetty et al. study, we investigated the effect of atorvastatin in a homogeneous population, including patients with type 2 diabetes only. We also investigated a larger number of patients and administered a two-fold higher dose of atorvastatin (40 mg/day).

We studied the effect of atorvastatin on plasma resistin, leptin, and CRP in 87 patients with type 2 diabetes (60 men and 27 women) in a randomized, open, placebo-controlled study, designed with an 8-week intervention period to either atorvastatin ($n = 52$) or placebo ($n = 35$). The relationships between paired variables before and after intervention were analyzed with the paired Student's t test. Two-tailed bivariate correlations were determined by the Pearson coefficient. Results were expressed as means ± SE.

At baseline, resistin levels were positively correlated with plasma CRP ($r = 0.35$, $P < 0.005$) and negatively with HDL cholesterol ($r = -0.26$, $P < 0.02$). Leptin levels were higher in women (22.2 ± 3.7 ng/ml) than in men (15.2 ± 1.3 ng/ml, $P = 0.03$) but did not correlate with plasma CRP. Atorvastatin treatment resulted in a significant reduction in resistin of almost 20% (3.5 ± 0.4 vs. 2.9 ± 0.4 ng/ml, $P < 0.001$) and was furthermore accompanied by a significant decrease in leptin by 40% (20.7 ± 2.3 vs. 12.5 ± 1.1 ng/ml, $P < 0.01$) and in CRP by 39% (3.8 ± 0.6 vs. 2.3 ± 0.3 mg/l, $P < 0.001$). No significant alterations of resistin, leptin, or CRP levels were observed in the placebo group.

These results show, for the first time, a statin-mediated significant reduction in two important adipocytokines in type 2 diabetes. The reduction of resistin, we observed, is similar to the one reported by Shetty et al. In that study, however, the change was not statistically significant because of a similar decrease in the placebo group that was most likely due to chance.

It has been shown that patients with type 2 diabetes benefit from low-dose atorvastatin therapy (3) and that the magnitude of protection may be larger than that observed in nondiabetic populations. This suggests that anti-inflammatory effects, referred to as pleiotropic effects, augment the lipid-lowering effect of atorvastatin therapy. Because proinflammatory adipocytokines are known to be dysregulated in patients with type 2 diabetes (4), it is tempting to speculate that, based on our findings, patients with type 2 diabetes might receive added benefits from a statin-mediated reduction of resistin and leptin.

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Plasma Adiponectin Concentrations Are Independently Predicted by Fat Insulin Sensitivity in Women and by Muscle Insulin Sensitivity in Men

Adiponectin is an abundant plasma protein, mainly secreted by adipocytes and closely linked to insulin sensitivity (1–4). Plasma adiponectin independently correlates with insulin sensitivity (5). Since women have greater plasma adiponectin levels than men (5–7), we determined sex-specific differences in associations between plasma adiponectin and tissue-specific insulin sensitivity in skeletal muscle, liver, and fat.

Plasma adiponectin concentrations were measured (intra-assay coefficient of variation <4%) in 28 men and 28 women (6 men and 6 women had impaired glucose tolerance according to World Health Organization criteria). Insulin sensitivity in skeletal muscle, liver, and fat was determined by insulin-mediated whole-body glucose disposal (*M* values), suppression of hepatic glucose output evaluated during a hyperinsulinemic-euglycemic clamp, and suppression of free fatty acid (FFA) concentrations during an oral glucose tolerance test (OGTT), respectively.

The BMI and body weights of men and women were similar (mean ± SD for BMI 32.11 ± 6.89 vs. 34.24 ± 6.44 kg/m^2, $P = 0.24$; weight, 100.77 ± 23.83 vs. 94.19 ± 19.43 kg, $P = 0.26$). Men were 9 years older than women (52.64 ± 5.29 vs. 43.89 ± 4.22 years, $P < 0.001$). The percentage body fat measured by bioimpedance in women (44.56 ± 5.59%) was 54.5% greater than that in men (28.84 ± 7.85%, $P < 0.001$). It is also important to note that *M* values in men (6.75 ± 3.39 mg · kg^{-1} · min^{-1}) and in women (6.81 ± 2.56 mg · kg^{-1} · min^{-1}) were similar ($P = 0.94$).

Fasting plasma adiponectin concentrations were negatively correlated with hepatic glucose output in men ($r = -0.384$, $P = 0.022$) and women ($r = -0.312$, $P = 0.05$) and were strongly correlated with *M* values in men ($r = 0.58$, $P = 0.001$), whereas this correlation did not reach statistical significance in women ($r = 0.229$, $P = 0.242$). Fasting plasma adiponectin concentrations were correlated with age, BMI, and percentage body fat in men ($r = 0.39$, $P = 0.038$; $r = -0.467$, $P = 0.006$; $r = -0.41$, $P = 0.02$, respectively), but not in women ($r = 0.027$, $P = 0.89$; $r = -0.13$, $P = 0.26$; $r = -0.06$, $P = 0.77$, respectively).

Plasma adiponectin concentrations were strongly correlated with percentage FFA suppression at 40 min in both men ($r = 0.50$, $P = 0.006$) and women ($r = 0.50$, $P = 0.006$) during an OGTT. Those correlations were examined at 40 min during the OGTT because percentage FFA suppression at 40 min correlated significantly with *M* values for both men and women.

When the data were stratified by sex, stepwise multivariate linear regression showed that in men, *M* value was a strong independent predictor (adjusted $R^2 = 0.31$, $P = 0.001$) and remained a strong independent predictor of adiponectin concentration (adjusted $R^2 = 0.39$, $P = 0.002$) when age was also included in the model. In women, however, the percentage FFA suppression was the only independent variable predicting plasma adiponectin concentration, and this model explained ~26.5% ($R^2 = 0.27$, $P = 0.005$) of the variance in plasma adiponectin concentration. When the data sets for men and women were combined, FFA suppression ($P < 0.001$) and sex ($P = 0.023$) were the only independent predictors of plasma adiponectin concentration. The association with sex was independent of body fat and age percentages.

In conclusion, plasma adiponectin is independently predicted by muscle insulin sensitivity in men but by fat insulin sensitivity in women. Of note is the relationship between plasma adiponectin and FFA suppression, rather than total fat mass, suggesting that fat function is more important than total fat mass in determining plasma adiponectin concentrations, particularly in women. Given that visceral adiposity alters insulin sensitivity, any differences in the relationship between plasma adiponectin and measures of fat function and fat location will require further investigation.

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Sexual Dysfunction in Women With the Metabolic Syndrome

Female sexual dysfunction is a largely uninvestigated, yet significant, public health problem, with 43% of women complaining of at least one sexual problem (1). Despite the high prevalence, which appears to surpass that of male sexual dysfunction, only recently has there been some focus on the sexual problems of women. We assessed the prevalence of sexual dysfunction in premenopausal women with the metabolic syndrome as compared with the general female population.

Premenopausal women ($n = 100$) were enrolled if they had three or more of the criteria to meet the diagnosis of the metabolic syndrome, as recommended by the Adult Treatment Panel (2). One hundred women, matched for age, body weight, and premenopausal state, served as the control group. Sexual function was assessed by completing the Female Sexual Function Index (FSFI), which is a validated 19-item self-report measure of six separate domains of female sexual function (3). Four domains are related to the four major categories of sexual dysfunction: desire, arousal, orgasmic, and sexual pain disorder. The fifth domain assesses the quality of vaginal lubrication, and the sixth domain is related to global sexual and relationship satisfaction. Each domain is scored on a scale of 0 or 1 to 6, with higher scores indicating better function. The full FSFI scale score, which could be 36 at the highest, is obtained by adding the six domain scores.

Women with the metabolic syndrome were matched with women of the control group for age (40.2 ± 4.3 vs. 39.1 ± 3.9 years), BMI (27.8 ± 2.9 vs. 26.9 ± 2.8 kg/m^2), and premenopausal state. Compared with the control group, women with the metabolic syndrome had a reduced mean full FSFI score (23.9 ± 5.4 vs. 29.9 ± 4.8, $P < 0.001$). We considered the functional results to be good when the FSFI score was ≥30, intermediate between 23 and 29, and poor when <23. The percentages of women falling within these three categories of FSFI score were 77, 21, and 2%, respectively, for control women and 55, 36, and 9%, respectively, for women with the metabolic syndrome ($P < 0.01$).

In our study, we have shown that women with the metabolic syndrome have an increased prevalence of sexual dysfunctions as compared with matched control women. The complexity of the female sexual response and the limited experimental models available have severely hampered progress in this field. Future research in this area will reveal the clinical significance and possible implications of our findings.

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Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects

The DIAD study

We were impressed by the results of the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects (DIAD) study (1), which found that silent myocardial ischemia (SMI) was present in 22% of a large cohort of asymptomatic patients with type 2 diabetes and that the strongest predictor for abnormal cardiac tests was an abnormal Valsalva test. We have also found that autonomic function predicts SMI but that abnormal sympathetic, rather than parasympathic, tests are predictive.

We selected 12 patients with type 2 diabetes and 12 nondiabetic patients with documented exercise-induced electrocardiogram (ECG) changes (Bruce protocol) and angiographically proven coronary artery disease from the cardiac catheterization database of the Royal Infirmary of Edinburgh, Scotland. The two groups were similar in age (59 ± 2 vs. 62 ± 3 years), number of diseased coronary arteries (2.3 ± 0.2 vs. 2.1 ± 0.2), and exercise characteristics (exercise time 326 ± 24 vs. 308 ± 39 s, maximum ST depression [2.2 ± 0.2 vs. 2.4 ± 0.3 mm]). All subjects underwent five well-validated and standard autonomic function tests (2): R-R interval variation with respiration (parasympathetic), R-R interval variation with the Valsalva maneuver (parasympathetic), supine and erect blood pressure (sympathetic), supine and erect heart rate (parasympathetic), and blood pressure response to sustained handgrip (sympathetic). Each test was scored 0 (normal), 1 (borderline), or 2 (abnormal), and all five

tests were then used to compile an autonomic score between 0 and 10.

Although all 24 patients developed ECG evidence of ischemia during treadmill testing, only 50% developed pain (angina pectoralis [AP] group). In the remaining 50%, exertional ischemia was painless (SMI group). Nine of the 12 patients in the SMI group had diabetes, whereas only 3 of the 12 patients in the AP group had diabetes ($P = 0.013$).

The SMI group had a significantly higher total autonomic score (4.5 ± 0.4 vs. 0.9 ± 0.4), which was largely driven by differences in the two measures of sympathetic autonomic function (supine and erect blood pressure −5.1 ± 3.3 vs. 6.3 vs. ± 4.6 mmHg, $P < 0.05$, blood pressure response to sustained hand grip 6.2 ± 1.8 vs. 14.9 ± 1.7 mmHg, $P < 0.0003$). Two nondiabetic subjects with SMI had clearly abnormal autonomic tests.

Although autonomic neuropathy makes SMI more likely in patients with diabetes, it also occurs in those with normal autonomic function (3). In nondiabetic subjects, autonomic neuropathy does not exhibit a clear associate with SMI, despite the findings in our small series (4,5).

We used a five-test battery of autonomic function tests and found that tests of sympathetic autonomic function were impaired in the SMI group. The DIAD study only used heart rate changes during deep breathing, the Valsalva maneuver, and standing, which tests predominantly parasympathetic function. Abnormal parasympathetic function has been reported in another cohort of patients with SMI and diabetes (4). We have no explanation for the difference between our finding and those of others.

In summary, we concur that SMI is common in subjects with diabetes and autonomic neuropathy. Both parasympathetic and sympathetic pathways may be involved.

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Replacement of Valsartan and Candesartan by Telmisartan in Hypertensive Patients With Type 2 Diabetes

Metabolic and antiatherogenic consequences

Angiotensin II type 1 receptor blockers (ARBs) are widely used in the treatment of hypertension and have been shown to restore impaired intracellular insulin signaling and reduce the incidence of type 2 diabetes (1–3). Telmisartan has a unique property that activates peroxisome proliferator–activated receptor-γ (PPAR-γ) (4–6). We studied the effect of this unique property of telmisartan on insulin resistance and circulating levels of adiponectin and highly sensitive C-reactive protein (hs-CRP) in hypertensive patients with type 2 diabetes.

The study comprised 18 participants with hypertensive type 2 diabetes (9 men and 9 women) aged 36–79 years (64 ± 12, mean ± SD) and treated with valsartan (80 mg/day, $n = 11$) or candesartan (8 mg/day, $n = 7$) for >6 months. None of the changes in clinical and biochemical findings occurred in the subjects during this period. Then, telmisartan (40 mg/day) was administered instead of the ARBs for 12 weeks. Fifteen subjects were treated with antidiabetic agents (13 sulfonylurea, 2 nateglinide) and 3 with diet therapy alone. There were no changes in diet and other medications. No subject received glitazone and insulin. Statistical analysis was performed using Wilcoxon's matched-pair signed-rank test.

Neither systolic nor diastolic blood pressure were significantly changed. Telmisartan treatment resulted in a significant decrease in fasting insulin level (10.7 ± 3.8 to 8.6 ± 2.7 mU/l, $P < 0.01$), although decreases in fasting plasma glucose (132.5 ± 55.1 to 126.5 ± 39.3 mg/dl) and HbA_{1c} (6.89 ± 0.89 to 6.79 ± 0.96%) were not statistically significant. Serum triglyceride levels were significantly reduced from 133.6 ± 51.1 to 118.7 ± 48.1 mg/dl, ($P < 0.05$). Mild improvements in total and HDL cholesterol were also observed after treatment (total cholesterol 197.2 ± 28.2 to 190.5 ± 30.5 mg/dl HDL cholesterol from 47.6 ±11.2 to 48.5 ±12.1 mg/dl). Serum adiponectin was significantly increased (6.95 ± 2.91 to 7.97 ± 3.48 μg/ml, $P < 0.005$), and hs-CRP was decreased (0.154 ± 0.155 to 0.109 ± 0.120 mg/dl, $P < 0.05$). This study also demonstrated the reciprocal association between adiponectin and hs-CRP ($r = -0.53$, $P < 0.01$). Body weight gain and edema never developed.

Adiponectin and hs-CRP are closely related to insulin resistance and development of atherosclerosis (6,7). Our results indicated that telmisartan has beneficial effects on the risk factors for cardiovascular disease, which is a major concern in the treatment of type 2 diabetes. Since all subjects were already treated with ARBs and blood pressure was not changed, the majority of our results were not produced by the further suppression of the rennin-angiotensin system. Our observation in this study is consistent with recent reports that telmisartan, not valsartan, activates PPAR-γ (8). Also, our results are in agreement with recent clinical reports that telmisartan improved insulin resistance or glycemic control (9,10).

Our present findings demonstrate that telmisartan has additional effects on insulin sensitivity and antiatherosclerosis, probably via its effects on PPAR-γ. These findings offer a new idea for the drug targeted to defend against type 2 diabetes with accompanying metabolic disorders.

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High-Dose Glibenclamide Can Replace Insulin Therapy Despite Transitory Diarrhea in Early-Onset Diabetes Caused by a Novel R201L Kir6.2 Mutation

Recently, mutations in the gene *KCNJ11* encoding the Kir 6.2 subunit of the ATP-sensitive K^+ channel (K_{ATP} channel) have been described in patients with permanent neonatal diabetes (1). The K_{ATP} channel complex is an aggregate of four subunits of the Kir6.2 inward rectifier channel plus four regulatory units known as the sulfonylurea receptor (SUR1). In pancreatic β-cells, glucose metabolism leads to a rapid rise in intracellular ATP levels, leading to closure of the K_{ATP} channel. The resultant cell depolarization is critical for normal insulin secretion. Sulfonylureas are able to close the K_{ATP} channel by interacting with SUR1 via an ATP-independent mechanism. As a result, four young patients carrying mutations in the Kir6.2 channel have been treated with sulfonylureas (2,3) and withdrawn from insulin.

To test whether Kir6.2 mutations are present in Chile and to evaluate the response to sulfonylurea treatment, we tested five Chilean patients with diabetes diagnosed before age 6 months (range 0.25-4.1), requiring insulin treatment since diagnosis. The coding region and intron-exon boundaries of the *KCNJ11* gene were sequenced as previously described (1).

A female patient had a novel heterozygous Kir6.2 mutation, R201L (CGT> CTT). She was underweight at birth (2,120 g at 37 weeks' gestation) and presented with severe ketoacidosis at the age of 4.1 months (pH 6.9, plasma glucose 790 mg/dl). Her postnatal development was normal, without seizures or hypotonia. Her parents, who have normal oral glucose tolerance tests, do not carry the mutation.

At the age of 17 months, the sulfonylurea glibenclamide was slowly introduced. Initially, a once-daily dose of 0.1 $mg \cdot kg^{-1} \cdot day^{-1}$ was given for a week and then changed to a twice-daily dose that increased weekly by 0.1 $mg \cdot kg^{-1} \cdot day^{-1}$, allowing a simultaneous decrease in insulin doses. After 8 weeks with the glibenclamide dose of 0.8 $mg \cdot kg^{-1} \cdot day^{-1}$, the insulin was stopped completely. HbA_{1c} levels at the beginning and end of the transition period were 7.3 and 5.9%, and mean patient blood glucose readings dropped from a mean 196 to 155 mg/dl. The patient exhibited mild transient diarrhea (three to six episodes per day of soft stools) when the glibenclamide started and every time the dose was increased up to a dose of 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$. Each episode lasted for 4 or 5 days. After a month off insulin, the patient remained in stable metabolic control with no recurrence of gastrointestinal problems. Optimal glycemic control was achieved by giving the glibenclamide in three equal doses every 8 h.

Insulin concentration did not increase during an intravenous glucose tolerance test (0.3g glucose/kg) performed before glibenclamide was begun. After the 0.8 $mg \cdot kg^{-1} \cdot day^{-1}$ dose was reached and insulin completely withdrawn, the test was repeated and insulin levels increased by 28 pmol/l.

In conclusion, we have described the first reported patient with a spontaneous mutation, R201L, in the Kir6.2 gene. This

novel mutation affects a highly conserved arginine at position R201, which has been shown to be key for ATP binding (1). As seen in the previously reported R201 mutations (R201H and R201C), our patient did not have neurological abnormalities. This child is the fifth reported Kir6.2 patient to be able to discontinue insulin therapy and improve control, although a very high dose (0.8 mg/kg) was needed (equivalent to 60 mg in a 75-kg adult). We report the first case of diarrhea associated with sulfonylurea therapy in a patient with a Kir6.2 mutation, probably related to the action of glibenclamide on inwardly rectifying K^+ channels in the human ileal mucosa (4). This unusual side effect is thought to be dose related and may be relatively common in patients with Kir6.2 mutations who require high doses of sulfonylureas. In our patient, this side effect was transitory, and given the potential benefits of sulfonylurea therapy, we recommend that diarrhea should not immediately lead to the discontinuation of treatment.

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Positive Correlation of Galanin With Glucose in Type 2 Diabetes

Compelling literature (1) has been accumulated regarding the action of galanin as an incretin on insulin secretion. Although galanin inhibits glucose-stimulated insulin release in animals, no such effect has been documented in humans (2). Actually, galanin administration in humans has been shown to suppress the initial postprandial rise in plasma concentration of glucose and insulin (3) with unaltered glucose-stimulated insulin release (2). Nevertheless, basal plasma galanin levels have been shown to diverge with obesity and hormonal status.

We enrolled 21 patients with type 2 diabetes (HbA_{1c} 7.8 ± 1.19%): 9 men (aged 54.6 ± 3.87 years, BMI 28.5 ± 1.6 kg/m^2) and 12 postmenopausal women (follicle-stimulating hormone [FSH] >30 mIU/ml, aged 55.6 ± 3.8 years, BMI 28.4 ± 2.9 kg/m^2) with a maximum disease duration of 4 years. Twenty-four healthy individuals participated in the study as control subjects: 12 men (aged 55.3 ± 3.1 years, BMI 27.4 ± 2.2 kg/m^2) and 12 women (FSH >30 mIU/ml, aged 54.17 ± 3.4 years, BMI 28.19 ± 2.2 kg/m^2) with no history of diabetes, hypertension, liver, or kidney disease. None of the nondiabetic healthy volunteers were taking any medication, and none had a first-degree relative with type 2 diabetes. Written informed consent was obtained from all study participants. Blood samples were collected at rest at 8:00 A.M., after an overnight fast and 24-h alcohol abstention. Human galanin (hGal) (1) was determined by a radioimmunoassay (Peninsula Laboratories, Belmont, CA). Insulin was measured by an enzyme-linked immunosorbent assay (AxSYM; Abbott Laboratories, North Chicago, IL). A two-site sandwich immunoassay, using direct chemiluminescent technology (ADVIA Centaur; Bayer, Leverkusen, Germany) was used for the determination of serum C-peptide.

Interestingly, a statistically significant increase of hGal was found in both women and men with type 2 diabetes compared with control subjects (women 25.6 ± 5.4 vs. 12.2 ± 0.3 pg/ml, $P < 0.001$; men 22.4 ± 2.01 vs. 12.2 ± 1.14 pg/ml, $P < 0.001$).

Additionally, a strong positive correlation of hGal with glucose ($r = 0.963$, $P < 0.001$) and HbA_{1c} ($r = 0.903$, $P < 0.001$) was recorded in the women with type 2 diabetes. In men with type 2 diabetes, the above correlation, though statistically significant, was less strong ($P = 0.05$ and 0.04, respectively).

The increment of insulin was shown in both type 2 diabetic men and women, as compared with control subjects (women 20.36 ± 2.89 vs. 4.0 ± 1.30 μIU/ml, $P = 0.002$; men 15 ± 3.1 vs. 4.36 ± 1.97 μIU/ml, $P < 0.001$), whereas C-peptide was increased significantly only in the women with type 2 diabetes (3.1 ± 1.2 ng/ml vs. 1.3 ± 0.4 ng/ml, $P = 0.001$). Of note, insulin showed a significant negative correlation with glucose only in the women.

In conclusion, a strong positive correlation of hGal has been established with glucose in the fasting state. Galanin appears to be related to the presence of type 2 diabetes and not to the patient's obesity and hormonal status.

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INSULOT

A cellular phone–based edutainment learning tool for children with type 1 diabetes

A particular type of education needs to be designed to encourage, motivate, and boost the confidence of type 1 diabetic patients. "Edutainment" has been recognized as an attractive approach to improving educational outcomes for such patients (1). As an edutainment tool, we have developed a cellular phone–based "game" that we call "INSULOT," a term coined to denote "insulin" and "slot machine." This tool has been implemented and preliminarily evaluated.

INSULOT is a special, three-window slot machine designed to teach the relationships among plasma glucose level, food (carbohydrate grams), and insulin dosage. INSULOT uses algorithms to simulate postprandial glucose levels, while considering distributions to incorporate clinical uncertainties. The first step is to calculate the "carbohydrate grams" in each food using the concept of total available glucose (2). Then, the insulin-to-carbohydrate ratio is used to simulate the amount of carbohydrates absorbed by a one-unit dose of insulin (3). The final carbohydrate gram level is then calculated by subtracting carbohydrates absorbed by insulin from the intake of carbohydrate grams. Finally, INSULOT demonstrates various images based on the appropriateness of the postprandial plasma glucose level, and the combination of these is used to determine the final score for each time the game is played. INSULOT is a Java 2 Micro Edition application, designed for third-generation cellular phone systems. The application can run as a stand alone and also be integrated into a World Wide Web environment. All personal settings for algorithms (e.g., body weight, age) used are stored in a web database system and can be updated from the cellular phone.

The game was evaluated by 30 diabetic patients (12–24 years of age) on the basis of entertainment, usability, and its clinical usefulness at a summer camp in Kochi Prefecture, Japan, in 2003. We used a structured survey of 13 questions with a response scale ranking from 1 to 7 (1 = strongly disagree and 7 = strongly agree). Generally, the patients felt the game was interesting (mean ± SE 5.57 ± 0.22). Approximately 80% of patients thought that INSULOT could be recommended to other type 1 diabetic patients. INSULOT's overall usability was highly scored, and most patients were able to play the game without any instruction. More than 80% of patients agreed that the game was useful as a learning tool (5.44 ± 0.29).

Advantages of cellular phone–based games are their interactivity and portability, which could enhance health care delivery and education. Although there are some concerns about the harmful effects of games on adolescents, it is our role as health professionals to develop ways to make the most of such applications, with the goal being health-outcome improvements. One of the most important, but difficult, issues for any edutainment system is how to establish a balance between education and entertainment. A game does not appeal to users if education is overemphasized; however, it cannot be called a learning tool if the game has little appropriate learning content.

In conclusion, we have successfully developed an edutainment tool that combines fun and learning for young people with type 1 diabetes. Our preliminary evaluation demonstrated that the edutainment provided by our INSULOT game was well received as an efficient and enjoyable learning tool. (More information is available at https://weds.shis.uth.tmc.edu/INSULOT.)

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Four-Digit Insulin Dosing Code

A simple solution for insulin dosing error

Medication errors continue to be an issue in health care. The Institute of Medicine's report, *To Err is Human: Building a Safer Health System*, estimated that medical errors are the eighth leading cause of death in the U.S., with ~7,000 deaths per year occurring from medication errors (1). Insulin is one of the most frequently cited agents and accounts for 13% of all medication errors (2). Human factors (knowledge or performance deficit, miscalculation or preparation of dosage, transcription errors, fatigue, and

Table 1—*Sample schema for insulin prescription*

Insulin type	AC breakfast	AC lunch	AC dinner	HS
NPH/lente	0	0	0	X
Ultralente	0	0	X	0
30/70	X	0	X	0
Regular/insulin analogs	X	X	X	0

AC, before; HS, at bedtime.

computer errors) account for about half (42%) of the medication errors (3). Latin apothecary abbreviations are also prone to misinterpretation. Tenfold insulin overdoses have resulted from the misinterpretation of the abbreviation "U" (for units) as a zero when closely followed by a number of written orders (4). The Institute for Safe Medication Practices recommends spelling out the word "units" for the abbreviation "U." Similarly, the letter "I " of IU (international units) may be misinterpreted as the number "1" (5). Recently, I had a case where despite spelling out the word "units," the patient received 10 times the prescribed dose of insulin because the nurse mistook the letter "U" in the word "Units" for a "0."

I believe that the following standard code to write insulin orders should be advocated to all health care providers and patients until a computerized physician-order entry system becomes the standard. Using the standard code, insulin dose is prescribed in a code of four numbers, where the first three numbers represent the premeal doses and the last number represents the bedtime dose. A schema is shown in Table 1.

For a patient receiving 10 units NPH insulin at bedtime and 6 units regular insulin before breakfast, 4 units before lunch, and 8 units before dinner, the doses could be simply written as follows. NPH: 0-0-0-10; regular: 6-4-8-0.

Each dose, as shown above, would be separated with a hyphen (-) and not with a slash (/), since a slightly different angle of slash could be mistaken for the number "1." For patients who are NPO and receiving insulin, the doses could be written in a similar form depending on the frequency of dosing. For example, analog insulin every 4 h may be written as 4-6-5-5-0.

Using this code, no other words or abbreviations that may be mistaken for zero or one (like U or IU) are added after the dose. I find this method to be a simple, safe, and effective communication tool and suggest promoting it as the standard code for insulin dosing to patients and health care professionals around the world.

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COMMENTS AND RESPONSES

The Burden of Treatment Failure in Type 2 Diabetes

Response to Brown et al.

In the July 2004 issue of *Diabetes Care,* Brown et al. (1) conclude by stating, "our results strongly suggest that the recommended [HbA_{1c}] threshold for [treatment] action should be 7.0% or lower" and "an even stronger signal would be provided by a treatment threshold of 6.0%, which has proved widely achievable in the test phase of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study."

We would like to point out that the ACCORD Vanguard ("test phase") results have not been published or presented and are not available in the citation given. (Brown et al. referenced a URL [http://apps.nhlbi.nih.gov/clinicaltrials/background.asp] that cannot be directly reached but can be accessed via http://apps.nhlbi.nih.gov/clinicaltrials/, selecting "Diabetes Mellitus," clicking on "submit," clicking on the ACCORD trial, and then clicking on "background.") More importantly, however, Brown et al. fail to acknowledge that treatment targeting HbA_{1c} <6.0% (or, in the authors' words, a "treatment threshold of 6.0%") has not been proven to improve health outcomes, either microvascular or macrovascular. Not only is such a treatment strategy extremely difficult, but there are potential adverse consequences, such as hypoglycemia and drug-specific side effects. There is currently no sound basis to recommend such targets in clinical practice.

The ACCORD trial is designed to determine whether a therapeutic strategy that targets HbA_{1c} <6.0% reduces cardiovascular disease events in type 2 diabetes. Microvascular events are a secondary outcome. Results from ACCORD and other pending studies are needed to inform clinical practice on this issue.

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Antihypertensive Therapy and Incidence of Type 2 Diabetes in an Elderly Cohort

Response to Padwal et al.

We read the study by Padwal et al. (1) with great interest and feel that it warrants comment. In this retrospective observational cohort study of a large number of elderly patients (n = 725,469, mean age 72–73 years) but of short duration (mean follow-up period of 9.5–11.6 months), the authors found that incidence of new-onset type 2 diabetes was not different among the four major classes of antihypertensive drugs (ACE inhibitors, β-blockers, calcium channel blockers, and thiazide diuretics). Their findings were in total conflict with other well-conducted prospective studies using ACE inhibitors. For instance, in the CAPPP (Captopril Prevention Project), HOPE (Heart Outcomes Prevention Evaluation), and the more recent PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) studies, it has been consistently shown that patients treated with ACE inhibitors (captopril, ramipril, and trandolapril, respectively) have significantly lower incidence of new-onset type 2 diabetes (2–4). These studies were of a sufficiently long follow-up period (>4 years).

Two factors may account for the surprise findings observed in the Padwal et al. study. First, the study subjects were all elderly patients with a mean age of 72–73 years. Patients who had already developed type 2 diabetes before their enrollment age (≥66 years) were excluded. Those who had not developed diabetes were clearly protected by certain intrinsic or environmental factors. Hence, there is a profound element of selection bias, something that is likely to exist in studies that are retrospective in nature. Second, the short mean follow-up duration of 9.5–11.6 months is hardly sufficient for drug-induced glucose intolerance to occur, even for their large sample size. Given these two critical limiting factors, it is not surprising that they even found β-blockers to be "protective" against the development of diabetes.

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Antihypertensive Therapy and Incidence of Type 2 Diabetes in an Elderly Cohort

Response to Chan et al.

We thank Chan et al. (1) for their interest in our article and agree that selection bias and a relatively short duration of follow-up (primarily due to a high rate of censoring) are potential limitations to our study. These and other potential limitations are described in detail in our discussion section (2). It should be noted that the cohort was comprised of 76,176 individuals in the primary analysis and 100,653 individuals in the secondary analysis (instead of 725,469 individuals, as referenced by Chan et al.).

We have previously systematically reviewed the evidence regarding antihypertensive drug therapy and type 2 diabetes incidence, including the ACE inhibitor drug class (3). Based on current evidence, we cannot confidently conclude that ACE inhibitors prevent diabetes. Chief among our concerns is the fact that no placebo-controlled ACE inhibitor trial has ever evaluated diabetes incidence as a blinded, predefined, primary end point, although such trials are currently underway (2). Chan et al. mention the PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial, in which diabetes incidence was assessed in a post hoc analysis (4). How many other ACE inhibitor trials have found nonsignificant results for this end point in post hoc analysis and, hence, have not published the results? Additional potential limitations of studies to date include treatment contamination, failure to control for concomitant drugs affecting glycemic control, the lack of a placebo control group, and a lack of laboratory confirmation of diabetes cases.

However, the critical question is not whether ACE inhibitors lower diabetes incidence, but whether this reduction represents a true preventative effect rather than the simple masking or delaying of latent diabetes by lowering glucose levels below an arbitrary diagnostic threshold. Do ACE inhibitors prevent diabetes-

related complications independent of their blood pressure–lowering effects? Does this putative, preventative effect persist when the drug is stopped? Does therapy stabilize or even reverse β-cell dysfunction and/or insulin resistance? Because the interval between the onset of β-cell dysfunction and overt diabetes averages 10 years (5), the answers to these and other questions will require rigorously designed trials with much longer durations of follow-up. Accordingly, we feel that the role of ACE inhibition in the prevention of type 2 diabetes is far from definitively established.

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Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections: The Impact of Baseline A1c

Response to Retnakaran et al.

Retnakaran et al.'s (1) recent pooled analysis showed improved glycemic control (when using rapid-acting insulin analogs) with continuous subcutaneous insulin infusion (CSII) therapy compared with multiple daily insulin injection (MDII). However, given that CSII users are known to be a well-motivated patient population with far greater adherence to particularly frequent glucose monitoring (often seven or more times per day) and also to have frequent contact with diabetes educators (specifically pump trainers), one wonders if similarly motivated, MDII-treated individuals might have had equivalent improvement in glycemic control. Do Retnakaran et al. have data reflecting objective determination of measures of motivation and adherence (such as frequency of blood-glucose monitoring, frequency of contact with diabetes educators, use or non-use of carbohydrate counting, etc.)? If so, could they comment as to whether this additional information would impact their analysis and conclusions?

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Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections: The Impact of Baseline A1c

Response to Blumer

We agree with Blumer's (1) contention that patients with type 1 diabetes using continuous subcutaneous insulin infusion (CSII) therapy represent a well-motivated patient population. In this context, he asks whether differences in patient motivation (as reflected in adherence to frequent self-monitoring of blood glucose and regular contact with diabetes educators) may underlie the finding of improved glycemic control with CSII as compared with multiple daily insulin injection (MDII) therapy in our recent pooled analysis of randomized controlled trials comparing CSII and MDII therapy using rapid-acting analogs in adults with type 1 diabetes (2).

Given the clinical trial setting and the crossover nature of the data reported, we feel that differences in patient motivation are likely not the basis for the observed results. Specifically, the data included in the analysis are from randomized clinical trials, in which treatment allocation (i.e., CSII vs. MDII) was randomized and clinical management (i.e., frequency of clinic visits) was standardized. Accordingly, one would not expect systematic bias regarding patient motivation and adherence to be a significant factor. Furthermore, it is particularly important to note that the pooled analysis (Fig. 2 in ref. 2) shows the impact of baseline glycemic control on mean improvement in A1c by treatment modality in those patients for whom crossover data were available. As such, the relationship between greater improvement in A1c with CSII versus MDII in those patients with poorer baseline glycemic control was demonstrated in a patient population in which intrapatient treatment effect could be studied (since the crossover patients, by definition, had standardized treatment periods using each of CSII and MDII during the clinical trials in question). Thus, because this

comparison between CSII and MDII was performed in the very same patients, we feel that differences in patient motivation likely did not affect the observed findings.

While patient motivation may not underlie our findings, we nevertheless strongly agree with the contention that patient-driven factors, such as willingness to assume substantial responsibility for their own care, can greatly impact the effectiveness of intensive insulin therapy in clinical practice. As recommended in the American Diabetes Association position statement on insulin pump therapy (3), patient motivation must remain an important factor to consider when evaluating the suitability of CSII for an individual patient.

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