OBSERVATIONS

U-Shaped Association Between White Blood Cell Count and Fasting Plasma Glucose Level

It is well known that hyperglycemia is associated with increased mortality from cardiovascular disease (CVD) and all-cause mortality. It has recently been reported that subjects with low fasting plasma glucose (FPG) levels also had a high risk of CVD and all-cause mortality (1). However, there is a paucity of information about the etiologic basis underlying the association between low FPG and increased CVD and all-cause mortality. Thus, in the present study, we investigated the association of FPG levels with white blood cell (WBC) counts, which indicate a state of low-grade systemic inflammation.

We investigated the cross-sectional association of WBC counts with FPG levels among 3,256 Japanese men aged 34–69 years. The subjects were divided into six categories according to FPG level: <80 mg/dl, 80 to <90 mg/dl, 90 to <100 mg/dl, 100 to <110 mg/dl, 110 to <126 mg/dl, and diabetes.

The crude mean WBC counts were 6,409, 6,308, 6,111, 6,111, 6,109, and 6,610 cells/mm^3 in the subjects with FPG levels of <80 mg/dl, 80 to <90 mg/dl, 90 to <100 mg/dl, 100 to <110 mg/dl, 110 to <126 mg/dl, and diabetes, respectively. The crude mean WBC counts differed significantly by FPG category and showed a U-shaped association with FPG levels (*P* value for quadratic trend <0.001). Even after adjusting for age, BMI, smoking, alcohol, health status, and other factors associated with elevated WBC count or glycometabolism, the respective adjusted-mean WBC counts were 6,273, 6,255, 6,175, 6,165, 6,075, and 6,429 cells/mm^3. The WBC count maintained a U-shaped association with FPG level (*P* value for quadratic trend = 0.041).

Although it is well known that hyperglycemia is the cause of microvascular complications in several organs, there are few studies on the adverse effect of hypoglycemia. Early studies of hypoglycemia focused on brain damage and heart dysfunction. An acute decrease in FPG is recognized as the cause of them, whereas the long-term effect of low FPG remains unclear.

Infection and inflammation may contribute to vascular injury and atherogenesis. Inflammation may also promote atherosclerotic plaque ruptures and thrombosis (2,3). WBC serves as an important biomarker for these disease processes.

This study shows that the U-shaped association between WBC counts and FPG levels (especially low FPG levels) involves higher WBC counts that could not be linked to inflammatory disease or other factors or to any disease known to increase WBC counts. These findings suggest that a state of low-grade systemic inflammation may be present not only in diabetic subjects but also in people with low FPG, possibly explaining in part the high risk of CVD and all-cause mortality of such people.

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Impact of an Intramural Competition on Outcome of Diabetes Care

The translation of research results in diabetes (1) to clinical practice continues to be a major challenge (2,3). Physicians in training present a unique opportunity for shaping practice behavior. We tested the effect of an intramural contest on the outcome of diabetes management by 155 medical residents at a major U.S. teaching hospital. The contest was approved by the house staff leadership and was set for a 6-month period (1 October to 30 April). The residents, organized into four firms (A, B, C, and D), used various strategies (e.g., didactic lectures, case-based learning, and journal reviews) during weekly firm meetings to enhance competitiveness.

The outcome measures were HbA_{1c} levels (primary) and testing frequency (secondary). These data, extracted from 100 randomly selected charts of diabetic patients from each firm, were compared during and 6 months before the contest. Data from patients who had two or more HbA_{1c} results during the contest were used for analysis of the primary outcome. The "baseline" HbA_{1c} was the first measured value during the contest, and the "final" HbA_{1c} was the last result obtained before conclusion of contest. For comparison, HbA_{1c} data obtained during the 6 months preceding the contest ("precontest") were analyzed. Results are means ± SE. Statistical analyses were by paired *t* test for changes in HbA_{1c} values, and the χ^2 test was used for HbA_{1c} testing frequency. The prizes included a plaque and

$1,500 to the firm with the greatest reduction in HbA_{1c} level, a plaque and $1,000 to the firm with second best HbA_{1c} result, and $500 to the firm with the third best HbA_{1c} outcome.

For the primary outcome, the number of patients with evaluable data (i.e., two or more HbA_{1c} values during the contest) were 35, 31, 32, and 38 in firms A, B, C, and D, respectively. The changes in HbA_{1c} were -0.70 ± 0.40, -0.12 ± 0.35, -0.54 ± 0.34, and -0.21 ± 0.28% for patients in firms A–D, respectively. Next, we evaluated the frequency of HbA_{1c} testing: of the 400 patients, 180 (45%) had one HbA_{1c} measurement during the precontest period as compared with 263 (66%; $P < 0.001$) postcontest. The number of patients with two HbA_{1c} tests in 6 months were 57 (14%) precontest and 136 (34%; $P < 0.001$) postcontest. Analyzing all HbA_{1c} data, the mean precontest value was 9.3 ± 1.8% ($n = 180$) vs. 8.8 ± 1.9% ($n = 263$) postcontest. Among patients with two or more HbA_{1c} data, the change in HbA_{1c} over 6 months was 0.01 ± 0.2% precontest and -0.5 ± 0.2% postcontest ($P = 0.015$).

This study shows that intramural competition can be an effective motivational tool for diabetes care providers. The contest generated an increased tempo of diabetes-related educational activities among house staff, which translated to improved glycemic control. Improvement in diabetes control requires a committed approach: more frequent patient contacts; prompt reaction to test result, including home blood glucose data; dietary reinforcement; and medication adjustments, among others. Because the skills developed during the diabetes contest could have a lasting effect on the practice style of physicians, disease-specific intramural contests might be a useful tool for enhancement of clinical skills during residency training programs. Competitive pressure, desire for recognition, and increased awareness of standards of care probably accounted for physician motivation in this exercise, rather than mere financial reward (4).

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Diabetes, Nitric Oxide, and Heat Shock Proteins

Heat shock proteins (Hsps) or stress proteins are a highly evolutionary conserved family of polypeptides that are cytoprotective, protecting proteins, lipids, and nucleic acids from damage by reducing oxidation, preventing apoptosis, suppressing proinflammatory cytokines, repairing ion channels, and aiding in protein folding (1). Hsps have recently been found to be low in individuals with type 2 diabetes, moderately low in the nondiabetic identical twin with a diabetic co-twin, and low in individuals with type 1 diabetes (2). Furthermore, in a study comparing 5,600 genes of nondiabetic subjects with those of insulin-resistant diabetic subjects, Hsp 70 was 1 of only 17 genes that were markedly lower in individuals with diabetes (3). The data suggest that low Hsps in diabetes may be an acquired as well as an inherited genetic defect. Interestingly, a study of individuals with type 1 diabetes with neuropathy observed that α-lipoic acid administration was associated with restoration of nitric oxide (NO) production, restoration of Hsp levels, and improvement in neuropathic symptoms (4). NO synthesis increases Hsp expression, whereas blocking NO synthesis lowers Hsp expression (5). Relevantly, medications that have been associated with improved outcome in diabetes—β-adrenergic blockers (6), HMG CoA reductase inhibitors (7), ACE inhibitors (8), and thiazolidinediones (9)—have all demonstrated restoration of endothelial NO synthase, which may result in Hsp expression and cytoprotection from the metabolic stresses of diabetes. Exercise increases NO production (10) and increases Hsp expression (11), perhaps contributing to the improved outcomes associated with exercise and diabetes. Importantly, a drug designed to increase Hsp expression, bimoclomol, improves diabetic retinopathy, neuropathy, nephropathy, wound healing, cardiac ischemia, and insulin resistance in laboratory diabetic animal models (12,13). Finally, heat therapy, via hot tub immersion, improves diabetic glycemic control and symptomatic diabetic neuropathy in patients with type 2 diabetes (14).

Decreased Hsps in type 1 and type 2 diabetes may be a primary factor leading to the development of diabetes and its diverse, widespread organ damage. Therapy directed at raising Hsps may limit the development of diabetes, but may also reduce the morbidity and mortality in those with diabetes.

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Heteroplasmic Mitochondrial DNA 3310 Mutation in NADH Dehydrogenase Subunit 1 Associated With Type 2 Diabetes, Hypertrophic Cardiomyopathy, and Mental Retardation in a Single Patient

The patient of this letter is a 57-year-old Japanese man with type 2 diabetes and mental retardation with maternal inheritance. The younger of his two sisters was healthy. An echocardiography and a myocardial biopsy revealed hypertrophic cardiomyopathy in the patient. Electron microscopic examination showed a marked increase of mitochondria and abnormal cristae in the myocardial fibers. Autopsy revealed both decrease and atrophy of pancreatic islets of Langerhans. Immunohistochemical staining showed a selective decrease of β-cells. Based on these findings, mitochondrial disease was suspected.

The mtDNA of the patient and his two sisters was studied by cloning and sequencing. Three unique point mutations were found in the patient's lymphocytes. Two point mutations (C11215T and A15874G) were silent. The other mutation was C3310T in the ND1 gene. Two clones of mtDNA without the C3310T point mutations were obtained from the patient's pancreas. However, all mtDNA extracted from the patient's other tissues and his sisters' lymphocytes had this mutation. None of the mtDNAs extracted from lymphocytes from 97 patients with type 2 diabetes and 82 normal control subjects that were evaluated by PCR–restriction fragment length polymorphism (PCR-RFLP) had this mutation. Informed consent was obtained from all participants.

The ND-1 gene encodes the NADH dehydrogenase (complex I) subunit 1. The C3310T point mutation replaces the hydrophobic amino acid proline with the hydrophilic serine. Other mutations in this region have been reported to be associated with diabetes (1,2) and Leber's hereditary optic neuropathy (3). All reported mtDNA point mutations in this region have been homoplasmic. It has been assumed that other unknown pathogenic mtDNA changes, nuclear DNA changes, or environmental factors are involved in disease causation (1).

We obtained two mtDNA samples without the mutation from the patient, suggesting that the C3310T point mutation is heteroplasmic and the single pathogenic gene. However, other samples, even from the healthy sister, had only mutant mtDNA. Therefore, other factors cannot be ruled out. Since this mutation was not detected by PCR-RFLP, it is likely to occur rarely.

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A New Case Of Lipoatrophy With Lispro Insulin In Insulin Pump Therapy

Is there any insulin preparation free of complications?

Lipoatrophy as a cutaneous complication of insulin therapy has been extremely rare since the introduction of recombinant human insulin. Lispro insulin was not reported to be associated with this complication, but recently, Griffin et al. (1) published the first two cases of lipoatrophy associated with lispro insulin in two insulin pump–treated patients. We observed a singular case in which lipoatrophy occurred in two different locations with both buffered human regular insulin and lispro insulin in a patient treated by continuous subcutaneous insulin infusion (CSII).

We studied a 29-year-old Caucasian woman diagnosed with type 1 diabetes at 23 years of age. She began intensified insulin therapy with two premixed insulin injections before breakfast and dinner and regular insulin before lunch (22 units/day, 64% NPH insulin). She developed a primary hypothyroidism 1 year later and started treatment with sodium levothyroxine. She was transferred to our hospital in 1998. In the following 2 years, several combinations of NPH and regular insulin were used to reduce hypoglycemia, but optimized blood glucose was not achieved.

She began CSII (MiniMed 507 C; Soft-set Micro) with human regular insulin (Actrapid; NovoNordisk) in December 1999. Under CSII, HbA_{1c} improved to 6.6–6.8% and the number of hypoglycemic episodes were reduced. Seven months after initiation of CSII, lipoatrophy was noted in the subcutaneous tissue of the anterior abdominal wall (Fig. 1*A*), although frequent change of catheter site every 3 days was performed. Initially, she was prompted to avoid the abdominal area for catheter insertion, but therapy was continued with buffered human regular insulin.

Treatment was also changed from buffered regular human insulin to lispro insulin 10 months later, due to deterioration of metabolic control. Eleven months after the initiation of lispro and using another 6-mm Teflon catheter (Quick-set), she noticed a new area of lipoatrophy on the right buttock, but it was of lesser extension (Fig. 1*B*). Both areas of lipoatrophy persisted until the date of submission for this article, and no further progression of skin lesions has been seen.

This case confirms a previous observation that lispro insulin might also induce lipoatrophy (1). Interestingly, lipoatrophy in our patient was associated

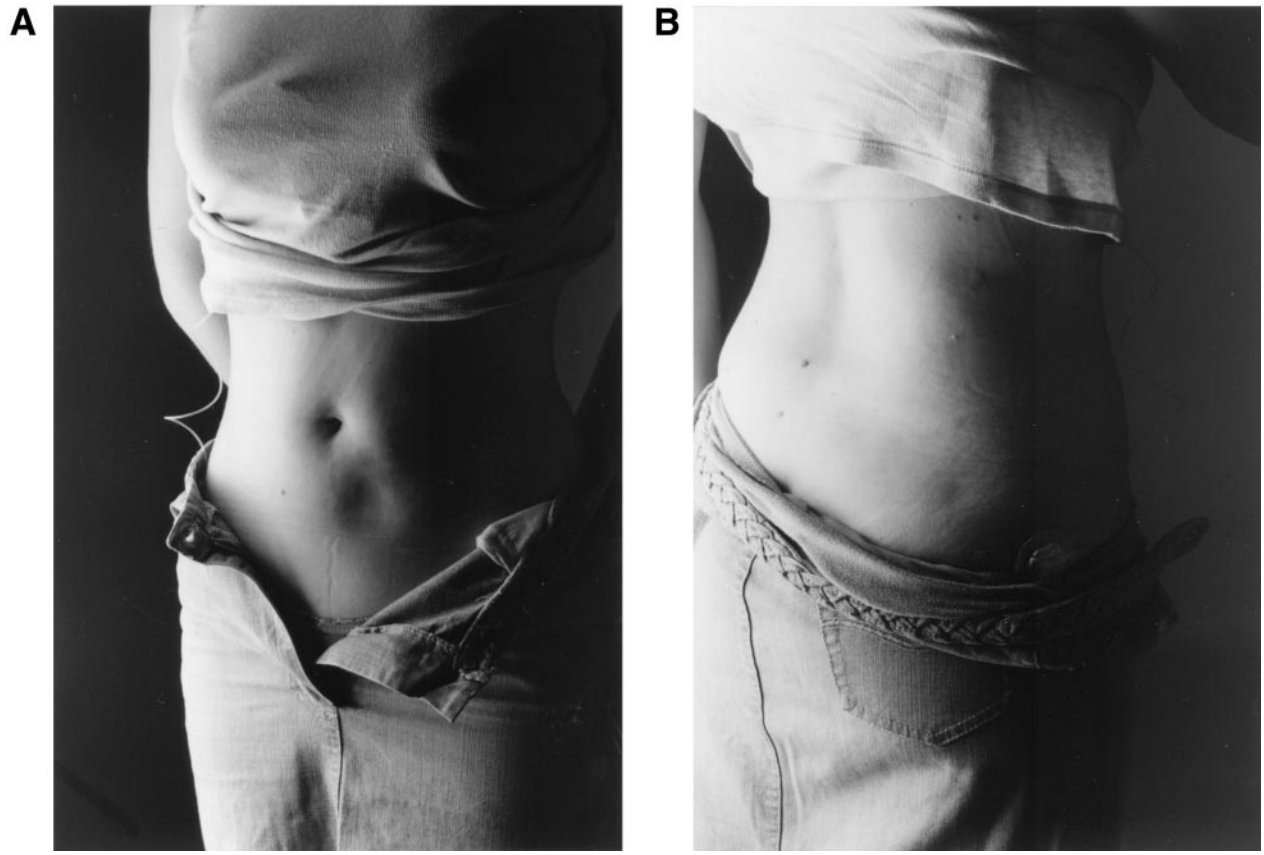

Figure 1—*Lipoatrophic area due to human regular insulin* (A) *and to lispro insulin* (B).

with both lispro and recombinant human insulin. Although the lispro-induced lipoatrophic area was smaller, this case pointed out that local factors related to CSII use might play also a role. Nowadays, teflon catheters are the most common infusion sets used by pump-treated patients. They are placed by means of specially-designed devices. Although teflon cannulae are soft and comfortable, they could also induce local changes that lead to lipoatrophy in susceptible patients.

It has been previously suggested that lipoatrophy results from a local immune reaction to insulin crystals (2). The inflammatory response includes local hyperproduction of tumor necrosis factor-α from macrophages that led to differentiation of adipocites (lipoblastoma-like lipoatrophy) (2). Because lispro and recombinant human insulin had similar immunogenicity (3), the exact role of insulin autoantibodies is unclear. The reason that the lispro-induced lipoatrophic area in our patient was smaller may be related to the reduced ability of lispro insulin to aggregate.

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Intensive Insulin Treatment and QT-interval

Rate-corrected QT-interval (QT_c) and QT-dispersion (QT_{disp}) are two related electrocardiographic variables that, apart from assessing the autonomic dysfunction, can also predict cardiac death in diabetic patients. Several studies have suggested that change of QT_{disp} reflects the "dynamic pathological process" in a variety of cardiac diseases. Particularly, QT_{disp} was found to increase significantly during ischemia and to decrease after anti-ischemic treatment during acute coronary syndromes (ACS) (1).

The beneficial effect of optimal metabolic control achieved by intensive insulin therapy on the outcome of diabetic patients suffering from acute myocardial infarction has already been reported (2). Nevertheless, hyperinsulinemia has also been reported to increase QT_c and QT_{disp} in healthy subjects (3). The potential effect of intensive insulin administration during ACS on the electrocardiographic ventricular repolarization variables remains to be elucidated.

We studied 66 non–insulin-treated type 2 diabetic patients with ACS without ST-segment elevation and no previous myocardial infarction. A total of 31 patients were randomized to receive conventional anti-ischemic therapy plus intensive insulin treatment (group A), and 35 received conventional therapy only (group B). Group A patients received soluble insulin by infusion for 72 h according to a predefined protocol aiming to maintain near-normal glycemia (4). Group B patients were treated according to coronary care unit usual care, with oral hypoglycemic drugs or two daily doses of intermediate-acting insulin.

QT-interval variables were determined on two occasions: admission and 72 h later. A single investigator with no knowledge of the clinical data interpreted QT-intervals manually. QT-values were corrected for heart rate using Bazett's formula ($QT_c = QT/RR^{-1}$). QT_{disp} was calculated as the difference between the longest and shortest measured QT-interval. Informed consent was obtained from all patients.

The two groups were comparable according to baseline clinical and investigative characteristics. In group A, glucose values were maintained within near normoglycemic range during the study period (group A versus B: 7.1 ± 1.6 vs. 10.9 ± 2.7 mmol/l^{-1}, $P < 0.001$). At 72 h, QT_{disp} decreased significantly only in group A patients (QT_{disp} 72 h: 46 ± 24 vs. 58 ± 19 m/s, $P < 0.05$), supporting the hypothesis that a more homogeneous electrical recovery state of myocardium was achieved by optimal glycemic control. Conversely, QT_c showed a trend to increased values in intensively treated patients (QT_c 72 h: 429 ± 37 vs. 409 ± 45 m/s, $P = 0.072$). This observation was rather disappointing, since QT_c prolongation is another key factor that predisposes to cardiac arrhythmias, especially in ischemic conditions. Importantly, the change in potassium was not correlated to the degree of QT prolongation.

Our findings stress that the impact of intensive insulin treatment on repolarization of the diabetic heart during ACS is rather controversial. One may remember the phrase of Hippocrates in one of his writings 25 centuries ago, "As to diseases, make a habit of two things—to help, or at least to do no harm" (5).

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Pitfalls in the Laboratory Diagnosis of Diabetic Ketoacidosis in Gitelman's Syndrome

Gitelman's syndrome (GS) is an autosomal recessive primary renal tubular disorder with hypokalemic metabolic alkalosis, hypocalciuria, and magnesium deficiency (1). The association of GS and type 1 diabetes is rare, and diabetic ketoacidosis (DKA) in GS has not been reported.

A 14-year-old male with known GS diagnosed at 5 years of age and type 1 diabetes diagnosed at 9 years of age was admitted to the hospital with nausea, vomiting, abdominal pain, and dehydration. Patient had history of omission of his insulin, potassium, and magnesium regimens. He was noted to be alert, afebrile, and tachycardic with normal respiration. Other clinical findings included a fruity breath odor, dry mucous membranes, and decreased skin turgor. Admission laboratory profile revealed the following: plasma glucose 555 mg/dl with strongly positive serum and urine ketones, arterial pH 7.37, calculated anion gap 34, serum sodium 134 mmol/l, potassium 2.2 mmol/l, bicarbonate 9 mmol/l, chloride 91 mmol/l, magnesium 1.3 mg/dl, and HbA_{1c} 10.3%. Electrocardiogram demonstrated sinus tachycardia and flat T-waves. Hospital management included restoration of intravascular volume and correction of serum electrolytes. Hyperglycemia, ketonemia, and the anion gap metabolic acidosis resolved after 2 days of intravenous insulin infusion. He was discharged after an extensive education focused on improving compliance with his prescribed therapy.

This is the first reported case of DKA in the setting of GS. In Gitelman's variant of Bartter's syndrome, a putative loss-of-function mutation in the thiazide-sensitive NaCl cotransporter located in the apical membrane of the distal convoluted tubule leads to polyuria, inappropriate kaliuresis, and hypomagnesemia (2). DKA has been described as the biochemical triad of hyperglycemia, ketonemia, and metabolic acidosis (3). The diagnosis of DKA can be confounded by the coexistence of combined acid-base disorders, where the metabolic acidosis is the less prominent component. The underlying chronic hypochloremic metabolic alkalosis associated with GS, compounded with acute vomiting, concealed the severe acute diabetic metabolic ketoacidosis on the initial presentation. This case presentation illustrates the importance of the anion gap calculation in the laboratory evaluation of DKA, where a misleading normal arterial pH due to a mixed acid-base disturbance may delay diagnosis, disposition, and optimal therapeutic interventions.

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Austronesian-Speaking People in Papua New Guinea have Susceptibility to Obesity and Type 2 Diabetes

Obesity is a common phenomenon in Europe and North America. The increasing prevalence of obesity is, however, not confined merely to these areas. The most striking increase is seen in the pacific region. With the increment of the prevalence of obesity, type 2 diabetes is also increasing across the world. Although the prevalence of diabetes in the Papua New Guinea (PNG) population was reported to be virtually 0% (1), recent surveys showed that type 2 diabetes has become a common disease in some urban Melanesians of PNG (2,3). To clarify the genetic background of this increase of type 2 diabetes in PNG, Pro12Ala substitution in peroxisome proliferator–activated receptor (PPAR)γ2 and Trp64Arg substitution in β3-adrenergic receptor (AR) were analyzed by the PCR/restriction fragment–length polymorphism method (4,5).

Blood samples were collected from Austronesian-speaking Balopa Islanders of PNG. This study was conducted in 12 Balopa villages in 1994 with approval of the PNG Medical Advisory (6). To elucidate whether these polymorphisms were associated with obesity, the subjects were enrolled into three groups: nonobese group ($20 \leq BMI < 23$ kg/m^2), overweight group ($25 \leq BMI < 30$), and obese group ($30 \leq BMI$). The subjects who had obvious family history of obesity were omitted from the nonobese group.

The Pro12Ala substitution in PPARγ2 gene was analyzed in a total of 252 subjects (135 in the nonobese, 44 in the overweight, and 73 in the obese). Analysis of PPARγ2 had revealed that the Pro12Ala substitution was not found in any groups. We then examined Trp64Arg polymorphism in β3-AR gene. The Trp64Arg polymorphism was analyzed in a total of 175 subjects (106 in the nonobese, 21 in

the overweight, and 48 in the obese). The frequencies of Trp/Trp, Trp/Arg, and Arg/Arg were 82.1%, 17.0%, and 0.9% in the nonobese group, 61.9%, 33.3%, and 4.8% in the overweight group, and 64.6%, 33.3%, and 2.1% in the obese group, respectively. The allele frequencies of the Arg64 in the nonobese, the overweight, and the obese groups were 9.4%, 21.4%, and 18.8%, respectively. The genotype frequencies of Trp/Arg and the mutant allele frequencies were significantly higher in the overweight and the obese subjects than in the nonobese subjects. There was no significant difference between the overweight subjects and the obese subjects.

Since it has been reported that the Pro12Ala substitution in PPARγ2 is associated with lower BMI, improved insulin sensitivity, and lower prevalence of type 2 diabetes (7), the Pro12Ala polymorphism in PPARγ2 is considered to have a preventive effect against the development of obesity and type 2 diabetes. The absence of the Pro12Ala substitution in PNG people had suggested that people in PNG have susceptibility to obesity and type 2 diabetes. In addition, the frequency of Trp64Arg polymorphism in the β3-AR in PNG subjects was significantly higher in the overweight and obese subjects than in the nonobese subjects. Thus, the Trp64Arg polymorphism in the β3-AR seems to be one of major genetic factors related to obesity in subjects of PNG.

As genes we had analyzed in the present study are considered to be thrifty genes, people in PNG are thought to have thrifty genotype. Austronesian-speaking people in PNG have been reported to share the same genotype with Polynesians. Therefore, it is expected that the prevalence of obesity and type 2 diabetes will increase at least to the same extent as currently seen in Polynesians with westernization of their lifestyle (8).

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Metformin-Induced Hemolytic Anemia in a Patient With Glucose-6-Phosphate Dehydrogenase Deficiency

Metformin-induced hemolytic anemia has been reported only twice. Here we describe another case of hemolysis associated with the initiation of metformin therapy.

A 68-year-old married woman of North-African Jewish descent was admitted to our internal medicine department due to newly diagnosed diabetes, with weakness, presyncope, and blood glucose levels as high as 500 mg/dl. There was no acidosis, HbA_{1c} was 14%, and C-peptide was below normal. A low-sugar diet was started, together with metformin 850 mg t.i.d. and repaglinide 1 mg t.i.d., in addition to ramipril 1.25 mg daily because of albuminuria and elevated blood pressure. On the seventh hospital day the patient was discharged euglycemic, in stable condition.

A week later she presented to the emergency room with extreme weakness, and anemia was noted, which was not present on previous laboratory examinations. The hemoglobin was 8 g/dl, having fallen from 12 g/dl the previous week. No history or signs of gastrointestinal bleeding were found, and stools for occult blood were negative. Mild jaundice was noted; otherwise the physical examination was unremarkable. Mean corpuscular volume was 96 fl, and the reticulocyte count was 11%, with marked polychromasia on peripheral smear. The serum iron, transferrin, serum levels of vitamin B12, and folic acid were normal, and ferritin was high. Serum bilirubin rose to 35 mmol/l, most of it (27 mmol/l) indirect; plasma lactate dehydrogenase concentration was at the upper limit of normal; plasma haptoglobin concentration was low; and the direct Coombs test was negative. The abdominal ultrasound was normal.

Metformin was discontinued, and treatment with ramipril and repaglinide was continued. After transfusion of two units of erythrocytes, the hemoglobin rose to 11 g/l and remained stable (>2 months of follow-up). One month after discharge, red cell glucose-6-phosphate dehydrogenase (G6PD) activity was found significantly decreased.

Metformin-induced hemolysis seems to be a very rare complication of therapy, as this is only the third case reported in the literature (1,2). In all three cases, hemolysis appeared during the first 12 days of therapy; only in one case was the Coombs test positive (2), and the G6PD activity was normal in both previous cases.

This is the first case in which G6PD activity was found significantly decreased. It is possible that in our patient, metformin caused G6PD-mediated hemolysis or the hemolysis induced by metformin was not related to the presence of the G6PD deficiency. There was no precipitating event (fever, other drug use), which would have caused hemolysis due to the G6PD deficiency.

Although hemolytic anemia is a rare adverse effect of metformin, the physician and pharmacist should be aware of this potentially serious side effect of the drug, particularly in a patient with G6PD deficiency.

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No Delay in Glucose Change at Antecubital Skin in Hypoglycemia of Normal Subjects

In the July 2001 issue of *Diabetes Care*, Jungheim and Koschinsky (1) reported that capillary blood glucose values at forearm lagged behind those at fingertip by maximum 30 min in their particular type 1 diabetic patient rendered to hypoglycemia. They warned that this might result in delay of hypoglycemia detection in diabetic patients and endangered their lives. They hypothesized that this was a physiological phenomenon rather than a pathological delay.

We investigated if their observation was physiological. We had 10 nondiabetic healthy volunteers (8 males and 2 females aged 35.0 ± 11.2 years with a BMI of 22.2 ± 3.0 kg/m^2) who were hypoglycemic with intravenous bolus injection of human insulin 0.1 unit/kg body

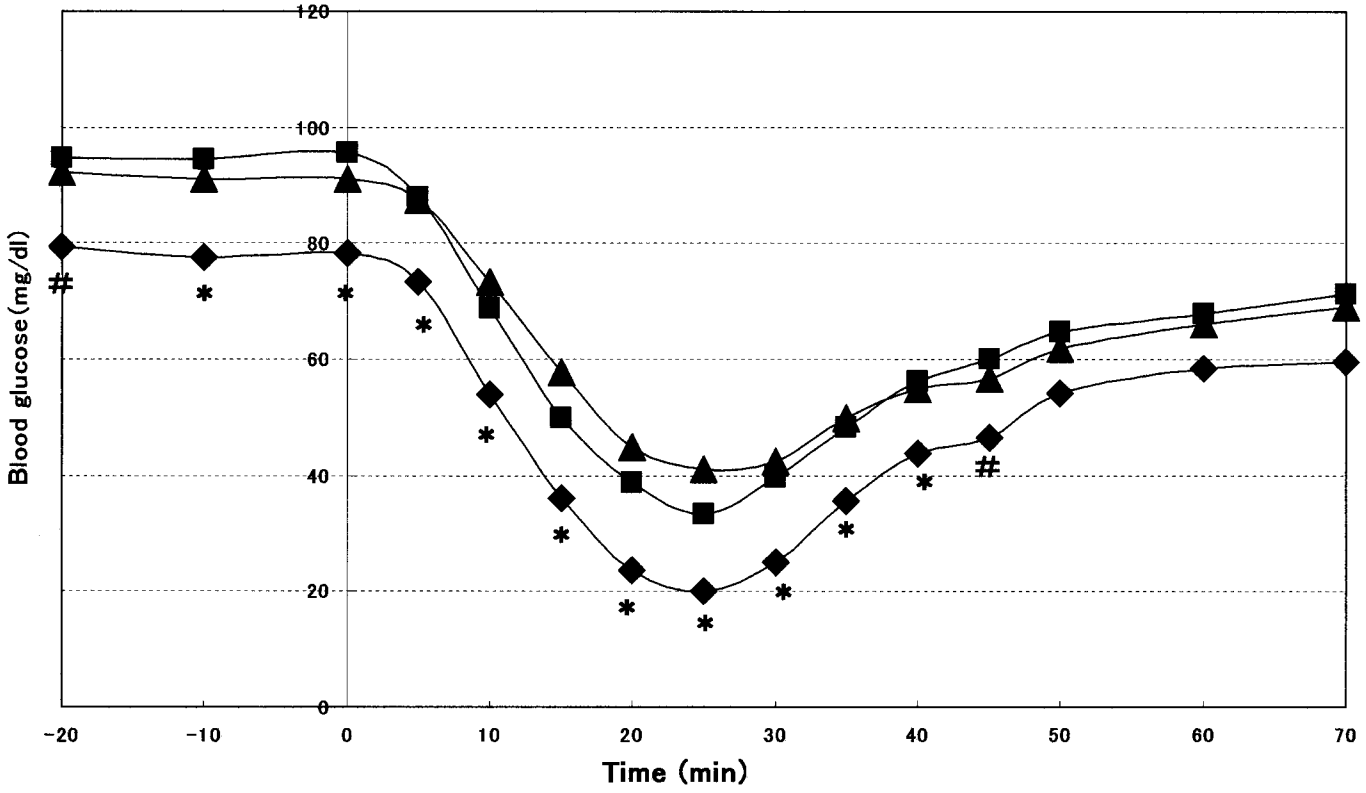

Figure 1—*Insulin-induced hypoglycemia in healthy subjects. Glucose levels are monitored at three sites of the forearm: fingertip (■), antecubital skin (▲), and antecubital vein (◆). Only average values are given. Bolus injection of human insulin is given at time 0. No significant differences are observed between glucose levels of fingertip and antecubital skin at any time in this study. Glucose levels in antecubital vein are significantly lower than those of the other two sites at the time marked by * or #. *P < 0.01, #P < 0.05.*

wt. Blood glucose levels were monitored at three different unilateral forearm sites: antecubital vein, capillary blood from antecubital skin, and fingertip. Three blood samples were taken strictly simultaneously with 5–10 min intervals for 90 min at three sites with venipuncture or pricking by three laboratory technicians. All blood samples from antecubital skin were taken after rubbing the skin. These samples were analyzed instantly for glucose by Free Style glucometers (Nipro, Osaka, Japan), which requires only 0.3 μl of whole blood for determination.

As described in Fig. 1, we found two major differences with Jungheim and Koschinsky's findings: *1*) we observed no significant difference in blood glucose levels between those from antecubital capillary blood and fingertip; and *2*) we noticed no delay in blood glucose nadirs among the three monitored sites. Changes at all sites were entirely concomitant. We see no advantage of measuring fingertip glucose over antecubital capillary blood glucose for these two reasons. Different from other two sites, antecubital venous blood glucose values were always significantly lower ($P < 0.01$–0.05) than those levels of either antecubital or fingertip from −20 to 45 min throughout. Therefore, if we want to detect hypoglycemia as early as possible, then we have to monitor venous blood glucose rather than either antecubital or fingertip. We do not think this is feasible and practical for the patients.

Blood glucose changes in hypoglycemia at antecubital and fingertip proceed synchronously without any delay in normal subjects (Fig. 1). We observed no delay in blood glucose changes in capillary blood at forearm as described by Jungheim and Koschinsky on their type 1 diabetic patient. They hypothesized that this could be a physiological delay, which is not consistent with our findings. Since diabetes is a disease of vascular complications and of autonomic neuropathy, one cannot rule out possible vascular reorganization or vascular nerve dysfunction after decades of hyperglycemia, leading to a possible delay in some cases of forearm glucose level detection than in fingertip. Their observation in type 1 diabetes, however, cannot be generalized as physiological; rather, it may represent an inconsistent and pathological finding observed in a limited range of patients. We need further investigation of diabetic patients with a variety of vascular or neural complications caused by various length or severity of diabetes to obtain a definite conclusion.

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Pregnancy Complicated by Diabetic Ketoacidosis

Maternal and fetal outcomes

Despite intensified insulin treatment and strict surveillance of metabolic control in diabetic women during pregnancy, diabetic ketoacidosis (DKA) complicates 2–9% of diabetic pregnancies (1) and represents the leading cause of fetal loss, with a fetal mortality rate of 30–90% (1–3).

From August 1991 to December 2001, 2,025 pregnant women with diabetes were admitted to the University of Tennessee Women's Hospital. Of these, 888 women (44%) received insulin therapy, and 11 women (1.2%) presented with DKA (blood glucose: 377 ± 27 mg/dl, pH: 7.22 ± 0.01, bicarbonate 7.9 ± 3 mEq/l, and positive serum ketones). White's diabetic classification included class A_2, four patients (27%); class B, five patients (45%); class C, one patient (9%); and class D, one patient (9%). The four women with gestational diabetes mellitus (GDM) were African-American, had a mean age of 25 ± 1 year, a BMI of 34 ± 3 kg/m^2, and an estimated gestational age of 29 ± 1 weeks. Patients with a previous history of diabetes had a mean duration of diabetes of 6 ± 1 year, a mean age of 27 ± 1 year, a BMI of 30 ± 2 kg/m^2, and a gestational age of 28 ± 1 weeks.

Infection (27%) and a history of the omission of insulin therapy (18%) were the most common precipitating causes. There were no maternal deaths, and the mean maternal length of hospital stay was 7 ± 2 days. Two patients presented with intrauterine fetal demise, and there was one additional fetal death giving an overall fetal death rate of 27%. During labor, four patients had nonreassuring fetal heart rate tracings in the form of late decelerations that resolved with correction of DKA. At birth, the mean (5 min) Apgar was 8.7 ± 0.4, and fetal weight was 1,278 ± 202 g.

Four obese women with DKA had newly diagnosed diabetes; one of them presented with an intrauterine fetal demise, and the remaining three reached full-term pregnancy. Insulin therapy was discontinued in all four patients after delivery; and two women remained off insulin after 6 months and 6 years of follow-up. GDM presenting with DKA is unusual (3). Our study indicates that DKA could be the clinical presentation of GDM and that many of these women can discontinue insulin treatment shortly after delivery. The four women with GDM and DKA were obese African-Americans resembling the phenotypic characteristics of patients with atypical diabetes (4).

In conclusion, DKA remains an important cause of fetal loss in diabetic pregnancies. Strict surveillance of glucose homeostasis and aggressive management might reduce the high perinatal mortality associated with DKA.

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Cost Effectiveness of the Direct Measurement of 3-β-Hydroxybutyrate in the Management of Diabetic Ketoacidosis in Children

A system for the precise quantification of β-hydroxybutyrate (β-HBA) levels in capillary blood has recently been introduced in clinical practice (1). This method allows quantitative measurement of major ketone in circulation during diabetic ketoacidosis (DKA) that correlates better than acetoacetate, with changes in acid-base status during the course of treatment for DKA (2). We studied the effectiveness of this quantitative test (MediSense Optium Ketone Sensor; Abbott Laboratories, Bedford, MA) against a commercial test for urine ketone bodies (UKBs) (Keto-Diabur-Test 5,000; Roche Diagnostics, Mannheim, Germany) in monitoring DKA in order to verify whether this ketone testing method was able to reduce monitoring costs and professional burden of nurses and physicians.

A total of 33 children with severe (arterial pH ≤7.2) or moderate (pH >7.2≤7.3) DKA were studied. The treatment was the same in all patients according to a standard low-dose insulin infusion protocol. Sixteen patients were randomly monitored with blood β-HBA (group 1) and 17 by UKB (group 2). The first advantage of the use of the β-HBA assay concerned monitoring each patients ketotic status hourly. The goal was achieved in all of the patients of group 1, independently from their dehydration degree. Dehydration status, on the contrary, affected the regular collection of urine specimen in the patients of group 2 and prevented UKB assessment in half of them. In response to therapy, capillary blood β-HBA levels declined 5.8 ± 0.5 h earlier than UKB levels. During the course of treatment for DKA, decreases in blood glucose and β-HBA levels resulted parallel with one another, and decreasing concentrations of β-HBA levels coincided with increasing concentrations of arterial pH ($r = -0.82$, $P = 0.0001$) and serum bicarbonate values ($r = -0.63$, $P = 0.001$).

Determination of β-HBA also showed that ketosis in group 1 patients cleared (β-HBA values <1.00 mmol/l) 4.6 ± 0.6 h sooner than patients monitored by UKB. Due to the fact that in our protocol the normalization of ketone bodies was used as end point for discharging a patient with DKA from the intensive care unit, the patients of group 1 had a shorter stay in the intensive care unit. This early discharge led in turn to a savings of 22 h for clinical assessment and 375 laboratory investigations for a total savings of €2,940 ($2,650), including costs for laboratory tests (29.8%) and clinical assessment (70.2%). Quantitative determination of β-HBA levels in addition to the traditional measurement of sensitive markers of metabolic decompensation, like serum bicarbonate and anion gap, seems to offer useful information for monitoring ketosis in newly diagnosed diabetic children and for reducing time and cost in an intensive care unit.

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Prediction of Wound Radius Reductions and Healing Times in Neuropathic Diabetic Foot Ulcers

Defining reliable predictors for wound healing in diabetic foot ulcers is an important issue. Usually, the percentage of wounds healed within a defined time period is used for this purpose, but this approach does not predict the time needed for healing in individual patients (1). We have recently established an equation to estimate the healing time in diabetic neuropathic foot ulcers (2).

This prospective study aimed to verify this approach by evaluating wound healing in 41 consecutive type 1 or type 2 diabetic patients (29 men, 12 women, aged 61.3 ± 11.1 years) with neuropathic but not angiopathic plantar foot ulcers (3). All patients received identical standard ulcer wound care, including use of proper footwear, non–weight-bearing limb support by half-shoes, debridement, daily careful monitoring of the ulcer, and antibiotic treatment when necessary. All patients were on insulin therapy. Ulcer healing was assessed by planimetric measurement of the wound area (in mm^2) after thorough wound debridement. Ulcer depth was assessed semiquantitatively using the Wagner grading system, with 13 ulcers grade 1 and 28 ulcers grade 2. The mean wound radius (R) was calculated from the mean wound area (A, in mm^2) by the equation $R = \sqrt{A/\pi}$ (2). The time course of wound healing was determined by plotting the mean wound radius derived from the measurements every fortnight against the time. The slope of the regression curve is interpreted as the weekly reduction of the mean wound radius. To predict the healing times, the wound area at beginning was transformed into the wound radius using the described formula and divided by the value of the wound radius reduction (0.45 mm/week) derived from our previous study (2).

The initial average wound area was

96.9 ± 13.1 mm^2, as compared with 3.61 ± 1.6 mm^2 after 10 weeks. The observed weekly wound radius reduction was 0.39 mm (95% CI 0.32–0.48) with an observed average healing time of 75.9 (95% CI 71–81) days, which was slightly less than the predicted healing time of 86.9 (95% CI 73–101) days. The observed and predicted healing times were significantly correlated with each other ($r = 0.55$, $P = 0.0002$). Both the wound area and the wound radius at study entry were significantly correlated with the healing times (area: $r = 0.94$, $P = 0.005$; radius: $r = 0.99$, $P = 0.0001$). The wound area reduction follows a second degree exponential function, with most of the wound area reduction taking place within the first weeks of treatment.

The results of this study confirm that the healing time in neuropathic foot ulcers can reliably be predicted by using the equation $R = \sqrt{A}/\pi/0.45$. Such calculations may be regarded as a useful tool in daily clinical practice, both to give an estimation of the time period needed for healing, and to recognize early those ulcers that do not respond adequately to the treatment.

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Evidence for Associated Cutaneous Microangiopathy in Diabetic Patients With Neuropathic Foot Ulceration

Diabetes complicated by diabetic neuropathy is a risk factor initiating chronic foot ulceration, which may lead to amputation (1).

We postulated that a form of functional cutaneous microangiopathy is associated with diabetic neuropathy, and we assessed the cutaneous vasoreactivity reserve (CVR) using laser-Doppler flowmetry.

We investigated 42 patients with type 2 diabetes but without cutaneous foot ischemia. They were divided into two groups, respectively comprising 30 patients with no current or previous foot ulceration and 12 with diabetic neuropathy and foot ulceration. A total of 17 healthy subjects served as the control group.

A laser-Doppler probe was placed on the dorsum of the foot. Blood flux was recorded as previously published (2), under three conditions: supine, sitting (to record the venous arteriolar reflex [VAR]), and after postocclusive hyperemia (H). CVR is the sum of these vasoconstriction (VAR) and vasodilation (H) capacities and is expressed in percent of the supine blood flux. In addition, we measured the transcutaneous oxygen pressure ($TcPO_2$) of the foot dorsum.

In diabetic patients with foot ulceration, CVR was 219 ± 86%, which was significantly lower than in either the group without foot ulceration (566 ± 76%, $P < 0.01$) or the healthy control subjects (472 ± 217%, $P < 0.017$).

In diabetic patients with foot ulceration, $TcPO_2$ was 44.5 ± 5 mmHg, which was also lower than in either the group without foot ulceration (50 ± 1 mmHg, P = NS) or the healthy control subjects (68 ± 8 mmHg, $P = 0.0005$).

In diabetic patients with neuropathy complicated by foot ulceration, this study demonstrated a significant reduction in CVR, indicating the presence of cutaneous microangiopahy.

Our study is the first to have explored both VAR and H simultaneously, thus enabling them to be summed in a single parameter (CVR) that expresses the cutaneous vasoreactivity reserve.

The relationship between neuropathy and cutaneous microangiopathy might involve two mechanisms: *1*) the impairment of microvascular reactivity and limitation of hyperemia by the neuropathy 2) disturbance of the vasa nervorum and interference in the pathogenesis of the neuropathy.

Note that the functional microcirculatory abnormalities shown by our results had nutritional consequences for the blood oxygen supply to the skin, as $TcPO_2$ was lower in patients with diabetes than in the control subjects, the lowest values being in the group with foot ulceration.

The cutaneous microvascular vasodilation capacity (i.e., hyperemia in response to injury) is of particular importance for ulcer healing, and the capillary hyperperfusion on dependency due to an abnormal postural venoarteriolar reflex accounts for edema and stimulates capillary basement membrane thickening. Therefore, the traditional causative chain of neuropathy + minor trauma → ulceration + faulty healing → gangrene → amputation does not take into account the associated cutaneous microangiopathy that may be expected to increase the proneness to trauma and foot ulceration and, hence, the possible failure of healing.

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COMMENTS AND RESPONSES

Coronary Artery Disease and Carotid Artery Intima-Media Thickness in Japanese Type 2 Diabetic Patients

We read with interest the article by Mitsuhashi et al. (1) concerning the role of carotid artery intima-media thickness (IMT) measurements in the detection of coronary artery disease (CAD) in Japanese type 2 diabetic patients. The article suggested that carotid IMT was significantly greater in diabetic patients with CAD (1.27 ± 0.07 mm) than in those without CAD (termed "control subjects") (1.03 ± 0.04 mm, $P <$ 0.05). In the subgroup with CAD, IMT was significantly greater in those who had undergone coronary artery bypass grafting (CABG) than in the non-CABG group (1.47 ± 0.11 vs. 1.07 ± 0.07 mm, $P <$ 0.05). Although statistical differences in IMT between the CABG and non-CABG subgroups of CAD patients and between control subjects and the total CAD group were emphasized, no test statistic was given for the comparison of control subjects with non-CABG subjects, where the difference would appear to be nonsignificant (1.03 ± 0.04 vs. 1.07 ± 0.07 mm).

We question the validity of the authors' conclusions that early atherosclerosis in the carotid artery suggests a high probability of coronary involvement in Japanese patients with type 2 diabetes, and that an increased IMT in diabetic patients should prompt further screening for CAD to prevent progression of CAD.

First, there is the issue of possible confounding by the CABG procedure itself, which the authors do concede in their conclusion. Second, there is no evidence of a gradient of IMT between the CAD non-CABG group and those post-CABG, nor is there any correlation with number of vessels involved or any mention of correlation with severity of exercise electrocardiogram (ECG) results. It appears that the authors have demonstrated that in post-CABG patients, the IMT measurement offers the self-evident conclusion that they have CAD. A clinically relevant marker that can predict progression and perhaps be used as a screening tool, not one that merely confirms a clinically manifest condition, is needed.

This study has shown a statistical difference in serum HDL concentration, uric acid, and hypertension between the control and CAD groups, which is consistent with other large studies such as the Framingham Heart Study and the Multiple Risk Factor Intervention Trial (2–4), but no statistical difference between the non-CABG and post-CABG groups. Furthermore, only 32 of 48 subjects with abnormal exercise ECG testing proceeded to angiography. One wonders whether exclusion of 25% of subjects apparently eligible for angiography in this group may have led to an underestimation of the efficacy of IMT.

Finally, the abstract states that "carotid IMT was significantly greater in the diabetic patients than in the control subjects, " which implies that the control subjects were not diabetic. This is later clarified in RESEARCH DESIGN AND METHODS, which states that the control subjects were "drawn from the diabetic patients."

Our conclusion is that, while this study has undoubtedly shown a statistical difference in IMT between type 2 diabetic patients with and without CABG, an increased IMT was only shown in those who had already undergone treatment for CAD. Therefore, it has not shown IMT to be a good marker to prompt further screening for CAD or treatment to prevent progression of CAD in type 2 diabetic patients.

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Response to Ostberg and Hurel

We appreciate the interest of Ostberg and Hurel (1) in our article (2) and the opportunity to clarify the point raised.

As we described in CONCLUSIONS in our article, intima-media thickness (IMT) may have become thicker after coronary artery bypass grafting (CABG), because one cannot establish temporal sequence with cross-sectional data. We measured IMT of 15 patients before the CABG procedure (mean IMT ± SD 1.44 ± 0.14 mm) and IMT of 5 patients within 3–6 months after CABG (1.56 ± 0.07 mm). IMT was not significantly different between these two groups ($P = 0.62$). Even if we had excluded the latter 5 patients' measured IMT after CABG, IMT would have been still significantly greater in the 15 CABG patients' measured IMT before CABG than in the controls drawn from the diabetic patients (1.44 ± 0.14 vs. 1.07 ± 0.07 mm, $P < 0.05$). And there is no conclusive proof that CABG itself has an effect on the change in IMT. Therefore, we did not consider that our result was confounded strongly by the CABG procedure itself. Yet, we need further studies, because the number of patients with CABG was relatively small, and we did

not compare IMT before and after CABG among the same patients.

Next, we state the correlation with the number of involved coronary vessels between two groups with and without CABG. The non-CABG group ($n = 20$) was divided into 9 patients with two-vessel disease and 11 patients with three-vessel disease. The CABG group ($n = 20$) included 4 patients with two-vessel disease and 16 patients with three-vessel disease. The CABG group had more severe disease than the non-CABG group, but the correlation was not significantly different ($\chi^2 = 2.849$, $P = 0.09$). In addition, we show the correlation between the severity of coronary artery disease (CAD) and IMT. In the group with two-vessel disease, the IMT was 1.08 ± 0.08 mm, and in the group with three-vessel disease, it was 1.36 ± 0.10 mm ($P = 0.07$). IMT was not significantly associated with the number of involved vessels, but had a tendency to associate with the number of total vessels. Moreover, as shown in Tables 2 and 3, IMT was independently associated with CAD by logistic regression analysis using all other independent variables. Thus, we consider that IMT could be used as a predictor of severity of CAD assessed by the number of involved vessels in diabetic patients.

With regard to the clinical characteristics, as shown in RESULTS, CAD patients had a significantly higher prevalence of hypertension and uric acid level and a lower HDL cholesterol level than the control diabetic patients. Both the Framingham Study (3,4) and Multiple Risk Factor Intervention Trial (MRFIT) (5), as referred to by Drs. Ostberg and Hurel, are studies to assess CAD mortality with and without diabetes, but the subjects of our study are all diabetic patients. Thus, we cannot compare these large studies with our study in the same way. Yet, it is well known that hyperlipidemia and hypertension are strong and independent predictors of CAD in diabetic patients (5–10). Similarly, our patients with CAD had more cardiovascular risk factors than those without CAD. On one hand, among only CAD patients, including the patients with and without CABG, as shown in Table 4, factors such as hypertension, hyperlipidemia, and hyperuricemia did not differ between the two groups. The reason was not obvious. But, as many of the patients without CABG already had hypertension and hyperlipidemia, there might not have been a significant difference between the two groups with and without CABG. However, the IMT was significantly greater in patients with CABG than in those without CABG. These results indicate that IMT is one important indicator of severe CAD that was needed for CABG.

Currently, only 32 of 48 patients with abnormal exercise electrocardiogram testing proceeded to angiography. Some patients received an angiography after the period, but we estimated only 32 patients who had CAD by angiography from February 1998 to January 1999. Furthermore, we agree with Drs. Ostberg and Hurel that we should also state that the control subjects were drawn from the diabetic patients within RESULTS as well as within RESEARCH DESIGN AND METHODS. To clarify the meanings, the sentence in RESULTS should be replaced as follows: Carotid IMT was significantly greater in the CAD patients than in the controls drawn from the diabetic patients.

We believe that IMT is a predictor of severity of CAD in diabetic patients, but further investigation in a large population is necessary.

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Acute and Prolonged Effects of Sildenafil on Brachial Artery Flow-Mediated Dilatation in Type 2 Diabetes

In a recent article by Desouza et al. (1), an improvement of brachial artery flow-mediated vasodilatation, a measurement indicating endothelium-dependent vasodilation, was reported with both acute and prolonged sildenafil treatment. No measurements of endothelium-independent vasodilation were performed. As the administration of sublingual nitroglycerin is mainly used to evaluate endothelium-independent vasodilation, it is understandable that possible

side effects related to the concomitant use of sildenafil and nitroglycerine were the main reason for omitting this measurement. However, we believe that although the presented data are very interesting, they do not support the main conclusion of the article, namely that sildenafil improves endothelial function.

Sildenafil is a type-5 phosphodiesterase inhibitor that works directly at the vascular smooth muscle cell by preventing a breakdown of cyclic guanosine monophosphate (cGMP). Therefore, it should not affect the nitric oxide production and release by vascular endothelial cell, but it should enhance its action on the smooth muscle cell as it prolongs the action of the cGMP that is generated by the action of the nitric oxide.

The only way to dissect the action of sildenafil on the endothelial cell and the vascular smooth muscle cell is to perform measurements that evaluate both the endothelium-dependent and -independent vasodilation. In case the endothelium-dependent vasodilation improves while the endothelium-independent remains unchanged, a claim can be made that sildenafil affects the endothelial function. However, in case there is also an improvement in the endothelium-independent vasodilation. Therefore, we believe that the data should be interpreted as indicating a direct action of sildenafil on the smooth muscle cell, while an additional effect on the endothelial cell cannot be excluded. In case a disproportional improvement in the endothelium-independent measurement is noticed, it can be reasonably concluded that sildenafil mainly affects the smooth cell function. It should also be noted that such data have been provided in a previous study of healthy men (2). In that study, sildenafil administration increased sensitivity to local nitroglycerin (endothelial-independent vasodilatation) in the subjects' hand vein, resulting in the decrease in a 50% effective dose by about fourfold. In contrast, sildenafil did not significantly affect the maximal venodilatory response to acetylcholine or flow mediated artery vasodilatation (endothelial-dependent vasodilatation).

In conclusion, we believe that the data by Desouza et al. (1) provide significant information regarding the effect of sildenafil on the vasculature, but the conclusions should be modified to state that sildenafil improves vascular reactivity (which encompasses both endothelium-dependent and -independent vasodilation).

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Acute and Prolonged Effects of Sildenafil on Brachial Artery Flow-Mediated Dilatation in Type 2 Diabetes

Response to Khaodhiar and Veves

We appreciate the comments of Drs. Khaodhiar and Veves (1). We agree that in order to dissect the action of sildenafil on the endothelial cell and the vascular smooth muscle cell it is necessary to perform measurements that evaluate both endothelium-dependent and endothelium-independent vasodilatation. However, the latter requires the use of nitrates, which have the potential for serious (and potentially fatal) hypotension when used concomitantly with sildenafil. When giving us an investigational new drug exemption to carry out this study, the Food and Drug Administration specifically asked us not to use nitrates. Nevertheless, our results clearly demonstrate a beneficial effect of sildenafil on vascular reactivity that lasts well beyond the time expected from pharmacokinetic studies of the drug (2). Such treatment is thus able to overcome what is well recognized as a defect in endothelial function—even if possibly mediated through actions on smooth muscle cells.

We note that Dishy et al. (3) have demonstrated that sildenafil administration increased sensitivity to local nitroglycerin. However, their studies were carried out in healthy volunteers, whereas we studied patients with diabetes who may have had asymptomatic coronary artery disease. Much as we would like to do the study as suggested by Khaodhiar and Veves, our overriding concern is for patient safety (as it should be in all clinical research).

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Response to Gómez-Ulla et al.

We strongly disagree with the assertion of Gómez-Ulla et al. (1) that European protocols did not define any standards by which diabetic retinopathy screening programs should be assessed. Recently, Bachmann and Nelson (2) pooled the data from many available screening studies, dated up to 1996, and determined that retinal photography was the screening test of choice. In fact, the U.K. National Screening Com-

mittee was considering this topic as a possible national priority. In addition, a cross-sectional epidemiologic study on 258 randomly selected diabetic patients in Spain was published by Hernáez-Ortega et al. (3) in 1998. The authors compared the efficiency of a 45° nonmydriatic retinal camera with a Polaroid instant film versus the standard method, and they concluded that fundus photography would be advisable for its use in medical settings that usually control for potential ophthalmologic complications resulting from diabetes (3).

Gómez-Ulla et al. (1) concluded in their article that sending digital retinal images via the Internet was a suitable method for detecting and grading diabetic retinopathy in a nonselected diabetic population. This conclusion was reached after comparison between grading by direct examination and grading by inspecting digital images. However, we would like to point out some methodological issues in their article that could invalidate the generalization of their results. What do we know about their patients? The authors stated that 70 consecutive diabetic patients were recruited either from an endocrinology and/or an ophthalmology unit, but they did not describe their study population (i.e., age, sex, diabetes type, diabetes duration, etc.). Otherwise, it seems that this diagnostic method will work equally well despite the population. It is well-known that older populations will have a lower degree of collaboration, higher degree of media opacities, and smaller pupil size. We also suggest that the authors pull together those patients excluded from their analysis (i.e., seven patients with opaque cataract and seven with poor image quality) to provide the percentage of eyes that did not allow detection of retinopathy with their proposed method (i.e., 10%). Hernáez-Ortega et al. (3) reported 6.6% of ungradable fundus photography in a much larger study population of diabetic patients in the North of Spain.

Kappa (κ), the measure of agreement corrected for chance, may be interpreted as the proportion of the best possible improvement in agreement beyond chance that was actually obtained by the observers. The authors calculated the intraclass correlation coefficient (ICC) to determine agreement on the stage of diabetic retinopathy. The authors should have noted that the ICC can be interpreted as a special form of weighted κ. In fact, when the variable is ordinal, calculating a weighted κ is preferable (4).

Therefore, we recommend that the authors provide the missing data on their study population to show how much it influenced their results. We also suggest the calculation of a weighted κ to determine agreement on degree of diabetic retinopathy.

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Response to Soto-Pedre et al.

We read with great interest the letter from Soto-Pedre et al. (1), which offered several observations on our article (2). Lin et al. (3) recently concluded that the optimal strategy for diabetic retinopathy (DR) screening remains uncertain, and a number of possible modalities have been considered. Our study, which started in 1998, intended to reaffirm the need of validation of digital technology that has come up in recent years (4,5). Including digital retinal images in health records (6) will improve the management of diabetic patients.

We agree with Soto-Pedre et al. on the suitability of retinal photography for the screening of DR, as we have already mentioned in our article. Our objective was to examine the reliability of the digitally captured retinal image, subsequently compressed and sent to a reference center via internet for analysis. For this we compared the digital image inspection to the direct examination of the eye fundus under mydriasis. This is important at the moment because the increasing use of new technologies makes the need for validating the use of digital images almost totally necessary for DR screening (6–10).

Soto-Pedre et al. cast doubt over some methodological issues such as age, sex, diabetes type, etc., that could invalidate our conclusions. This information, though collected as part of the protocol of study, has not been included in the article. We decided not to because the aim of the study was simply to compare the findings in the digital image with those findings obtained by direct examination of the eye fundus, regardless age, sex, or other parameters mentioned by Soto-Pedre et al. We agree, however, that factors such as those mentioned above may impair image quality and therefore reduce the agreement between direct inspection and digital image examination. We expect that further studies will clarify this and other questions.

The proposed method would function as population screening in all cases in which the eye fundus can be photographed with good quality. As mentioned in our article, we were unable to obtain photographs of the eye fundus in 5% of the initial 140 eyes because of a cataract; in 5% of the remaining 133 eyes, the quality of the digital image was not good enough to make a diagnosis because of pupil narrowing or moderate media opacity. Thus, in 10% of patients, the method used was not adequate, and the patient had to be referred to an ophthalmologist. In another paper published by our group (11), we also found that this problem appeared in 13% of cases, which is in agreement with observations reported by other

authors (9). Some studies report figures that range from 3.7 to 22% (12). Recent data suggest that the degree of technical error would be <5% when mydriasis is performed (13).

Since the first formal introductions of κ, more than 40 years ago, numerous papers both using and criticizing its various forms have appeared in the statistical as well as in the medical literature. κ coefficients were designed to measure correlation between nominal, not ordinal, measures (14). In a later study, Cohen and Fleiss (15) have shown that under a squared error weighting system, weighted κ is asymptotically equivalent to the intraclass correlation computed using the category ranks. Although there are several inherent problems in the use of weighted κ statistic for the analysis of ordinal agreement (15), we believe that weighted κ could be a reasonable (though not a unique) choice as a reliability measure. The intraclass correlation has been advocated as an agreement index for both continuous and ordinal data (16), and we have preferred this approach because of the high number of categories for grading diabetic retinopathy.

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Technical Issues in Retinopathy Screening

The article by Gómez-Ulla et al. (1) in the August issue of *Diabetes Care* presents a strong case for a simplified method of detecting people at risk for vision loss from diabetic retinopathy. Their work reports that the use of a two-field imaging protocol for each eye, telemedicine and centralized analysis, achieve diagnostic capabilities comparable to physician-provided ophthalmoscopy. This increases cost-effectiveness and allows retinopathy screening to meet the key criteria of a population-based screening program (2).

However, this report raises an important question regarding image quality. The authors suggest that JPEG compression permits rapid data transmission, requires less server space, and preserves "adequate definition of the lesions." However, they admit underestimation of retinal neovascularization from image analysis, since "high-grade DR [diabetic retinopathy] has image features that may be lost when inspection of the digital images is made." Yet, proliferative disease is precisely the most critical clinical situation in which patients may benefit from immediate laser therapy, thus preventing a predictable pattern of events that results in permanent vision loss.

We believe that the inability to detect crucial pathology is caused by both the original image acquisition (low-resolution video camera used along with a frame

grabber, which further reduces the available resolution) and by the JPEG compression algorithm.

Image-based screening systems rely on visible surrogate markers, lesions that denote alterations of the retinal microcirculation. When these markers are centrally located and unobscured by overlying media opacities (and assuming they are large enough to be rendered by several overlying pixels to provide morphologic clues), observers should be able to detect them. Problems arise when they are located toward the image periphery (in which case optical aberrations may obscure their true shape), when lenticular changes or vitreous turbidity mask them, or when not enough pixels are used to render them. Clearly, if the original image was barely adequate to portray unambiguous lesions, then those markers that are more difficult to visualize would be under-reported.

The proposed screening programs in England (3) and Scotland (4) specify that the original image exhibit a minimum pixel matrix of 1,300 × 1,000. This enhances the detection of retinopathy when the image is displayed on a large CRT monitor at full resolution. In the U.S., Canon Medical Products and Digital Healthcare offer a high-resolution pure digital system, based on the Canon EOS D30 or D60 digital camera and CR-6 45NM fundus camera, that exceeds the U.K. standards. We have been using this system for more than a year and find that store-and-forward data transmission using digital subscriber lines is a practical means of connecting the camera with the reading center.

We hope that publication of the work of Gomez-Ulla et al. signals that the American Diabetes Association is willing to revisit their position statement on diabetic retinopathy (5), first published 4 years ago. With recent advances in digital technology allowing even greater sensitivity, high-resolution digital screening of high-risk patients, using a simplified protocol, offers a practical method of reducing the risk of vision loss in diabetes.

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Response to Merin and Reeves

We appreciate the comments of Merin and Reeves (1) concerning our article (2). There is no doubt that image quality is the most crucial aspect of diabetic retinopathy screening. Both spatial and color resolution play an important role in both the acquisition and display devices.

In our study we used the fundus camera Canon CR5-45NM with a Sony video camera (DXC950). Unfortunately, at that time, the system mentioned by the authors of the letter (CR6-45 NM fundus camera with a Canon digital camera) was not available; indeed, though, it offers a relevant improvement over the older configuration.

The system we have used may not be able to provide enough image quality to detect every retinal lesion. It generated image files in JPEG format from a digital image of 800×600 pixels, which is lower than the recommended 1,300×1,000 and much lower than the new cameras that may reach 2,600×2,300 pixels. To minimize image degradation, we used the lowest JPEG compression available in our image grabber (1:3 ratio). However, despite these limitations, our data show that the grading of the retinopathy made after digital image inspection and after direct eye fundus examination shows agreement in the vast majority of cases and, therefore, an adequate follow-up or treatment of most patients could be made. Although JPEG compression may not have been the best choice, a recent article (3) shows that higher compression ratios than the one we used do not produce serious degradation of the images.

We mentioned in our article that we lost image features in high-grade diabetic retinopathy. This was not because of the resolution of our system but because hemorrhages and media opacifications deteriorated the visibility of the retina. We believe they would have been missed even with a higher resolution camera.

The review by Aiello et al. (4) suggests that, at the time their article was written, digital images obtained with nonmydriatic fundus cameras were not a replacement of standard seven-field stereoscopic 30° fundus photography. We did not compare our digital images with standard fundus photography; therefore, we cannot suggest such a replacement. Instead, we showed that there is agreement between digital image inspection and direct fundus examination in grading diabetic retinopathy. Thus, we believe that digital fundus images may be adequate for this purpose. We expect, as Merrin and Reeves mention, that new advances in technology will improve image quality, and will increase not only spatial and color resolution but also time resolution and stereoscopic viewing from which patients may benefit.

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Response to Schade

To pump or not to pump?

In the editorial published in the November issue of *Diabetes Care*, entitled "To Pump or Not to Pump" (1), Dr. David Schade provides an excellent review of the recent history of the "intensive insulin therapy" approach for the management of type 1 diabetic patients and the gradual development of continuous subcutaneous insulin infusion utilizing an external insulin infusion pump (CSII). Surprisingly, despite the overwhelming evidence that CSII is superior to some multiple insulin injection (MDI) programs, including the report in the same issue by DeVries et al. (2), Dr. Schade concludes that CSII should be reserved for a "minority" or a subset of individuals with diabetes.

Most clinical trials (3,4), meta-analyses (5), and observational studies (6) have demonstrated greater reductions in HbA_{1c}, lower rates of hypoglycemia (a major deterrent for the implementation of intensive insulin therapy in type 1 diabetes [7]), less daily glucose variability, improved clinical outcomes, and better quality of life in patients treated with CSII when compared with those in MDI programs. There are no data to support the notion that the advantages of CSII over MDI programs are offset by the higher cost of the CSII regimen, since most cost analyses do not take into account the savings associated with less frequent hospitalizations and emergency room visits, as well as the unequivocal benefits (7) of sustained prolonged lower HbA_{1c} levels achieved over time in patients treated with CSII. In our recently published experience (8), we found less frequent hospitalizations and emergency room visits in type 1 diabetic patients who were treated on intensive insulin pump programs compared with those on multiple insulin injections.

Although we agree with Dr. Schade that "[. . .] placing individuals on CSII who are unable to master MDI first is a prescription for failure," extending CSII to the "majority" of patients with type 1 diabetes (and perhaps to selected insulin-requiring type 2 diabetic individuals) who are currently on intensive insulin therapy programs is recommended, consistent with good clinical practice, and based on scientific evidence. CSII programs can be easily and safely implemented in the outpatient setting and can result in substantial improvement in clinical outcomes (8).

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Response to Cersosimo

We thank Dr. Cersosimo for his letter addressing our editorial and are pleased to address his concerns (1,2). In our article "To Pump or Not to Pump?" (2), we pointed out that both emotions and scientific evidence

have contributed to the debate on the role of continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI). It is worth remembering that the only real benefit of CSII relates to the kinetics of delivery of subcutaneous insulin. We emphasized that all previous studies in which NPH insulin was used as the background insulin in MDI were of limited value because insulin glargine now provides a more physiological insulin profile (3). In addition, very few studies comparing CSII and MDI used a randomized, blinded treatment design. Without such a protocol, selection bias is very difficult to exclude. This problem is illustrated by the study cited by Cersosimo, which was neither randomized nor blinded (4). In this study, a significant difference in the two groups was present, both in the starting HbA_{1c} levels (8.0 ± 1.2% for CSII and 8.6 ± 1.0% for MDI) and in the number of individuals in each group (35 for CSII and 50 for MDI). Without equivalence of groups at the initiation of the study, conclusions concerning their outcome parameters are difficult to make.

A second issue that is frequently overlooked when comparing CSII with MDI is the degree of interaction between the volunteer and the investigator's health care team. Initiating CSII requires extensive training in diet, carbohydrate counting, hypoglycemia awareness, attention to pump detail, and insulin delivery algorithms. This training and close follow-up are often more extensive than that which occurs with initiation of MDI. What percentage of the high success rate reported with CSII therapy is due to intensive educational and motivational training is unknown.

A third issue of concern is the cost of CSII versus MDI. We agree with Cersosimo, from the viewpoint of long-term cost analysis, that CSII may not be more costly than MDI. In fact, it may be cost effective. However, cost can be a major obstacle to the individual diabetic patient who may not have medical insurance and is therefore not be able to cover the immediate costs of CSII from his or her own resources. For many individuals in the U.S. currently without health insurance, starting CSII is not financially possible.

Our editorial attempted to make one major point—that additional data are urgently required before CSII can be broadly recommended over MDI in the general population of people with type 1 diabetes. Not only do we need studies utilizing insulin glargine in the MDI regimen, but these studies also need to be randomized and blinded to the greatest extent possible. Until such data become available, the decision to prescribe either CSII or MDI should be based on the criteria that we listed in our editorial. The health care team must determine which treatment modality has the greatest potential for benefit in each diabetic patient. K.M. Bolderman (5) appropriately states this concept in her excellent book on CSII by stating, "Discovering the character and source of motivation through careful screening of the patient is the key to ensuring success in pump therapy."

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