OBSERVATIONS

Relationship Between Periodontal Disease and Diabetic Retinopathy

Recently, various studies have reported that periodontal disease adversely affects diabetes (1). The control of periodontal disease in elderly individuals has been reported to improve the control of blood glucose (2). Severe periodontal disease is associated with elevated blood lipopolysaccharide levels as a result of periodontogenic bacteria, which induce higher levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (3,4). Control of periodontal disease is now considered not only a dental problem but also an issue affecting the patient's overall quality of life. Proinflammatory cytokines such as IL-6 have been shown to be involved in the pathogenesis of diabetic retinopathy (DR) (5), while the relationship between diabetic retinopathy and periodontal disease remains unclear. We investigated whether periodontal disease is correlated with diabetic retinopathy.

The study was based on a prospective review of 73 eyes in 73 consecutive diabetic patients. The mean duration of diabetes was 14.3 ± 7.1 years (range 2–33), and the mean HbA_{1c} was 7.5 ± 1.6% (5.2–13.7). IL-6 and TNF-α levels in the vitreous fluid samples from 32 eyes obtained during vitrectomy and in paired plasma samples were measured by enzyme-linked immunosorbent assay. Nondiabetic patients included 10 with macular hole and 2 with epiretinal membrane. Institutional ethics committee approval was obtained, and all participants gave informed consent. The severity of diabetic retinopathy was quantified according to the modified Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity scale (6). The severity of periodontal disease was quantified according to bone loss and then graded and evaluated (7). Patients with periodontal disease were classified as positive or negative based on median values. Diabetic patients were classified as having nonproliferative or proliferative diabetic retinopathy. Data are presented as means ± SD. The Mann-Whitney *U* test was used to compare IL-6 and TNF-α levels. To determine the relationship between the severity of periodontal disease and ETDRS, retinopathy severity, or angiogenic factors, as well as between X and Y parameters, Spearman's rank-order correlation coefficient and logistic regression model were applied.

The severity of periodontal disease was significantly correlated with the severity of diabetic retinopathy ($P = 0.0012$), and the risk of proliferative diabetic retinopathy was significantly higher in the presence of periodontal disease (odds ratio = 2.80, $P = 0.036$). There was no significant relationship between the severity of periodontal disease and HbA_{1c} or duration of diabetes ($P = 0.098$ and 0.295, respectively). There was a significant relationship between the severity of diabetic retinopathy and duration of diabetes ($P = 0.002$). The vitreous fluid level of IL-6 (mean 154.2 ± 164.6 pg/ml [range 0.993–597.0]) was significantly elevated in patients with diabetic retinopathy compared with that in nondiabetic patients (mean 1.34 ± 0.91 pg/ml [0.6–3.68]) ($P < 0.0001$). Furthermore, the vitreous fluid level of IL-6 was significantly correlated with the severity of periodontal disease ($P = 0.012$). There was no significant relationship between the vitreous fluid level of IL-6 and HbA_{1c} or duration of diabetes ($P = 0.293$ and 0.705, respectively). In contrast, the vitreous fluid level of TNF-α was not significantly correlated with the severity of periodontal disease. The IL-6 concentration in vitreous fluid (mean 154.2 ± 164.6 pg/ml [0.993–597.0]) was significantly higher than that in plasma (mean 1.89 ± 3.47 pg/ml [0.156–18.8]) ($P < 0.0001$).

There was a significant relationship between periodontal disease and severity of diabetic retinopathy, but it was unclear whether periodontal disease directly affects the progression of diabetic retinopathy because this was a cross-sectional study. Further prospective studies, including evaluation of systemic factors, are necessary.

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Effect of Diabetes Intervention Programs on Physical Activity Among Migrant Mexican Women With Type 2 Diabetes

The 2000 Dietary Guidelines for Americans and the dietary guidelines for the control of diabetes in Mexico include recommendations that adults participate in at least 30 min of moderate physical activity, preferably daily (1,2). However, to our knowledge, there have been no studies that explore the effect of diabetes intervention programs on physical activity among migrant Mexican women with type 2 diabetes.

All women from seven diabetes education groups from three different Mexican institutions located in Tijuana were invited to answer a previously validated questionnaire on physical activity. Of 111 questionnaires, 100 were adequately answered. The mean age was 53 ± 12 years. The majority of the sample was migrants from other Mexican states, and 40% were classified as overweight and 31% as obese. Of the women, 62, 45, and 15% reported >20, >30, and >60 min of physical activity per day, respectively. Seventy-three percent reported >80 min of weekly physical activity. Daily outdoor activity of participants was 39 ± 4.2 min (mean ± SE), and daily indoor activity was 5.72 ± 0.27 h. Total light activity (<3.0 metabolic equivalents [METs]) was 5.28 ± 0.24 h/day, total moderate activity (3–6 METs) was 55 ± 14 min/day, and total vigorous activity (>6.0 METs) was 4.2 ± 0.6 min/day. The average physical activity level was 1.54 ± 0.03. The main indoor activities were cooking (11 h/week), dishwashing and clothes washing (3.2 h/week), cleaning (3.1 h/week), and shopping (1.9 h/week), and the main outdoor physical activities were walking (3.1 h/week), semiactive exercise and stretching (1.26 h/week), running (0.23 h/week), and bicycle riding (0.18 h/week). The main resting activity was sleeping (49.16 h/week), followed by watching television (11.3 h/week), resting in bed (2 h/week), driving or sitting in a car (1.5 h/week), and sitting at home (1.38 h/week).

This study shows that the majority of Mexicans with diabetes who are willing to participate in diabetes education groups at the primary health care clinics engage in >20 min of daily physical activity, which therefore reinforces the need for promoting culturally based interventions (3,4). These results are better than the national data for adults with type 2 diabetes in Mexico and the U.S. (5,6); however, the groups we studied were especially motivated subjects interested in obtaining better metabolic control through diabetes education groups. On the other hand, the population from this study, which has a low socioeconomic status, usually confronts major environmental or economic barriers that prevent access to safe recreational areas or fitness facilities. Thus, even with economic constraints and inadequate environmental access to physical activity, promoting physical activity in a culturally based intervention is a worthwhile strategy that should be supported. Although further studies in large populations are still required to evaluate the effectiveness at a larger scale, at the primary care level of Mexican institutions, stronger emphasis should be placed on promoting physical activity.

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Alternative Site Testing at the Earlobe Tip

Reliability of glucose measurements and pain perception

There is growing interest in alternative less painful sites for capillary blood glucose (CBG) monitoring. The earlobe tip is a potential site (1) that has been occasionally used by nurses when fingertip testing is refused or difficult. We investigated the clinical value and accuracy of earlobe CBG measurements as an alternative to fingertip and forearm testing.

A total of 50 patients with type 2 diabetes (aged 42–82 years, 28% with neuropathy) were enrolled in the study. The duration of diabetes was 9.5 ± 8.3 years (means ± SD). Testing sites (lateral aspect of the fingertip, earlobe tip, and flexor surface of the forearm) were rubbed and cleaned before lancing was performed by a physician using Lifescan Unistick-2 lancets (Lifescan, Milpitas, CA). The forearm was lanced using the Microlet-Vaculance device (Bayer, Tarrytown, NY). The order of site testing was randomized. Pain was immediately assessed after the first attempt using a 100-mm graphic visual scale (2). CBG was measured with an Accu-Check Advantage glucose meter (Roche, Indianapolis, IN).

First-attempt sampling success rates were 88% (fingertip), 74% (earlobe), and

62% (forearm). After earlobe pricking, bleeding lasted for <60 s in all subjects (<30 s in 90%). Earlobe pain (median score 5.5 mm) was less uncomfortable than fingertip pain (17 mm, $P < 0.01$, Wilcoxon test) but not statistically different from forearm (8.0 mm). Although earlobe pain was more tolerable, a limitation in this study is that it did not evaluate pain perception after repeated testing on multiple days, when skin soreness might become relevant.

CBG measurements from the earlobe deviated from the fingertip by 9.5 ± 1.0% (mean ± SE). The correlation coefficient between these two sites was 0.97 ($P < 0.01$). Of earlobe measurements, 97.8% were within clinically acceptable zones A+B by error grid analysis (3). When earlobe was compared with forearm, CBG deviation was 10 ± 1.4%, correlation coefficient 0.96 ($P < 0.01$), and 95.3% of measurements were within zones A+B by error grid analysis.

In contrast to other sites that require vacuum-assisted lancing devices or sophisticated glucose meters, our observations demonstrate that CBG monitoring at the earlobes is attainable with regular standard lancets and that earlobe CBG concentrations correlate well and deviate minimally from either fingertip or forearm values. Earlobe testing was also clinically accurate by the error grid analysis method, which takes into account the effects on the clinical decision that would have been made if the CBG had been measured in the reference site. These data support the notion that earlobe CBG concentrations can be used in substitution of fingertip values. However, one limitation in our data series is that glucose values <70 mg/dl were not observed. Therefore, earlobe testing should be avoided if hypoglycemia is suspected.

For many patients, the earlobe pricking technique may be less convenient because it requires a second person to lance the skin and collect the blood. This certainly limits the applicability of the technique in the outpatient setting. Nevertheless, earlobe testing seems to be a useful alternative that could minimize costs and discomfort in patients assisted by a relative or nurse in hospitals and nursing homes.

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Needle Reuse and Tip Damage

Questions about needle reuse are raised in recommendations by the American Diabetes Association (1) and by practitioners and manufacturing companies (2). As an initial approach to examining these questions, we investigated whether multiple insertions of needles through the rubber stoppers on insulin vials would cause damage to needle tips (3). New needles were selected, attached to a precision manipulator, and inserted into insulin vials attached to a transducer that measured the force necessary to insert and remove a needle through the stopper. If needles were damaged by multiple insertions, an increase in force required to penetrate the rubber stopper would be expected.

In five experiments, we found that there was no significant difference in the mean force required to penetrate the rubber stopper of an insulin vial between 17 initial (41.5 g) and 17 subsequent (42.0 g) insertions. This suggests that needle tips are not dulled or damaged by multiple insertions to a degree that more force would be required to penetrate a vial stopper. Light micrographs and scanning electron micrographs supported the conclusion that little or no damage to needle tips occurred as a result of multiple insertions. We observed no hooks, bending, or other needle tip damage, although there was some evidence for deterioration of the silicon lubricant coating of needles.

At the same time, our examination of new, unused needles revealed imperfections when observed at high magnification. Our observations make it clear that damage attributed to reuse must be distinguished from inherent imperfections associated with the manufacturing process.

Clinical and manufacturer recommendations that discourage reuse of needles because of assumed dulling, bending, and/or fragmenting of needle tips are at variance with our findings, in which repeated penetration of insulin vial stoppers did not damage needle tips (2). Although we found no evidence of needle damage when penetrating the rubber stopper on insulin vials, there is need to ascertain the effect of cutaneous tissue penetration on needle tips. The reuse of needles by a significant number of patients with diabetes as a matter of convenience, or out of concern for cost and/or the creation of nonbiodegradable waste, indicates that further examination of needle reuse in vial stoppers and cutaneous tissue is warranted.

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The Diabetes Treatment Satisfaction Questionnaire

A cross-cultural South African perspective

Reliable and valid multicultural instruments are important in multicultural societies that are typical of modern cities, and clinicians, using psychosocial assessments, need to ensure that their diagnostic and screening tools are appropriate. This study was conducted with 176 diabetic outpatients from two culturally distinct groups (95 Bantu-speaking and 81 Afrikaans-speaking subjects) to *1*) ascertain the underlying dimensions of treatment satisfaction as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ status) (1), *2*) determine the reliability (internal consistency) of the measures, and *3*) investigate the effects of objective (HbA_{1c} results) and subjective metabolic control, health (2), and well-being (3) on satisfaction with diabetes treatment.

Principal components analysis was conducted on the 8-item DTSQ (1). All communality estimates exceeded the criterion of 0.30 (4) for both Bantu-speaking and Afrikaans-speaking patients (range 0.62–0.79 and 0.55–0.76, respectively). Two factors explained 71% of the variance for Bantu-speaking patients and 68% of the variance for Afrikaans-speaking patients. The first factor consisted of the six treatment satisfaction items, and the second factor consisted of the two subjective metabolic control items. Reliability (internal consistency) coefficients were excellent (5) and very similar for both groups (>0.80 on all measures).

Treatment satisfaction was associated with fewer incidents of hyperglycemia ($r = -0.58$, $P < 0.01$) and hypoglycemia ($r = -0.32$, $P < 0.01$), higher general well-being ($r = 0.56$, $P < 0.01$), and better health ($r = 0.44$, $P < 0.01$) for Bantu-speaking patients. For Afrikaans-speaking patients, greater treatment satisfaction was associated with fewer incidents of hyperglycemia ($r = -0.29$, $P < 0.01$), higher general well-being ($r = 0.54$, $P < 0.01$), and better health ($r = 0.50$, $P < 0.01$). Language, sex, age, and employment status were not related to treatment satisfaction or general well-being ($P > 0.05$), confirming the construct validity of the measures. HbA_{1c} results were not significantly related to treatment satisfaction, subjective metabolic control, general well-being, or general health for either group ($P > 0.05$).

For Bantu-speaking patients, fewer incidents of hyperglycemia significantly predicted 33% of the variance ($P < 0.001$) in treatment satisfaction; an additional 11% of the variance ($P < 0.001$) was explained by general well-being. For Afrikaans-speaking patients, general well-being predicted 29% of the variance ($P < 0.001$) in treatment satisfaction; an additional 7% of the variance ($P = 0.001$) was explained by general health.

In conclusion, the study demonstrated that the underlying dimensions of the DTSQ for both groups were treatment satisfaction and hyper- and hypoglycemia, all measures had excellent reliability (5), and well-being is an important predictor of treatment satisfaction for both groups of patients. These findings were consistent with those reported in the U.K. and Sweden (6–7) and support the idea that the DTSQ can be used in multicultural settings.

Acknowledgments— We thank Novo Nordisk (South Africa) for funding the interviewers' salaries. We also thank Professor Clare Bradley for permission to use her measures and Rosalind Plowright for constructive comments on the application of the DTSQ in multicultural settings.

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Depression, Diabetes, and Glycemic Control in Pima Indians

Few studies have addressed the relationship of depression and diabetes in ethnic minority groups, especially Native Americans (1). We examined the relationship between depression and diabetes in a community-based sample of 541 Pima Indians aged ≥18 years (192 with and 349 without diabetes) examined from September 2002 through February 2003.

Depression was defined by five or more depressive symptoms lasting ≥2 weeks, as assessed with PRIME-MD (Mood Module in the Primary Care Evaluation of Mental Disorders) (2). Diabetes was defined by a glucose tolerance test (fasting plasma glucose ≥7.0 mmol/l or 2-h plasma glucose ≥11.1 mmol/l) or previous clinical diagnosis.

The prevalence of depression was 16.3% (18.7% in women and 12.6% in men, $P = 0.06$). In both sexes, the prevalence of depression was higher in diabetic individuals (men 17.2 vs. 10.9%, women 20.2 vs. 17.6%), although these differences were not statistically significant (for total sample: age- and sex-adjusted odds ratio 1.3 [95% CI 0.7–2.1]). In diabetic individuals, HbA_{1c} was higher by 1.2% in those with depression (9.3 vs. 8.1%, $P < 0.01$), although depression was not related to HbA_{1c} in nondiabetic individuals (5.2 vs. 5.3%, $P = 0.2$). This association remained significant in a multivariate linear regression model that included age, sex, duration of diabetes, and BMI (HbA_{1c} higher by 1.1% in depressed persons, $P = 0.01$). Fasting plasma glucose was also higher, but not significantly so, in depressed diabetic individuals (10.2 vs. 9.5 mmol/l, $P = 0.3$).

Although studies of depression in Native-American communities are limited, our findings are consistent with previous suggestions that depression is several times more prevalent among Native Americans than in the general U.S. population (3). Our finding that the prevalence of depression was somewhat higher in diabetic individuals is also consistent with previous studies (1,4–6). Our study lacks precision to estimate the association of depression with diabetes because of the relatively small sample size (541, as compared with 21,513 to 1.3 million in other recent reports [4–6]). The high prevalence of depression in our study suggests that certain social, cultural, or economic factors may overshadow the influence of diabetes on depression in this population.

The higher HbA_{1c} in depressed diabetic individuals is consistent with previous findings in other populations (7). Treatment of depression reportedly improves glycemic control in diabetic patients, although the long-term effects are not known (8,9). This study adds to the sparse literature on depression and diabetes in ethnic minority groups. Identification and treatment of depression may be an important aspect of treating diabetes in Native Americans.

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Acknowledgments— We thank Dr. Richard Rubin, Dr. Patrick Lustman, and Dr. Mary de Groot for advice; Dr. Diane Montella and Priscilla Foote, MSW, of Gila River Health Care; and the members of the Gila River Indian Community for their participation.

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Improper Insulin Compliance May Lead to Hepatomegaly and Elevated Hepatic Enzymes in Type 1 Diabetic Patients

We have encountered hepatomegaly and pronounced elevation of liver enzymes AST and ALT in four patients with type 1 diabetes. These patients shared similar clinical features. They were all female (aged 11–14 years) with poor glycemic control. All had frequent hyperglycemia and intermittent hypoglycemia related to their history of poor compliance. Most of them had multiple hospital admissions for severe hyperglycemia and/or diabetic ketoacidosis. In addition to their high daily doses of insulin (1.3–2.2 units $\cdot$ kg^{-1} $\cdot$ day^{-1}), most were receiving extra doses of insulin to correct their frequent hyperglycemia. A1C levels were all higher than normal (ranging from 9.2 to 14.5%). Their initial AST and ALT levels were at least 30- and 14-fold higher than the normal limits, respectively, but the other liver function tests, such as alkaline phosphatase, prothrombin/partial prothrombintime, and total bilirubin, were normal except for one patient who had a minimal increase in alkaline phosphatase and total billirubin. The degree of hepatomegaly did not correlate with the liver enzyme levels, nor did it correlate with glycemic control or HbA_{1c} levels.

Upon admission to the hospital, proper insulin dosing was established. Three of the four patients were able to lower their insulin dose to 0.9–1.2 units $\cdot$ kg^{-1} $\cdot$ day^{-1} and achieve normal glycemic control. The AST and ALT levels were quickly decreased in just a few days after the patients obtained better glycemic control during hospitalization. Except for one patient, who was admitted for diabetic ketoacidosis, the patients had no apparent symptoms of liver disease before the admission. Their hepatomegaly was an incidental finding. Other than poorly controlled diabetes, the investigations did not reveal any other causes for hepatomegaly and increased liver enzymes. The normal creatine phosphokinase level and negative

myoglobinuria from one patient ruled out the possibility of rhabdomyolysis. The liver biopsy obtained in one patient revealed abundant glycogen deposits in hepatocytes that were consistent with the abdominal computed tomography finding of "fatty" appearance of those enlarged livers in all four patients. There were also some features that these patients did not share. One patient with the most profound hepatomegaly had significant delay in growth and puberty consistent with Mauriac syndrome as previously described (1), whereas the other three patients had normal growth and puberty. One patient, who was found to have hepatomegaly and elevated hepatic enzymes during one of her admissions to the hospital for diabetic ketoacidosis, had some nonspecific gastrointestinal symptoms that might have been related to her diabetic ketoacidosis rather than the hepatic disorder. Although all of our cases were girls, similar cases have been identified in boys (2).

Hepatomegaly and elevated hepatic enzymes, reported in both adult and pediatric patients with type 1 diabetes (2,3), could be relatively common but may be under-recognized or misidentified as the more common nonalcoholic steatohepatitis (NASH) because of similar clinical features. NASH is commonly seen in obese type 2 diabetic patients with insulin resistance. The hepatic enzyme elevation is slow to resolve. Our patients, however, were all nonobese type 1 diabetic patients. Their pronounced elevation of hepatic enzymes was resolved in just a few days once they achieved reasonable glycemic control at insulin dosages that were lower than what they were prescribed at home. Though the mild hepatomegaly and abnormal liver enzymes were believed to be associated with liver steatic change in NASH, whether the pronounced elevation of the liver enzymes was directly caused by liver glycogen deposit is not known. The pathogenesis for these problems has not been well studied. Nevertheless, both the increased hepatic enzymes and glycogen deposits may be related to poor glycemic control. Most of our patients received relatively high doses of insulin at home. We question the possible role of insulin over-treatment that might contribute to the pathogenesis of hepatomegaly because insulin is clearly a promoting agent for glycogenesis. Similar cases of hepatomegaly and elevated hepatic enzymes have been reported in children and adolescents who were chronically over-treated with insulin (4,5).

We therefore advocate the high vigilance in promoting patient compliance to insulin dosing rather than simply increasing insulin dosage in response to hyperglycemia. The swift reduction of hepatic enzymes in our cases after achieving reasonable glycemic control suggests that liver biopsy and other extensive work-up may be unnecessary in managing similar patients.

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Acute Hyperglycemia

Implications for contrast-induced nephropathy during cardiac catheterization

Acute hyperglycemia exacerbates ischemic injury of the brain and heart (1,2). Renal contrast agents are nephrotoxic, largely due to acute ischemia secondary to renal artery vasoconstriction (3). Historically, diabetic patients have been identified as a high-risk group for the development of contrast-induced nephropathy following cardiac catheterization; however, the mechanism for this increased risk is unclear (4). The purpose of this study was to determine whether acute hyperglycemia is an independent risk factor for the development of contrast-induced nephropathy after cardiac catheterization procedures.

A prospective, observational study was performed on all patients with diabetes (insulin dependent and independent) or any patient with a baseline serum creatinine ≥1.2 mg/dl receiving a cardiac catheterization procedures in a university-affiliated cardiac catheterization facility between June 2001 and January 2002. Patients with a diagnosis of acute renal failure or patients on dialysis were excluded. Patients were divided into two groups, hyperglycemic (AHG) (serum glucose ≥150 mg/dl) and nonhyperglycemic (NHG) (serum glucose <150 mg/dl), at the time of cardiac catheterization procedures. Contrast-induced nephropathy was defined as an increase in serum creatinine ≥0.3 mg/dl or >25% above the patient's baseline, determined 3–5 days following cardiac catheterization procedures.

The mean age, baseline creatinine, presence or absence of diabetes, hydration status, type and dose of contrast agent received, and use of specific medications, including acetylcysteine, were not different between groups. The percentage of inpatients was greater in the AHG group (74%) than in the NHG (26%), $P = 0.049$. Ventricular function, as measured by left ventricular end-diastolic pressure, was the same between groups (AHG = 17 ± 10 mmHg vs. NHG = 13 ± 3 mmHg, $P = 0.21$), and left ventricular ejection fraction was significantly lower in the AHG group (AHG = 45 ± 13% vs. NHG = 59 ± 14%, $P = 0.023$). A total of 38 patients were studied, including 33 diabetic subjects (87%). One-half of the study group (19 patients) was found to have hyperglycemia at the time of their cardiac catheterization procedure. Mean serum glucose was 217 ± 78 mg/dl for the AHG group vs. 124 ± 15 mg/dl for the NHG group, $P < 0.001$. The incidence of contrast-induced nephropathy for the entire study

population was 24% (9 of 38). The incidence of contrast-induced nephropathy in the AHG group was 42% (8 of 19) and was significantly greater than that for the NHG group, 5.3% (1 of 19), $P = 0.01$.

Acute hyperglycemia is a potential independent risk factor for the development of contrast-induced nephropathy in diabetic patients undergoing cardiac catheterization procedures. The glucose molecule has been shown to be a potential cytotoxin in the context of hyperglycemia (5). Acute hyperglycemia in patients with or without diabetes can detract from clinical outcomes in cardiovascular disease (1). The mechanism by which acute hyperglycemia worsens ischemic myocardial injury is currently under study. Conceivably, hyperglycemia may exacerbate acute renal ischemia associated with administration of radiographic contrast agents. The observational design of this study limits the relationship between acute hyperglycemia and contrast-induced nephropathy to that of a temporal association and does not address causality. Confounding variables, such as the slightly worse left ventricular ejection fraction in the AHG group, may have contributed to the development of contrast-induced nephropathy; however, the hyperglycemia in the AHG group may have contributed to poorer ventricular function. The relationship between acute hyperglycemia and contrast-induced nephropathy reported here will require a randomized controlled clinical trial for definitive characterization. This report suggests that a temporal association exists between acute hyperglycemia and contrast-induced nephropathy at the time of cardiac catheterization procedures in diabetic patients with mild renal dysfunction, and this topic bears further study.

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Influence of the Polymorphisms Tpr64Arg in the β3-Adrenergic Receptor Gene and Pro12Ala in the PPARγ2 Gene on Metabolic Syndrome–Related Phenotypes in an Indigenous Population of the Brazilian Amazon

Metabolic syndrome is a cluster of risk factors for type 2 diabetes and cardiovascular disease. Multiple mechanisms, including genetic factors, may contribute to this condition. The Trp64Arg variant in the β3-adrenergic receptor has been associated with features of the metabolic syndrome (1). A relatively common gene variant, Pro12Ala of the peroxisome proliferator–activated receptor-γ2 (PPARγ2) has been previously studied for association with obesity and type 2 diabetes (2,3).

The Parkataje Indians, from the Brazilian Amazon region, remained largely isolated. Recently, they underwent a rapid and intensive process of acculturation, with important changes in their lifestyle. Accompanying these changes, an increasing prevalence of obesity and other features of the metabolic syndrome have been observed. This study examines the relevance of the Trp64Arg mutation in the β3-adrenergic receptor gene and the Pro12Ala mutation in the PPARγ2 gene as a susceptibility factor to features of the metabolic syndrome in this population.

Participants were individuals aged ≥20 years; those with admixture and pregnant women were excluded. The study population comprised 85 (52 men and 33 women) individuals (mean age 41 ± 14.9 years). The degree of relatedness among the individuals was determined, and 37 nuclear families from six pedigrees were verified. Polygamy, including polyandry, occurs in this population. BMI, waist-to-hip ratio, systolic and diastolic blood pressures, and serum lipoproteins were studied. Fasting and 2-h blood samples were drawn for glucose and insulin measurements. Changes in body weight were analyzed in 80 individuals for a 3-year period. Genotypes were determined by PCR/restriction fragment–length polymorphism, as previously described (1,2).

A principal component analyses from the correlation matrix of the variables measured was performed. Statistical analyses (ANOVA and family-based association test) were done with the first two principal components because the measured variables are all related to the metabolic syndrome. The principal component, therefore, reflects the variance common to these variables and avoids corrections for multiple independent tests.

Obesity rates were higher in women than in men (27.2 vs. 3.8% at baseline, $P = 0.006$ and 45.2 vs. 16.3% at 3-year follow-up, $P = 0.01$), and for both sexes, there was an increase in these rates during the follow-up period (12.94 vs. 27.5%, $P = 0.03$). Diabetes was diagnosed in one individual, impaired glucose tolerance in another, and the remaining were classified as normal glucose tolerant according to World Health Organization criteria.

Frequencies of the β3-adrenergic re-

ceptor Arg and the PPARγ2 Ala variants were 0.33 and 0.31, respectively. These frequencies are in the Hardy-Weinberg equilibrium. The β3-adrenergic receptor Arg allele frequency (0.33) is much higher than those reported in other populations, except for Pima Indians (4). Similarly, the PPARγ2 Ala allele was more prevalent in the Parkateje Indians than in the other populations, whose frequency ranges from 0.12 among Caucasians to 0.01 in Chinese (5). ANOVA (with Welch's correction) showed that the first principal component was heterogeneous among the genotypic classes of the PPARγ2 locus; the AlaAla genotype was different from the others ($F = 3.51$, $P = 0.035$). The β3-adrenergic receptor locus showed no differences among the genotypes. The FBAT analyses showed that the PPARγ2 locus presented a significant segregation distortion with the recessive model ($P = 0.032$) but not with the additive or dominant models.

Among the Parkateje Indians, the Pro12Ala variant in the PPARγ2 gene, but not the Trp64Arg variant in the β3-adrenergic receptor, was associated with features of the metabolic syndrome.

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Elevated Serum Ferritin Concentrations in a Glucose-Impaired Population and in Normal Glucose Tolerant First-Degree Relatives in Familial Type 2 Diabetic Pedigrees

Two large epidemiological studies have recently reported a strong association between elevated serum ferritin concentration and increased risk for diabetes (1,2). Moreover, other studies have revealed the relationship among excess ferritin, coronary heart disease, and insulin resistance and have therefore renewed interest in ferritin as a risk factor for diabetes.

This study further investigates the association between ferritin metabolism and different status of glucose tolerance, including 121 type 2 diabetic subjects, 86 impaired glucose tolerant (IGT) subjects, 58 normal glucose tolerant (NGT) first-degree relatives in type 2 diabetic pedigrees, and 85 healthy control subjects. All patients underwent an oral glucose tolerance test (OGTT) and insulin release tests after 8 h of fasting, and blood levels of ferritin, HbA_{1c}, glucose, insulin, C-peptide, and lipids were measured. Serum ferritin levels were measured with the radioimmunoassay kit (Beijing North Institute of Biological Technology). Normal ranges for ferritin concentration are ~12–245 ng/ml for adult men and ~5–130 ng/ml for women. We defined elevated concentrations of ferritin as ≥295 ng/ml for men and ≥155 ng/ml for women.

Levels of fasting and postprandial plasma glucose in the NGT group were remarkably higher than in the healthy control subjects. Fasting insulin concentrations in the NGT group were also higher than those of the other groups, while postprandial insulin concentrations increased significantly when compared with healthy control subjects. Ferritin concentrations were the highest in type 2 diabetic subjects, followed by the IGT group, the NGT group, and the healthy control group (412.88 ± 155.58, 354.19 ± 173.03, 231.31 ± 130.32 [$P <$ 0.05 compared with healthy control subjects], and 164.69 ± 110.54 ng/ml, respectively). In the type 2 diabetic group, the newly diagnosed patients had higher ferritin concentrations than previously diagnosed (461.72 ± 132.41 vs. 354.19 ± 173.03 ng/ml, $P < 0.05$).

We also compared concentrations of serum ferritin in men and women for each group. In general, concentrations of ferritin in men were higher than in women ($P < 0.05$) except for in the healthy control group. In male subjects, ferritin concentrations of both newly and previously diagnosed type 2 diabetic, IGT, NGT, and healthy control groups showed the same trend as the whole group (494.30 ± 142.6, 425.01 ± 136.77, 390.07 ± 125.09, 284.74 ± 112.04 [$P < 0.001$ compared with the healthy control subjects], and 197.93 ± 110.41 ng/ml, respectively). However, in female subjects, ferritin concentrations in newly (425.65 ± 137.5 ng/ml) and previously (295.37 ± 150.98 ng/ml) diagnosed type 2 diabetes and IGT (330.72 ± 131.03 ng/ml) were higher than the NGT (174.06 ± 123.45 ng/ml) and healthy contol (137.28 ± 89.63 ng/ml) groups ($P <$ 0.001). No significant difference was

found between female NGT and female healthy control subjects. Moreover, in newly diagnosed type 2 diabetes, the concentrations of ferritin were significantly higher than in the previously diagnosed type 2 diabetic and IGT patients.

Using multiple regression analysis, we found an association between ferritin concentration and BMI, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure. HbA_{1c}, FPG, 2-h plasma postprandial glucose, triglycerides, and total cholesterol were positively related to ferritin concentrations, while HDL cholesterol levels were inversely related to ferritin concentrations.

In recent years, the issue of the potential pathology of serum ferritin in type 2 diabetes has gained remarkable interest (3). In this study, we found that serum ferritin concentrations were remarkably increased in type 2 diabetes, especially in newly diagnosed patients. Subjects with higher concentrations of ferritin consequently had higher HbA_{1c}, glucose, and insulin concentrations. These results further proved a positive association between type 2 diabetes and high plasma ferritin concentrations.

The exact mechanism through which elevated ferritin promotes the development of type 2 diabetes is unknown. Some investigations argued that abnormalities in ferritin metabolism might be a primary cause of type 2 diabetes (4–6). In our study, ferritin concentration in IGT subjects, the high-risk population for type 2 diabetes, already significantly increased when compared with normal control subjects, implying that hyperferritinemia occurs before elevation of plasma glucose concentrations. This observation was further substantiated by evidence that NGT first-degree relatives in the type 2 diabetic pedigrees had higher ferritin concentrations than normal control subjects.

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Simultaneous Bilateral Facial Palsy in a Diabetic Patient

Unilateral facial paralysis is a relatively common condition with an incidence of 20–25 per 100,000 population. However, simultaneous bilateral facial palsy (facial diplegia) is an extremely rare clinical entity and occurs in 0.3–2% of facial paralysis patients (1). The annual incidence is approximately 1 per 5 million (2).

A 78-year-old diabetic patient presented to the emergency room of our hospital with dysarthry and bilateral symmetrical facial weakness. He was unable to show his teeth, close his eyelids, or dilate his cheeks. From the neurologic examination, there were no other important findings, except for a minor instability during walking. The patient did not refer head injury or febrile viral infection in the recent past. We made the presumptive diagnosis of bilateral peripheral facial paralysis. Five weeks after his admission to our hospital, he made a full recovery. We have to note that glucocorticoids were not administered to him.

His full blood count, erythrocyte sedimentation rate, liver function tests, tumor markers, thyroid hormones, serum protein immunoelectrophoresis, serum ACE levels, C-reactive protein, and rapid protein reagent (RPR) were all within normal limits. HbA_{1c} was 7.0%, and the autoantibody screen was negative. Purified protein derivative was 5 mm. Serological tests for varied infectious agents, including herpes simplex virus (HSV)-I and -II, Varicella-Zoster virus (VZV), Epstein-Barr, Coxsackie, HIV-I and -II, cytomegalovirus (CMV), and hepatitis B viruses, as well as *Mycoplasma* and *Borrelia Burgdorferi*, were all negative.

Lumbar puncture revealed a normal pressure. Glucose, protein, and white blood count of the cerebrospinal fluid (CSF) were all within normal limits. Furthermore, stains and cultures for microorganisms were negative, as were tests for viruses (HSV and HSV-II, VZV, amd CMV), *Borrelia Burgdorferi*, and syphilis (venereal disease reaction level [VDRL] test).

Magnetic resonance imaging (MRI) of the brain and computed tomography (CT) scans of the head, thorax, and abdomen were all normal.

Facial diplegia may have diverse etiologies and may prove to be a diagnostic dilemma. The most common causes are bilateral Bell's palsy, Lyme disease, Guillain-Barre syndrome, sarcoidosis, Moebious syndrome, leukemia, viral infections, syphilis, basilar skull fractures, and pontine gliomas.

The most common infectious cause of facial diplegia is Lyme disease, caused by *Borrelia Burgdorferi* (3). Regarding the case presented, the IgG antibodies against this agent in serum, as well as in CSF, were negative. Other rare infectious causes include syphilis and *Mycoplasma* (4). However, VDRL tests in CSF and RPR in serum were negative, while antibody titer against *Mycoplasma* was negative.

Guillan-Barre syndrome is thought to be a postinfectious inflammatory polyradiculoneuritis. Up to 50% of the fatal cases have bilateral facial paralysis (5). The diagnosis is made on lumbar puncture (with a typically elevated protein in the absence of a raised number of cells)

and peripheral areflexia. Our patient had neither peripheral muscle weakness nor areflexia, and the CSF examination was normal.

Basilar skull fractures and pontine gliomas were excluded by means of both brain CT and MRI. Because there was no hilar adenopathy on chest CT and because serum ACE levels were normal, sarcoidosis was rejected.

Bilateral Bell's palsy does not seem to be a plausible diagnosis because our patient had neither a preceding viral infection nor the characteristic symptoms of this condition (facial numbness or pain, change in taste, numbness of the tongue, hyperacusis, etc.).

Diabetes has previously been associated with facial diplegia (4,6,7). According to Adour, Wingerd, and Doty (7), diabetes was present in 28.4% of 67 patients with recurrent or bilateral facial palsy. A plausible explanation could be that diabetic patients are more prone to nerve degeneration. In another series of 43 patients with bilateral seventh nerve palsy, there was one case associated with diabetes (4). Thus, having excluded all the other possible causes of this disorder after extensive evaluation, we could assume that the most likely cause of facial diplegia in the case presented is diabetes.

In conclusion, bilateral facial paralysis may be due to a life-threatening condition and, therefore, the practitioner should be aware of the diagnostic possibilities that cause this extremely rare condition. A review of the literature reveals that diabetes is associated with facial diplegia and should always be included in the differential diagnosis of this condition.

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Reduced Fear of Hypoglycemia in Successful Islet Transplantation

The recent dramatic improvement in clinical outcomes in islet transplantation in type 1 diabetes with the Edmonton Protocol has led to considerable excitement in the field of diabetes (1,2). The unprecedented 1-year success rates provide considerable evidence of the clinical effectiveness of the procedure (2,3). However, the benefits of freeing or reducing insulin requirements for these patients must be weighed against the risks of the procedure itself, as well as the lifelong immunosuppression. Before making this treatment available to a larger number of people with type 1 diabetes, measures of quality of care and of clinical effectiveness must be incorporated to fully evaluate the benefit of this treatment.

Episodes of severe hypoglycemia, a common occurrence in patients with labile type 1 diabetes and hypoglycemia unawareness, result in considerable fear and anxiety (4,5). When these concerns become an overwhelming burden for patients with type 1 diabetes, islet transplantation with the Edmonton Protocol is a potential solution (1–3). To determine the potential impact of islet transplantation on self-reported health-related quality of life (HRQL) outcomes, we compared islet-transplanted patients with pretransplant patients on measures of fear of hypoglycemia and anxiety.

Patients were asked to self-complete a battery of measures, including the Hypoglycemia Fear Survey (HFS) (4,5) and the Health Utilities Index Mark two (HUI2) (6). The HFS contains 23 questions that assess patients' concerns and worries about hypoglycemia and the behaviors in which patients may engage to avoid low blood glucose. The emotion attribute of the HUI2 can be used as an index of anxiety (6). Our standard protocol for administration of HRQL questionnaires occurs at baseline (pretransplant); midtransplant (i.e., between the first and second); 1, 3, 6, and 12 months posttransplant; and annually thereafter. Because islet-transplanted patients may have completed multiple surveys during follow-up, we initially used only the last available HRQL assessment. Surveys were completed by 81 (46 pretransplant and 35 islet-transplanted) patients. Among the islet-transplanted patients, questionnaires were completed a median of 11.9 months (range 1–36) after transplant. Scores between the two groups of patients were compared using nonparametric statistical tests.

Fear of hypoglycemia was significantly lower in islet-transplanted (median 5.0) compared with pretransplant (median 47.0) patients for the HFS total score ($P < 0.001$). The magnitude of the difference in HUI2 emotion scores between pretransplant and islet-transplanted patients would be considered clinically important (6) (1.00 vs. 0.86, respectively), although the difference was not statically significant ($P = 0.96$). Among all islet-transplanted patients, the small number ($n = 3$) without C-peptide secretion and requiring exogenous insulin had substantially more fear about hypoglycemia ($P = 0.041$) and reported more anxiety on the HUI2 emotion attribute ($P = 0.023$) than islet-transplanted patients with successful transplants.

Because anxiety pre- and posttransplant could be related to the procedure itself, we also compared HFS and HUI2 emotion scores between pretransplant and islet-transplanted patients in the immediate posttransplant period; for these comparisons, we used all available HRQL assessments at 1 and 3 months posttransplant. We found that fear of hypoglyce-

mia was lower, with a median HFS total of 30.0 for islet-transplanted patients ($n = 20$) at 1 month and 6.5 ($n = 18$) at 3 months, both of which were significantly lower ($P < 0.01$) than pretransplant. Conversely, the HUI2 emotion score was not significantly different from pretransplant at either 1 or 3 months posttransplant.

These initial evaluations of self-reported HRQL outcomes of in islet transplant recipients demonstrate that clinical success is associated with substantial reduction in emotional burden through reduced fear of hypoglycemia. General anxiety in islet-transplanted patients is reduced overall, which seems to be related to the freedom from requirement of exogenous insulin rather than to recovering from the transplant procedure itself. Although the interpretation of our initial data is interesting and informative, several limitations and questions remain. These initial data were collected cross-sectionally and on a relatively small but growing sample of islet-transplanted patients; even with the small sample sizes, the observed differences were statistically significant. Longitudinal assessments to measure within-person change over time are required to fully assess the impact on HRQL.

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A Case of Lipoatrophy With Lispro Insulin Without Insulin Pump Therapy

Localized lipoatrophy occurring in the subcutaneous insulin injection area in diabetic patients was a phenomenon practically forgotten after the introduction of human insulin in medical practice. In recent years, there have been very few publications in relation to this matter.

Three cases of patients with type 1 diabetes who presented with subcutaneous localized lipoatrophy areas and who were in treatment with Lispro insulin were recently reported (1,2). The three patients used a continuous subcutaneous insulin infusion (CSII) system; therefore, the authors posed the doubt of whether such an administration system locally played a determinant role in the occurrence of subcutaneous localized lipoatrophy.

We present a case of localized lipoatrophy associated with treatment with Lispro insulin administered in a multiple dose regimen that disregards the role of CSII as a necessary factor for its genesis.

Our patient is a 35-year-old woman diagnosed in January of 1992 at 22 years of age. From the start, she was treated with recombinant DNA human insulin (Humulin Regular and Humulin NPH; Lilly) in a regimen of three daily doses. She always exhibited a good degree of metabolic control, with HbA_{1c} between 6 and 7%. Seven years after diagnosis, she began to exhibit episodes of hypoglycemia not perceived with accompanying neuroglycopenia, which persisted in spite of several changes of her prior insulin regimen. For that reason, in November of 2000 it was decided that she would change to LisPro insulin administered before breakfast, lunch, snack, and dinner, and NPH insulin administered before breakfast and dinner. With the new regimen, metabolic control remained similar to the previous control and the episodes of neuroglycopenia persisted. Anti-insulin antibody (IAA) levels were measured and were high (49.6%, reference value <8.5%). In October of 2002, 23 months after beginning with LisPro, the patient consulted the physician because she had a circumscribed localized lipoatrophy area of ~3 cm in diameter on the anterior aspect of the right thigh, one of her normal injection areas. Six months later, a period in which injection in said area was avoided, the lesion remained unchanged, but an incipient localized lipoatrophy area could be observed in the same area of the contralateral thigh. For this reason, it was decided to change from Lispro to Aspart insulin.

Six months after said change of insulin, which was when this letter was sent, neither progression nor improvement of the localized lipoatrophy lesions had been observed. IAA levels were 30.5%, slightly lower than the previous levels.

The development of localized lipoatrophy in the insulin injection area is a practically exclusive complication of type 1 diabetic patients, although cases have been reported in patients with type 2 diabetes (3). From the etiopathogenic point of view, it is considered an immunological phenomenon. Although this has not been sufficiently clarified, a strong association between the lesions and high IAA plasma levels and the presence of insulin and immunoglobulin G deposits in subcutaneous tissue of the affected areas (4) have

been reported. The consequences of this immunological activation are the local inhibition of adipocyte differentiation, probably mediated by the local hyperproduction of tumor necrosis factor-α (5).

In affected patients, the pharmacokinetic variations of insulin due to high IAA levels and the erratic absorption of the drug when it is injected in the areas affected with localized lipoatrophy imply a glycemic variability making it very difficult to achieve suitable metabolic control.

Although the immunogenic profile of the patients treated with Lispro insulin and recombinant human insulin are comparable (6), the recent occurrence of descriptions of localized lipoatrophy associated to this analogue can decrease the therapeutic alternatives of this complication when, especially in recent years, in the few published cases of human insulin–induced localized lipoatrophy the attempted solution to the problem was to change to Lispro. It is possible that the use of CSII may favor the occurrence of localized lipoatrophy but, as can be seen in the case we present, it is not a factor *sine qua non* for its development. Curiously, severe cases of human insulin–induced localized lipoatrophy have been previously reported that responded satisfactorily after the introduction of CSII (7).

The association of localized lipoatrophy and Lispro insulin without the concourse of CSII has not been reported previously. We therefore believe it is interesting to disclose our case and to encourage publishing for other diabetologists who have observed similar cases for the purpose of clarifying its pathogenesis and therapeutic approach.

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Diabetes In A Nonpancreatectomized Child With Nesidioblastosis

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (Online Mendelian Inheritance in Man [OMIM] 256450), formerly known as nesidioblastosis, is a glucose metabolism disorder characterized by profound hypoglycemia and inappropriate secretion of insulin (1). Affected children run the risk of severe neurological damage unless immediate and adequate steps are taken (2). Treatment with diazoxide and/or somatostatin analogue is the first line of therapy. However, it not always effective, especially in familial cases, which may necessitate an alternative intervention such as pancreatectomy (3).

Several studies have suggested that partial pancreatectomy endangers future islet cell function (4,5). The incidence of diabetes increases with age and correlates with the extent of surgical resection (6,7). However, there was no report of occurrence of overt diabetes in medically treated patients (8). In this report, we described an adolescent female with neonatal nesidioblastosis who developed diabetes after medical treatment with diazoxide/octreotide. To our knowledge, this is the first nesidioblasosis case subject who developed diabetes following medical therapy.

A 14-year-old Saudi female presented with severe persistent hypoglycemia during the first few days of life. She was diagnosed with hyperinsulinemic hypoglycemia of infancy based on her intravenous glucose requirement of >14 mg · kg^{-1} · min^{-1}, an insulin-to-glucose ratio of >0.3 (her insulin level was 98 μU/ml at a serum glucose of 32 mg/dl), negative urinary ketones, a 30-min glucose increment of ≥30 mg/dl in response to intramuscular 0.5 mg glucagon, and normal blood spot acylcarnitine profile determined by tandem mass spectrometry. She also had a normal growth hormone level of >20 mU/l and a normal cortisol level of >500 nmol/l during hypoglycemia. She was treated initially with frequent feeding supplemented with complex carbohydrates (polycose/corn starch) and then started on diazoxide 15 mg · kg^{-1} · day^{-1} divided three times a day, which kept her euglycemic with occasional hypoglycemic episodes. In 1992, octreotide was first introduced in our hospital as an adjunctive therapy to diazoxide. She was started on 25 μg · kg^{-1} · day^{-1} of subcutaneous octreotide divided four times a day. She responded to medical treatment with no hypoglycemic episodes. She was continued on diazoxide and octreatide until the age of 10 years, when she became euglycemic and these two medications were stopped. At the age of 14, she developed hyperglycemia associated with weight gain. Her blood glucose ranged from 200 to 300 mg/dl, and her weight was 75 kg (>95%). She had an insulin level of 10 μU/ml and C-peptide level of 0.16 nmol/l at a serum glucose level of 350 mg/dl. Antiglutamic acid decarboxylase, insulin, and islet cell antibodies were negative. She responded to metformin 250 mg twice a day with a serum mean glucose level of 109 mg/dl and HbA_{1c} of 7.5%.

The long-term outcome of PHHI is not well documented. Previous reports suggested that subtotal or near total pancreatectomy in infants will endanger the future islet function (4–8). Long-term follow-up studies in medically treated patients with diazoxide or octreotide showed that some of these patients re-

sponded to medical therapy and became euglycemic (9–11). Some patients were weaned off medical therapy and continued to be euglycemic; however, none of them became hyperglycemic or diabetic. Leibowitz et al. (8) followed six conservatively treated patients with PHHI. Intravenous glucose tolerance was performed in all patients and showed a blunted insulin response in two with no overt hyperglycemia. Histologically, Kassem et al. (12) showed that β-cell proliferation and apoptosis, which normally occurrs in the normal developing human pancreas, also occurs in the PHHI pancreas with a higher frequency of apoptosis. They suggested that this phenomenon will result in a slow, progressive, and complete loss of β-cell mass. This histological report and the development of diabetes in our nonpancreatectomized PHHI patient may suggest that patients with PHHI will naturally develop diabetes whether they were treated medically or surgically or even if they are left untreated. This hypothesis was further raised when the natural history of this disease was discussed in knockout mouse models. Transgenic mice engineered to express a dominant-negative form of Kir6.2 or mice with ATP-sensitive K^+ channel deficiency developed hyperinsulinemic hypoglycemia followed by hypoinsulinemic hyperglycemia. Diabetes in these transgenic mice was thought to be due to sustained unregulated Ca influx and premature β-cell apoptosis (burn-out phenomenon) (13,14). Seino et al. (15,16) reported another possible predisposing factor to hyperglycemia in PHHI patients. They showed that hyperglycemia in Kir6.2 knockout mice was more evident with age and increasing weight. They suggested that the Kir6.2 knockout mouse provides a model of type 2 diabetes, and that both the genetic defect in glucose-induced insulin secretion and the acquired insulin resistance due to environmental factors are necessary to develop diabetes in the Kir6.2 knockout mouse.

We hypothesized that diabetes was induced by weight gain and obesity in our patient. She responded to metformin, which may suggest that her diabetes is due to insulin resistance induced by both weight gain and insulin insufficiency. Simple type 2 diabetes is still a possibility, although there was no history of diabetes in the family. This patient could be the human example of the Kir6.2 knockout mouse model. We recommend, based on this human clinical evidence, weight control in aged PHHI patients to decease the incidence of diabetes.

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Oral Glucose Tolerance Test Evaluation With Forearm and Fingertip Glucose Measurements in Pregnant Women

It is known that glucose levels in capillary blood in the fingertip after a liquid glucose load are constantly higher when compared with venous blood measurements (1). Recently alternative sites

for capillary blood drawing (e.g., forearm) have been proposed (2) that are less painful compared with fingertip. Data have shown that there was no significant difference between the capillary blood drawn from forearm and fingertip in diabetic patients with glucose values in a wide range (3). Nevertheless, some data have shown that glucose results from alternative sites and fingertip were not identical. This difference was more pronounced when there was a rapid increase or decrease of blood glucose values (4). It seemed that significant differences appeared when glucose values declined at a mean rate >2 mg $\cdot$ dl^{-1} $\cdot$ min^{-1} (5), but not at a lower rate (6). All the abovementioned reports compared capillary blood drawn from either the forearm or fingertip, but so far, it appears that no direct comparison has been made between venous plasma blood and capillary forearm blood.

Thus, the purpose of this investigation is to study the pattern of capillary forearm blood and that of capillary fingertip blood glucose using the same glucometer (FreeStyle; Therasense) and to compare both with venous blood laboratory measurements during a 100-g oral glucose tolerance test (OGTT) in pregnant women. A total of 47 pregnant women (age 31 ± 3 years, BMI 24 ± 3 kg/m^2, and gestational age 24–28 weeks) underwent a 100-g OGTT. Half of these women ($n = 23$) had simultaneous glucose samples drawn from the forearm after rubbing (7) using FreeStyle in 0′, 60′, 120′, and 180′, whereas the other half ($n = 24$) underwent the same procedure with blood drawn from the fingertip. The two groups were matched for age, BMI, and gestational age. Glucose difference in percentage (GDP) was calculated for both groups separately. Mean GDP between finger glucose and venous glucose samples was significantly higher at 60′ (14.6 ± 20.4%), 120′ (25.2 ± 34.7%), and 180′ (26.4 ± 26.7%) than at 0′ (−3.1 ± 14.1%) ($P < 0.01$). Mean GDP between forearm glucose and venous glucose samples was significantly higher at 120′ (16.3 ± 21.5%) and 180′ (16.3 ± 21.5%) than at 0′ (−2.5 ± 16.3%) ($P < 0.01$). On the contrary, mean GDP at 60′ (6.7 ± 20.9%) was not found significantly different.

These findings confirmed the already reported observation that up to 3 h after a liquid glucose load, capillary finger glucose levels are constantly higher (15–26%) than venous glucose levels. On the contrary, forearm glucose levels were closer to venous plasma glucose levels: There was no significant difference between them after 1 h, whereas a significant increase of 16% appeared at 2 and 3 h. These findings are in accordance with the concept of slower glucose kinetics at the forearm than the fingertip due to lesser arteriovenous anastomoses (4). To be sure, this physiological difference needs to be taken into consideration in the detection of hypoglycemia in diabetic patients. However, it is precisely this physiological difference that supports the suggestion that capillary forearm glucose measurements using a portable glucose meter may be useful for the 50-g challenge test for gestational diabetes screening in an outpatient environment.

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Silent Hypoglycemia Presenting As Dysesthesias

Hypoglycemia is not often in the differential diagnosis for dysesthesias but should be considered when involved in the care of diabetic patients. Such symptoms may herald silent hypoglycemia and resultant nerve injury, as illustrated in the following case.

A 26-year-old female with type 1 diabetes presented with a 2-month history of numbness and tingling in her hands and feet upon waking in the morning. Symptoms began when her treatment was altered from NPH 50 units q A.M. to NPH 35 and Regular 3 q A.M. and NPH 8 and Regular 5 at dinner. The patient monitored her glucose more than four times each day and reported three to four glucose values a week that were <60 mg/dl without symptoms. Her morning glucose levels averaged 60 mg/dl. The symptoms were more pronounced in her hands than feet and resolved within minutes. On exam, she showed no objective sensory loss, possessed good muscle tone, bulk, and strength, had intact reflexes (2+) bilaterally, and had no focal neurological signs. HbA_{1c} was 6.8%.

Symptoms were attributed to peripheral neuropathy secondary to hypoglycemia. Her insulin regimen was adjusted to NPH 35 and Regular 3 q A.M., NPH 4 q HS, and Regular 5 before dinner for glucose >200 mg/dl. One month later, she reported the disappearance of the symptoms and a reduction in the frequency of values <60 mg/dl to once a week.

Hypoglycemia has been proposed to induce nerve injury by several mechanisms. Lack of substrate leads to a reduction in axonal transport, causing an accumulation of intraneural metabolites and neuronal injury (1). Hypoglycemia can induce a reduction in blood flow, leading to neural hypoxia (2–4). These mechanisms may all play a role in nerve injury; disturbance in neural blood flow may be the initial manifestation of hypo-

glycemia, while prolonged hypoglycemia may induce axonal damage (2).

Peripheral neural injury has been reported in patients with hypoglycemia due to insulinomas (5). These patients displayed paresthesias and/or muscle wasting and weakness. After tumor resection, patients showed resolution of sensory symptoms, while muscle wasting persisted.

We propose that practitioners consider undetected hypoglycemia as a possible cause of paresthesias in diabetic subjects. Frequent episodes of hypoglycemia can hinder patients' efforts to achieve normoglycemia. Early measures taken to reduce such episodes will promote normoglycemia.

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Exercise Increases Adiponectin Levels and Insulin Sensitivity in Humans

Adiponectin is an abundant circulating adipocytokine with anti-inflammatory properties (1) linked to cardiovascular disease, type 2 diabetes, and obesity (2–5). Numerous reports (3–5), including the present one, confirm plasma adiponectin levels to be inversely related to insulin resistance. Longer term, a rise in adiponectin has been shown to occur in response to weight loss and glitazone therapy, but not after chronic exercise training. However, understanding of the shorter-term regulation of adiponectin in particular remains unclear. As an extension to a previously reported exercise intervention in sedentary males by our group (6), we have now examined the effects of this training intervention on adiponectin levels in overweight males. We demonstrate that the short-term exercise training increased circulating adiponectin levels with accompanied improved insulin sensitivity.

Twenty-six overweight males participated in an exercise program, as previously described (6). Full data were available on 19 subjects who completed the entire program. At baseline and postexercise intervention, all subjects were assessed for anthropometric measures (dual-energy X-ray absorptiometry, magnetic resonance imaging, and BMI), insulin sensitivity (insulin clamp), and indirect calorimetry (for fat oxidation rates), and overnight fasting plasma samples were collected for adiponectin levels. Briefly, exercise consisted of aerobic exercise (brisk walking mixed with light jogging) 4–5 days per week for 40 min per session (~55–70% $V\text{O}_{2\text{max}}$) over 10 weeks (6). Plasma adiponectin was determined using a radioimmunoassay kit (Linco Research, St. Charles, MO). Two-tailed paired Student's *t* tests were used for comparisons between time points before and after exercise, and associations between continuous variables were investigated using simple regression analyses. Analyses were performed using StatView software (version 4.5; Abacus Concepts, Berkeley, CA).

The subjects' mean age was 37.1 ± 1.3 years, and before exercise mean BMI was 30.7 ± 0.7 kg/m^2 and $V\text{O}_{2\text{max}}$ was 48.4 ± 0.8 ml · kg fat-free mass (FFM)$^{-1}$ · min^{-1}. Correlations between glucose infusion rate (GIR), a measure of insulin sensitivity, and indexes of adiposity in the sedentary males were highly significant (all $P < 0.0001$). Fasting plasma adiponectin levels were strongly inversely related to insulin resistance in these subjects ($r = -0.52$, $P = 0.0007$) and to total fat ($r = -0.39$, $P = 0.015$), central subcutaneous fat ($r = -0.37$, $P = 0.02$), and visceral fat mass ($r = -0.32$, $P = 0.05$). Two to three bouts of moderately intense aerobic exercise performed within ~1 week of baseline assessments resulted in a mean 23% increase in GIR (35.0 ± 2.7 vs. 43.0 ± 2.8 μmol · min^{-1} · kg FFM^{-1}, $P < 0.0001$) and a mean 37% increase in basal fat oxidation rate (1.05 ± 0.14 vs. 1.44 ± 0.08 g · day^{-1} · kg FFM^{-1}). These effects were maintained after 10 weeks of exercise training (42.4 ± 3.1 μmol · min^{-1} · kg FFM^{-1} and 1.35 ± 0.07 g · day^{-1} · kg FFM^{-1}, respectively). Body weight was unchanged after two to three bouts of exercise (93.5 ± 1.9 vs. baseline 93.4 ± 1.8 kg) and was not significantly reduced at 10 weeks (92.6 ± 1.9 kg, $P = 0.08$) in this cohort.

Adiponectin levels rose by 260% after two to three bouts of exercise (~1 week) (7.0 ± 0.7 vs. 18.2 ± 1.9 μg/ml, $P < 0.0001$) despite unchanged body weight and remained elevated (16.4 ± 1.9 μg/ml, $P < 0.0001$) after 10 weeks. However, individual changes in adiponectin levels after two to three bouts (~1 week) and after 10 weeks of exercise were not correlated with the respective changes in insulin sensitivity or fat oxidation rate. Our results contrast with Hulver et al. (7) where adiponectin is unaltered with exercise training despite enhanced insulin action. However, we assessed the acute effect of exercise after two to three bouts of exercise (6), whereas they took their "basal" samples 6 weeks after a ramping exercise period before the 6-month endurance exercise training program (7). Our data indicate that elevated adiponectin levels are first apparent after 1 week (two to three bouts) of moderately intense exercise. We suggest that it is likely that this short-term moderate exercise training can modify regulation of adiponectin, and this could be postulated to provide another mechanism by which exercise re-

duces atherogenic risk, at least in overweight males.

Acknowledgments— We acknowledge the assistance of the nursing staff of the Clinical Research Facility, laboratory technicians of the Diabetes Research Group, Dr. Judith Freund and technicians of the Nuclear Medicine Department, St Vincent's Hospital Sydney, and volunteers who participated in this study.

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High Glucose Levels Induce an Increase in Membrane Antioxidants, in Terms of Vitamin E and Coenzyme Q10, in Children and Adolescents With Type 1 Diabetes

Oxidative stress is defined as an imbalance between prooxidants and antioxidants in favor of the former (1), and diabetic patients are considered a risk group for increased oxidative stress (2,3). Studies regarding oxidant/antioxidant balance in type 1 diabetic children and adolescents have given conflicting results (4–7). The aim of this study was to determine whether serum hydroperoxides (reactive oxygen metabolites [ROMs]) as oxidative markers and plasma α-tocopherol (vitamin E) and coenzyme Q10 as indexes of antioxidant capacity could be related to metabolic control in 75 unselected children, adolescents, and young adults with type 1 diabetes. ROMs are the first markers of oxidation and one of the most reliable indicators of oxidative stress. Vitamin E is an important chain-breaking antioxidant factor controlling LDL oxidation. Coenzyme Q10 is an electron carrier–proton translocator in the respiratory chain and is an antioxidant factor by directly scavenging radicals or indirectly by regenerating vitamin E. ROMs were assayed using the kit d-ROMs test (Diacron), which is based on the Fenton reaction (8). Vitamin E was determined by reversed-phase high-performance liquid chromatography. Coenzyme Q10 was also determined by reversed-phase high-performance liquid chromatography, according to the method of Grossi et al. (9). Statistical significance was assessed using Student's *t* test and Pearson correlation index for normally distributed data and using Mann-Whitney and Spearman rank correlation for nonnormally distributed data. All results that were nominally significant at $P < 0.05$ are indicated. Diabetic patients did not have different ROMs, vitamin E, and coenzyme Q10 levels from age-matched control subjects. Significant positive correlations were found between the following parameters: vitamin E and coenzyme Q10, coenzyme Q10 and HbA_{1c}, and vitamin E and HbA_{1c}. No correlation was observed between ROM levels and coenzyme Q10, vitamin E, or HbA_{1c} values. Vitamin E and coenzyme Q10 values were higher in patients ($n = 37$) with poor control ($HbA_{1c} > 8\%$) than in those ($n = 38$) with good control ($HbA_{1c} < 8\%$) (vitamin E, 25.2 ± 9.5 vs. 20.9 ± 4.6, $P = 0.044$; coenzyme Q10, 1.12 ± 0.56 vs. 0.82 ± 0.33, $P = 0.012$, respectively). The patients with retinal or renal complications ($n = 19$) compared with those without had higher values of vitamin E (25.8 ± 7.1 vs. 20.9 ± 4.8, $P = 0.009$).

Therefore, in our patients vitamin E levels increased in all of the situations where an increase of oxidative stress was putative, i.e., in the presence of poor metabolic control and complications. This result is in disagreement with most of the data of the literature (5,7,10,11), but in agreement with a few studies (12,13). However, a further confirmation of this result is indirectly provided by our findings regarding coenzyme Q10. In fact, coenzyme Q10 levels, like vitamin E levels, are also higher in poorly controlled than in well-controlled patients and are positively correlated with HbA_{1c} values. This finding is not surprising because these two antioxidants have strict physiological interrelationships and are positively inter-

correlated in both the patients and control subjects. On the other hand, it has already been demonstrated that high-glucose conditions produce an overexpression of intracellular antioxidant enzymes in human endothelial cells in culture (14) or in skin fibroblasts from diabetic patients (15) and that the decreased susceptibility to oxidative stress in diabetic rats is associated with an increase in mitochondrial glutathione and coenzyme Q contents (16). This effect seems to represent an adaptive response to increased oxidative stress. In very young patients, this response is high enough to neutralize the increase in reactive oxygen species. In fact, we found this unchanged in the blood of our patients.

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Increased Oxidative Stress Is Associated With Serum Levels of Triglyceride, Insulin Resistance, and Hyperinsulinemia in Japanese Metabolically Obese, Normal-Weight Men

Metabolically obese, normal-weight (MONW) subjects (BMI <25 kg/m^2) are characterized by an excess (≥100 cm^2 by abdominal computed tomography scanning) visceral fat area (VFA), insulin resistance, and hyperinsulinemia (1,2). The criteria for MONW subjects and the insulin resistance syndrome are very similar, and the pathophysiological events occurring in MONW subjects have recently been the focus of many investigators (1–4).

Several studies have reported the association of oxidative stress with insulin resistance and hyperinsulinemia in obese subjects (5,6). However, the degree of oxidative stress and its correlation with insulin resistance and insulin secretion have not yet been evaluated in MONW subjects.

The present study comprised 18 Japanese MONW (aged 34.7 ± 1.7 years, BMI 23.9 ± 0.3 kg/m^2, and VFA 146.3 ± 5.8 cm^2 [means ± SE]) and 18 age-matched normal (BMI <25 kg/m^2 and VFA <100 cm^2) men (aged 33.8 ± 1.4 years, BMI 21.9 ± 0.5 kg/m^2, and VFA 59.3 ± 5.3 cm^2).

According to the American Diabetes Association's diagnostic criteria, all subjects had normal glucose tolerance based on the 75-g oral glucose tolerance test (OGTT) (7).

The plasma levels of free 8-epi-prostaglandin F2α (8-epi-PGF2α) were measured as marker of oxidative stress using a commercially available enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI).

8-epi-PGF2α plasma levels in MONW men (40.4 ± 6.2 pg/ml; $P <$ 0.01) were significantly increased compared with normal subjects (8.5 ± 1.5 pg/ml). The glucose infusion rates (index of insulin resistance during the euglycemic-hyperinsulinemic clamp study) in

MONW subjects (53.9 ± 3.2 μmol·kg^{-1}·min^{-1}; $P < 0.02$) were significantly decreased compared with normal subjects (65.0 ± 2.5 μmol·kg^{-1}·min^{-1}). Fasting serum levels of insulin (49.1 ± 4.1 pmol/l; $P < 0.01$), insulin area under the curve (AUC) during the 75-g OGTT (44721.7 ± 3811.3 pmol/l; $P < 0.02$), and serum levels of triglycerides (1.6 ± 0.1 mmol/l; $P < 0.01$) were significantly increased in MONW subjects compared with normal subjects (fasting insulin levels 29.9 ± 2.9 pmol/l, insulin AUC 31341.7 ± 3388.9 pmol/l, and serum levels of triglyceride 0.9 ± 0.1 mmol/l).

The 8-epi-PGF2α plasma levels were significantly correlated with the glucose infusion rate ($r = -0.513$, $P < 0.05$), VFA ($r = 0.868$, $P < 0.01$), serum levels of triglyceride ($r = 0.658$, $P < 0.02$), fasting serum levels of insulin ($r = 0.502$, $P < 0.05$), and the insulin AUC ($r = 0.655$, $P < 0.01$) only in MONW subjects.

Bakker et al. (8) have previously reported that elevated concentration of cytosolic long-chain acyl-CoA, which is associated with increased cytosolic triglyceride stores, induces mitochondrial oxygen free radical production due to intramitochondrial ADP deficiency. Therefore, increased trigylceride content in nonadipose tissue together with increased serum levels of trigylcerides may play an important role in the production of oxidative stress in Japanese MONW subjects.

8-epi-PGF2α plasma levels were significantly correlated with insulin resistance in MONW men. This relationship was also observed in obese men (6). Although correlation does not prove causation, these findings suggest that oxidative stress may contribute to the development of insulin resistance in obese and MONW men.

The results of the present study are in agreement with a previous study (9,10) that showed increased cytosolic long-chain acyl-CoA and oxidative stress lower glucose-induced insulin secretion from pancreatic β-cells. On the other hand, it has been reported that hyperinsulinemia reduces oxidative stress production (11,12). Hyperinsulinemia may also have a protective role against increased oxidative stress in MONW men.

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Efficacy of Conversion From Bedtime NPH Insulin Injection to Once- or Twice-Daily Injections of Insulin Glargine in Type 1 Diabetic Patients Using Basal/Bolus Therapy

The efficacy of glycemic control in type 1 diabetic patients with either once- or twice-daily glargine insulin injection was evaluated in this long-term, prospective, nonrandomized study. Eighty-two type 1 diabetic patients were followed over 12–15 months after conversion from a single bedtime NPH insulin injection to a single bedtime insulin glargine injection. These patients were switched with the availability of glargine insulin to reduce frequency and severity of nocturnal hypoglycemia and to improve fasting glucose levels. This group of type 1 diabetic patients was switched to glargine insulin in place of twice-daily NPH. These patients continued their same bolus therapy with either insulin lispro or aspart and underwent frequent (three to five times daily) home glucose

monitoring. This study showed the expected fewer nocturnal hypoglycemic events, but the primary outcome was an improvement in glycemic control based on the HbA_{1c} values. Patients HbA_{1c} values were determined every 8 weeks, and insulin doses were titrated, with glargine adjusted based on morning fasting glucose values. If the HbA_{1c} remained above goal, the intensity of home glucose monitoring was increased and bolus therapy was adjusted accordingly. In one-quarter of patients, the lunch bolus titration resulted in mid-afternoon hypoglycemia, and when reduced, the patients had elevated presupper glucose values. Patients who had an increase in their HbA_{1c} and/or persistent elevation of presupper glucose despite titration of both bolus insulin and glargine insulin were then placed on twice-daily glargine injections. A spilt dose of glargine was given only after titration of glargine insulin resulted in morning hypoglycemia and/or persistent elevation of the afternoon blood glucoses that could not be corrected with bolus titration.

Sixty-two subjects were using glargine insulin once daily, and the remaining 20 (24.2%) subjects required twice-daily therapy. The 24.2% of patients on split glargine were converted from once-daily glargine injections after an average of 289 ± 203 days (median 259). At that time, their HbA_{1c} had deteriorated from an initial value of 7.9 ± 1.5 to 8.1 ± 1.4% ($P = 0.16$) and titration was limited by the symptoms outlined above. Subjects on split glargine did not differ from those subjects using once-daily glargine injections in regard to their age ($P = 0.21$), duration of diabetes ($P = 0.21$), baseline HbA_{1c} ($P = 0.91$), presence of detectable C-peptide ($P = 0.78$), or the presence of microvascular complications: retinopathy ($P = 0.37$), nephropathy ($P = 0.44$), neuropathy ($P = 0.30$), or macrovascular complications ($P = 0.88$).

In the single-daily injection patients, the HbA_{1c} improved significantly (from 7.8 to 7.3%, $P = 0.01$) after 476 ± 178 days on glargine insulin. The split glargine injection subjects also had an improvement in the HbA_{1c} from 7.9 to 7.4% ($P = 0.03$) over a 3- to 6-month period. The ending HbA_{1c} between groups was not significant ($P = 0.80$). The decrease from the mean starting HbA_{1c} was identical between groups; however, a more significant drop in the HbA_{1c} from the time of spilt to the end of the study (8.1 to 7.4%) did reach statistical significance ($P = 0.001$). To achieve this improved glycemic control in these patients, 70% more glargine was required (44 ± 26 vs. 26 ± 13 units, $P > 0.008$).

In conclusion, in this prospective, nonblinded, nonrandomized, prospective study, one-quarter of type 1 diabetic patients required twice-daily glargine insulin injections to achieve acceptable glycemic control. The reason for this was that more glargine insulin could be safely and/or effectively used when split in this population. Regardless, type 1 diabetic patients on glargine insulin improved their glycemic control, as measured by the HbA_{1c} values. Patients who do not achieve control after a titration period should receive split daily doses to achieve glycemic control.

This is the first study to demonstrate an improvement in HbA_{1c} in type 1 diabetic subjects using basal-bolus therapy after conversion from basal NPH insulin to basal glargine insulin. Previous studies were not continued beyond 6 months, and the protocols restricted glargine to once-daily dosing (1–3). Using our study data to project the outcome, if all patients remained on single daily dosing, then the average HbA_{1c} reduction would have been 0.3%, which is similar to other studies, and would not have been statistically significant.

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COMMENTS AND RESPONSES

Memory Impairments Associated With Postprandial Hyperglycemia and Glycemic Control

Comment on Greenwood et al.

It was with interest that we read the study by Greenwood et al. (1), which investigated the impact of postprandial hyperglycemia on memory function in type 2 diabetic patients and demonstrated impaired memory function after carbohydrate ingestion. As they thoroughly discussed, the impact of glycemic control and transient hyperglycemia has been under investigation since the mid-1980s (2,3), with study results that are heterogeneous and not very conclusive. In fact, data from a study at our diabetes center (4) comprising 53 type 2 diabetic patients suggest that glycemic control has no influence on cognitive functioning, including memory (Auditory Verbal Learning Test), whereas patients with diabetic complications show lower performance.

One reason for the heterogeneity of results probably stems from the lack of consensus on which instruments to use for cognitive function assessment (5) and the usually small sample sizes. In this respect, unfortunately, Greenwood et al. did not use the standard versions of the tests for memory assessment but instead used instruments that were constructed of parallel forms and had obviously undergone profound changes, like omitting items. The precise nature of the test that

was applied is not described in their previous study either (6). Although they thoroughly addressed parallels of the versions used, the possible interference effects of several verbal memory tests used in a row are not discussed.

Taken together with the small sample size, the large interindividual variability of performance within the groups, and hence the fact that the adequacy of regression analysis is disputable, in our point of view the conclusions of Greenwood et al. are daring. Surely, neuropsychological effects of transient hyperglycemic excursions are worth being studied further, but concluding that ingestion of one-half bagel and grape juice leads to acute memory impairment seems, in our opinion, too far-reaching.

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Memory Impairments Associated With Postprandial Hyperglycemia and Glycemic Control

Response to Kubiak et al.

We thank Kubiak et al. (1) for their thoughtful appraisal of our study relating to memory response in adults with type 2 diabetes following carbohydrate ingestion (2). We agree entirely with their comment that the underlying origins of memory impairment in this population is poorly understood and that lack of consensus on standardized neuropsychologic testing procedures may, in part, be contributing to this confusion (3). Clearly, as Kubiak et al. point out, a major contributor to the variance in cognitive performance observed in this population is the high prevalence of other risk factors for cognitive decline, including cardiovascular disease, hypertension, and depression (4,5), making it challenging to isolate the potential contribution of diabetes per se.

We sought to explore cognitive function in adults with type 2 diabetes by perturbing the system through the administration of glucose, which is a treatment commonly used in studies of cognitive aging to explore the system's plasticity in the face of underlying age-related deficits (6,7). A major advantage of applying this approach to the type 2 diabetic population is that changes observed in response to the challenge were unlikely to be directly attributable to vascular complications. Our data provided evidence for cognitive deficits, primarily related to declarative memory function, following the ingestion of 50 g of glucose in the form of rapidly absorbed carbohydrate foods (bagel and juice). We then argued that this impairment was consistent with observations in healthy senior adults, in whom moderate elevations in blood glucose resulted in memory enhancement and more extreme increases in blood glucose were associated with deficits (what is often referred to as an inverted-U dose-response relationship) (8). Based on this argument, we concluded that adults with type 2 diabetes likely responded to a glucose challenge in a manner comparable with that of older adults, with the caveat that they were more likely to attain levels of hyperglycemia associated with cognitive impairment given their underlying disease. Clearly, this is a conclusion requiring further verification.

One issue of concern raised by Kubiak et al. is that we include alternate versions, developed by us and others (9), of standardized neuropsychologic tests, although we apply these versions using standardized methodology. Our within-individual design, i.e., requiring multiple testing of subjects, necessitates their use. While we do not provide the precise details used to develop these alternate versions, we previously directed readers to those publications that we relied on to do so. Importantly, we have never stated or implied that these alternate versions should be used clinically from a diagnostic perspective; rather they are only used as experimental research tools. We agree that the use of these alternate versions potentially adds unwanted variance to our measures, but disagree that this detracts from the results obtained. Rather, the additional variance contributed by the use of alternate test versions makes it more, not less, difficult to observe change following glucose ingestion or associations between subject characteristics and performance levels. We address test version variability through the random allocation of different test versions both between and within subjects to uniformly distribute this additional variance (as much as possible) throughout the data, thereby minimizing potential bias associated with their use.

Another concern expressed was the limited number ($n = 19$) of subjects in our study, which is in essence an extension of those concerns related to test version variability. While not commented on in the original publication, this sample size was based on power analyses drawing on our results in healthy senior adults receiving glucose in the form of carbohydrate foods and including the same alternate versions of the neuropsychologic tests (9). Thus we believe our study to be statistically sound. Nevertheless, as

with all studies, the extension of the results to the broader population is complicated by the fact that subjects willing to participate in experimental procedures are somewhat unique and, in this sense, differ from the more heterogeneous population typically observed in clinical practice—a factor of importance in all studies drawing on human volunteers.

Finally, Kubiak et al. comment on concerns related to interference when multiple tests probing declarative memory are used. This factor is not discussed in this work but is addressed by us previously (9) in studies conducted on healthy senior adults. This comment raises multiple issues of interest. The first is that the exact nature of the declarative memory deficits observed in adults with type 2 diabetes remains largely unexplored. Clearly, multiple components of cognitive function are recruited and contribute to performance on end measures of delayed verbal recall; yet the precise deficit, potentially including interference and inhibitory control, remains largely unexplored. Admittedly, we observed deficits in our study on the second, not the first, verbal recall test used, thus raising the possibility that interference is an important contributor and one requiring further exploration. Yet this does not detract from the fact that performance on this second test was poorer when subjects were tested following carbohydrate ingestion compared with when they were tested following placebo (water) ingestion. The second issue relating to the comment by Kubiak et al. is the degree to which one controls for external factors influencing cognitive performance. Clearly, our data suggest that the fed/fasted state of the individual may be an important contributor to observed variance. Similarly, time of day of testing is another recognized contributor to within-individual variance in cognitive function and shifts in peak performance times occur in states, such as aging, wherein disruptions to circadian sleep rhythms are apparent (10). This is clearly a pattern disruption to which adults with type 2 diabetes may be especially vulnerable. Yet rarely do authors address when during the day testing occurred and whether a fixed time of day was used, as we did in our studies. All of these factors are likely important and contribute to the "unexplained" variance in regression models. Some will view this as exciting opportunities for new exploration, whereas others will see this as reason to discount "explained" variance in function.

Certainly, it is essential that as we wade through conflicting data regarding the origins of cognitive deficits in adults with type 2 diabetes, be they primarily or secondarily associated with the high prevalence of other risk factors in this population, that we not lose sight of the shared and common interest, which is helping those with type 2 diabetes prevent or minimize their risk of cognitive dysfunction. Kubiak et al. state that we were daring to conclude that transitory food-induced hyperglycemic episodes could be associated with acute cognitive deficits in this population. We continue to stand by our conclusions but recognize that further studies will either support or refute our conclusions.

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Off-Loading in Trials in Neuropathic Diabetic Foot Ulceration

No, it's not time for a paradigm shift

Professor Boulton and Dr. Armstrong (1) argued recently that "all future trials of therapy should use a nonremovable off-loading device." In doing so, they betray a failure to understand how the structure of trials must be determined by their purpose: those designed to determine the efficacy ("Can it work in ideal circumstances?") may differ from those designed to determine effectiveness ("Does it work in practice?"). Two factors that underlie the capacity of a controlled trial to demonstrate efficacy are *1*) the effect, or lack of it, of the intervention and *2*) the effect of the control. Boulton and Armstrong concluded (with no evidence) that the failure of Veves et al. (2) to demonstrate any benefit of Promogran was "likely" to be the result of a failure to standardize off-loading techniques. Another interpretation is that the product is comparatively ineffective in routine practice.

The classical total contact cast (TCC) does not have a dressing window, and so how can it be used in trials of dressings

and applications designed to be changed more often than the off-loading device? A TCC, but not their modified walker, can be modified by incorporating a dressing window, but dressing windows have their problems. If too small, they limit the ability to clean and dress the wound properly. If too large, they limit the effectiveness of off-loading by allowing the ulcerated area to prolapse.

Crucially, however, Boulton and Armstrong fail to satisfactorily address the questions of acceptability and safety. They acknowledge that TCCs have adverse effects and suggest that these may be overcome with their modified walker, but admit that relevant trials have not been completed. In truth, many people find nonremovable devices unacceptable, with reasons that include secondary ulceration of the index foot, abrasions on the contralateral foot, unsteadiness (especially in the elderly, those with postural hypotension or impaired proprioception), and falls from tripping, not to mention the ease—or lack of it—with which patients can shower or take a bath. Trials of nonremovable off-loading devices may be critically biased by population selection.

In conclusion, we emphasize our enormous respect for the work undertaken by Boulton and Armstrong but think that their arguments are simply not justified. The recent Cochrane review of off-loading (3) concluded that "there is very limited evidence of the effectiveness of total contact casts" and highlighted the fact that there has been no comparison undertaken between TCC and Scotchcast (or equivalent) removable boots, which are widely used in many countries. The TCC is an option, but not sine qua non in either clinical practice or future trials.

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Off-Loading in Trials of Neuropathic Diabetic Foot Ulceration

Further evidence of the need for a paradigm shift

We are happy that our recent editorial (1) stimulated interest from other experts in the diabetic foot. However, we find ourselves in disagreement with the letter by Jeffcoate and Game in this issue of *Diabetes Care* (2) in several respects. They suggest that our editorial betrays "a failure to understand how the structure of trials must be determined." Surely, this cannot be the case. Any trial assessing dressings, drugs, or constructs should be designed to provide the maximum opportunity for the product to demonstrate efficacy by removing all possible confounding variables. As we have recently demonstrated (3), those patients provided with removable cast walkers only wear their device for 28% of activity daily, so we proposed that future trials should therefore standardize off-loading, preferably using a nonremovable device. As off-loading in the trial of promogram (4) was "left to the individual center," we stand by our assessment that a likely explanation of the failure to demonstrate efficacy was related to a failure to standardize off-loading.

Having demonstrated the efficacy of any new product, it then behooves us to translate the results into clinical practice. Here we agree with Jeffcoate and Game that not all patients can tolerate casts; however, our experience to date suggests that the instant total contact cast (TCC) is better tolerated by patients than the TCC (5). (The instant TCC is a removable cast walker rendered nonremovable by wrapping it with cast material.) Further studies on this will be published in 2004. Rather than stating that many patients cannot tolerate nonremovable devices, surely research should be directed at improving the design of such casts to make them more safe and acceptable. We suggest that the failure to develop satisfactory off-loading in recent years is responsible for the poor results of trials of potential new therapies for plantar ulcers.

Jeffcoate and Game then assert that TCCs do not have dressing windows. Coincidentally, in the very next issue of *Diabetes Care*, Ha Van et al. (6) describe a TCC incorporating just such a window.

Further support for our position appears in several articles published in the months since the appearance of our editorial. In addition to describing the incorporation of a dressing window into a nonremovable cast, Ha Van et al. reported that only 10% of patients complied with the removable off-loading device in their studies, suggesting that the 28% reported in our study (3) was likely realistic, if not optimistic. Secondly, Caravaggi et al. (7) demonstrated that trials of new dressings could be successfully executed using a nonremovable cast. Finally, Piaggesi et al. (8) provide pivotal histological evidence strongly demonstrating the importance of adequate off-loading. It is now clear why so many trials have failed to demonstrate efficacy in recent years. Hence, we reiterate the need for a paradigm shift in the design of future clinical trials of putative therapies for plantar neuropathic ulcers.

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C-Reactive Protein and Glycemic Control in Adults With Diabetes

Response to King et al.

King et al. (1) recently suggested an association between glycemic control and systemic inflammation, i.e., between HbA_{1c} levels and highly sensitive C-reactive protein (hsCRP) levels, based on data from 1,018 participants in the Third National Health and Nutrition Examination Survey. This report prompted us to search for a similar association in our clinical practice.

Since hsCRP levels can be lowered by statins, thiazolidinediones (TZDs), and anti-inflammatory drugs, we first looked at 64 C-peptide–negative type 1 diabetic patients whose only medication was insulin and found no association ($r = 0.0748$, $P = 0.28$) between HbA_{1c} levels and hsCRP. With this negative association, we investigated 108 C-peptide–positive type 2 diabetic patients, all of whom were on a statin, an aspirin, and a TZD, to see whether there was an association between hsCRP and HbA_{1c} in this homogenous group on maximal hsCRP-lowering therapy. The association was again negative, with an r value of 0.0424 and a P value of 0.78.

Why then did King et al. find an association of HbA_{1c} with hsCRP and we did not? We believe that King et al.'s association was with insulin resistance and not hyperglycemia. An association of insulin resistance and hsCRP has been well documented, and theoretically at least, the greater the insulin resistance the worse the glycemic control and, conversely, the higher the glucose the greater the insulin resistance (glucotoxicity). In our group of type 2 diabetic patients who were all on a TZD, insulin resistance should be maximally treated so that if hyperglycemia did affect the hsCRP, its effects would not be confounded by the effects of insulin resistance.

That insulin resistance was not a factor in the King et al. study could be concluded from the inclusion of fasting insulin levels in the regression model. When diabetic subjects are treated with insulin, insulin secretagogues, or insulin sensitizers, the effectiveness of a fasting serum insulin level as a marker for insulin resistance is negated and the conclusion that insulin resistance was eliminated as a factor nullified.

To resolve this problem of differing conclusions from an epidemiological cross-sectional study and a retrospective cross-sectional clinical study, a prospective longitudinal study should be performed. An ideal study would be of type 1 diabetic patients at onset who are clinically free of infection, with measurements of hsCRP being performed before insulin therapy and 2 months later when they are well controlled in the honeymoon period. This is of clinical importance because if hsCRP levels are elevated due to hyperglycemia, then hsCRP levels should only be measured when glycemia is controlled to avoid unnecessary prescribing.

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C-Reactive Protein and Glycemic Control in Adults With Diabetes

Response to Bell, Hardy, and Desmond

We thank Bell, Hardy, and Desmond (1) for their comments regarding our recent article (2), and we appreciate the opportunity to respond to the issues they have raised. Based on their analysis of two groups of patients in their practice, Bell, Hardy, and Desmond question whether there is an association between CRP and glycemic control. Several possible explanations exist for the difference in our findings. First, we used a nationally representative population-derived database that may be more diverse than the one used by them. Second, we specifically excluded people on anti-inflammatory and cholesterol-lowering medications, precisely because the use of such individuals is likely to confound the relationship between C-reactive protein (CRP) and HbA_{1c} (insulin-sensitizing drugs were not widely available at the time of the study [1988–1994]). Another reason for the difference in our findings could be our ability to account for several other factors that might confound or mask the relationship, including age, race, sex, BMI, smoking, length of time with diabetes, and fasting insulin levels. Further supporting our

findings, other researchers have found a similar association between CRP and HbA_{1c} in nondiabetic individuals (3).

Bell, Hardy, and Desmond correctly note the limitation of fasting insulin level as a measure of insulin resistance. However, their conclusion that CRP is related to insulin resistance rather than glycemia may also be premature, since the term insulin resistance is a very general one that includes several possible underlying mechanisms. Our report did not address specific mechanisms for the association we found, but instead called for more research to further delineate the nature of the association. We agree with Bell, Hardy, and Desmond that more definitive prospective and interventional studies are needed to investigate the association between CRP and glycemia, as we urged in our article.

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