OBSERVATIONS

The Effect of *Ipomoea batatas* (Caiapo) on Glucose Metabolism and Serum Cholesterol in Patients With Type 2 Diabetes

A randomized study

There is considerable and growing interest in neutraceutical products for the treatment of diabetes (1). Recently, it has been shown that caiapo, the extract of white-skinned sweet potato (*Ipomoea batatas*), improves glycemic control in rodents by reducing insulin resistance (2). The aim of our study was to assess the effect of caiapo on glucose metabolism and its tolerability and mode of action in male Caucasian type 2 diabetic patients in a randomized, double-blind prospective study in parallel groups controlled with placebo.

A total of 18 male type 2 diabetic patients (age: 58 ± 8 years; weight: 88 ± 3 kg; BMI: 27.7 ± 2.7 kg/m^2; means $\pm$ SEM) treated by diet alone were randomized to receive placebo or 2 (low dose) or 4 g (high dose) caiapo (four tablets each containing 168 or 336 mg powdered white-skinned sweet potato [*I. batatas*], respectively) before breakfast, lunch, and dinner for 6 weeks. The study protocol was approved by the Ethics Committee of the University of Vienna, and informed consent was obtained from all patients before inclusion into the study. Safety parameters (hematology and blood chemistry, including hepatic enzymes and urinanalysis) were controlled before and at the end of the study, and patients were asked to report any adverse events. Patients were seen weekly during the 6-week trial, and fasting blood glucose was measured. Each subject underwent a frequently sampled intravenous glucose tolerance test (FSIGT) in randomized order before and after 6 weeks of caiapo administration for measurement of insulin sensitivity. Plasma glucose was measured using glucose oxidase (Glucose Analyzer II; Beckman, Fullerton, CA) and plasma insulin (coeffcents of variation: 8%) by radioimmunoassay (Pharmacia-Upjohn, Uppsala, Sweden).

The FSIGT was performed according to the protocol used for the analysis with the minimal model of glucose disappearance (3). FSIGT data were analyzed by the minimal model method (4), and the insulin sensitivity index (S_I; min$^{-1} \cdot \mu U^{-1} \cdot$ ml^{-1}), which describes the ability of insulin to promote glucose disappearance, was obtained.

The comparison among the values of the biochemical parameters of the three groups before and after treatment was evaluated by analysis of variance. In every group, paired Student's *t* test was used to assess the statistical significance of the differences of insulin sensitivity. The statistical evaluation was performed using the computer programs Statview (Abacus, Berkley, CA) and S-plus (Insightful, Seattle, WA). Data are expressed as means $\pm$ SEM.

The biochemical parameters before and after treatment (Table 1) show a decrease ($P < 0.05$) of fasting plasma glucose as well as of cholesterol (total and LDL cholesterol) after 6 weeks of treatment with high-dose caiapo. No statistically significant changes occurred after treatment with low-dose caiapo or placebo. Body weight and blood pressure remained unchanged in all three groups. In patients receiving low-dose caiapo, the FSIGT demonstrated an increase of S_I by 37% (2.02 ± 0.70 vs. 2.76 ± 0.89 10^4 min$^{-1} \cdot \mu U^{-1} \cdot$ ml^{-1}, $P < 0.05$); in those on high-dose caiapo, the FSIGT demonstrated an increase of S_I by 42% (1.21 ± 0.32 vs. 1.73 ± 0.40 10^4 min$^{-1} \cdot \mu U^{-1} \cdot$ ml^{-1}, $P < 0.03$). No changes were seen for S_I in patients receiving placebo (1.52 ± 0.28 vs. 1.35 ± 0.21 10^4 min$^{-1} \cdot \mu U^{-1} \cdot$ ml^{-1}).

No adverse events have been reported by the patients. The results of the hematology and blood chemistry, including hepatic enzymes (except for glucose and cholesterol [Table 1]) and urinanalysis, were not altered by 6 weeks of treatment with caiapo. Body weight remained stable.

This pilot study demonstrates that ingestion of 4 g caiapo/day for 6 weeks reduces fasting blood glucose and total as well as LDL cholesterol in male Caucasian type 2 diabetic patients previously treated by diet alone. The improvement of insulin sensitivity in the FSIGT indicates that caiapo exerts its beneficial effects via reducing insulin resistance. The treatment was well tolerated, with no apparent side effects.

The increase of insulin sensitivity has been observed for both the low- and the

Table 1—Metabolic parameters before (upper line) and after (lower line) treatment with caiapo in the single groups

	Placebo	Low dose	High dose
n	6	6	6
Fasting plasma glucose (mmol/l)	8.2 ± 0.2	8.8 ± 0.4	8.3 ± 0.6
	8.4 ± 0.3	8.4 ± 1.1	7.2 ± 0.4*
Fasting plasma insulin (pmol/l)	8.7 ± 1.7	8.3 ± 1.6	13.4 ± 2.5
	8.7 ± 1.2	9.0 ± 1.8	13.2 ± 2.5
Total cholesterol (mmol/l)	5.69 ± 0.23	6.05 ± 0.31	4.97 ± 0.21
	5.66 ± 0.31	5.68 ± 0.34	4.45 ± 0.18*
LDL cholesterol (mmol/l)	3.72 ± 0.23	4.11 ± 0.28	3.12 ± 0.16
	3.78 ± 0.41	3.80 ± 0.28	2.72 ± 0.16*
HDL cholesterol (mmol/l)	1.40 ± 0.10	1.27 ± 0.10	1.16 ± 0.05
	1.42 ± 0.16	1.16 ± 0.10	1.11 ± 0.05
Triglycerides (mmol/l)	1.26 ± 0.15	1.45 ± 0.35	1.52 ± 0.19
	1.37 ± 0.30	1.61 ± 0.30	1.33 ± 0.13
HbA$_{1c}$ (%)	7.0 ± 0.3	7.3 ± 0.4	7.1 ± 0.3
	7.0 ± 0.2	7.3 ± 0.4	6.8 ± 0.3
Blood pressure (mmHg)	134 ± 13	147 ± 18	135 ± 20
	130 ± 18	133 ± 19	128 ± 21
BMI (kg/m^2)	28.9 ± 0.9	25.5 ± 0.8	28.6 ± 1.3
	29.2 ± 0.8	25.8 ± 0.9	28.1 ± 1.5

Data are means $\pm$ SEM. *$P < 0.05$ compared with pretreatment.

high-dose caiapo group according to the FSIGT data. The results of the dynamic study (FSIGT) indicate that an increase of insulin sensitivity independent of body weight seems to be the mechanism responsible for the improvement of metabolic control with caiapo administration. This mechanism of action is supported by beneficial changes in hyperinsulinemia (by 50%), free fatty acids, and glucose tolerance in response to 100 mg · kg^{-1} · day^{-1} caiapo powder in obese Zucker fatty rats (2). In this model, this effect was similar to the effect of treatment with 50 mg · kg^{-1} · day^{-1} troglitazone. The direct effect on insulin sensitivity was demonstrated in this study by an enhanced ^{14}C-glucose uptake in isolated adipocytes. Parallel histological examinations of the pancreas showed a remarkable regranulation of pancreatic B-cells. Contrary to troglitazone, no weight gain could be seen after caiapo treatment in the animals.

Recently, the antidiabetic component of caiapo was isolated as an acidic glycoprotein (5) that is currently subject to further characterization. Unexpectedly, a simultaneous lowering of total and LDL cholesterol was observed after treatment with high-dose caiapo in our study. This effect could be independent of improved insulin sensitivity and suggests that caiapo also could contain more than one metabolically active ingredient. In regard to triglyceride levels, no significant changes were observed, despite an improvement of insulin resistance. This might be due to the relatively short period of the study.

Despite careful randomization, the subjects in the high-dose group showed higher insulin levels, whereas those in the low-dose group were leaner and more insulin-sensitive compared with those in the high-dose and placebo groups. We cannot exclude that the higher baseline insulin level of high-dose subjects might have predisposed these subjects to a better treatment effect. In this regard, however, it is remarkable that low-dose caiapo exerted its effect on insulin sensitivity, even in those moderately insulin-resistant patients, which further supports the contention of caiapo as an insulin-sensitizing agent.

In conclusion, this pilot study shows beneficial effects of high-dose caiapo on plasma glucose and total as well as LDL cholesterol levels in patients with type 2 diabetes. These effects relate to a decrease

in insulin resistance, as also described in rodents (2), and were observed without affecting body weight or causing side effects. Therefore, the results of this pilot study indicate that caiapo could potentially play a role in the treatment of type 2 diabetes.

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Tissue Polypeptide–Specific Antigen Serum Concentrations in Children, Adolescents, and Young Adults With Type 1 Diabetes

Tissue polypeptide–specific antigen (TPS) is a marker of proliferation activity (1–3). Because diabetes is characterized by proliferative lesions in various organs, we hypothesized that serum TPS concentrations might be elevated in young patients with type 1 diabetes. Thus, for the first time, serum TPS concentrations in young patients with type 1 diabetes were determined and compared with those of age-matched healthy control subjects. Furthermore, their relation to age, sex, BMI, Tanner stage, insulin requirements, existence of complications, and duration and metabolic control of the disease, as expressed by HbA$_{1c}$, were investigated. This study was approved by the institutional ethics committee, and informed consent was obtained.

We investigated 97 subjects, 60 with type 1 diabetes (29 male and 31 female subjects) and 37 healthy control subjects (18 male and 19 female subjects). Those with type 1 diabetes were recruited consecutively during the study period (January 2000 to December 2000) from the patients attending our Diabetes Center. Control subjects were healthy siblings and young students. The subjects' characteristics appear in Table 1. Pubertal status, assessed through Tanner staging, was in accordance with age in both groups. Five type 1 diabetes patients presented complications (microalbuminuria, overt proteinuria, or retinopathy).

Fasting serum TPS concentrations were measured by a sequential chemiluminescent enzyme-labeled immunometric assay and were found to be significantly higher (means ± SD) in type 1 diabetes patients compared with healthy control subjects (54.38 ± 33.27 vs. 29.03 ± 13.10 units/l [95% CI 15.8–34.9]; $P < 0.0005$), even when excluding patients with complications from the analysis (53.12 ± 32.80 vs. 29.03 ±

Table 1—*Demographic data and biochemical findings in participating subjects with type 1 diabetes and healthy control subjects*

	Type 1 diabetic subjects	Control subjects	P
Age (years)	15.31 ± 5.22 (5–23.7)	13.55 ± 5.89 (4–22.8)	NS
BMI (kg/m^2)	20.68 ± 3.38 (13.7–28.7)	19.56 ± 4.06 (13.2–24.3)	NS
Tanner stage			
1	12	14	
2	6	3	
3	4	5	
4	6	4	
5	32	11	
HbA$_{1c}$ (%)	8.83 ± 1.85 (6.10–14.0)	—	
Insulin requirements (units · kg^{-1} · day^{-1})	0.89 ± 0.27 (0.36–1.80)	—	
Disease duration (years)	5.31 (0.01–17.58)	—	

Data are means ± SD (range), *n*, and median (range).

13.10 units/l; $P < 0.0005$). Serum TPS concentrations were significantly correlated with HbA$_{1c}$ ($r = 0.26$; $P = 0.042$). A significant correlation was also found in a multiple regression model between serum TPS concentrations and HbA$_{1c}$ ($P = 0.047$; adjusted $R^2 = 0.05$; B = 4.5; SE[B] = 2.2; CI 95% 0.06–8.9) when HbA$_{1c}$, age, and BMI were introduced as independent variables. No other correlation existed between serum TPS concentrations and age, sex, BMI, Tanner stage, disease duration, insulin requirements, or the presence of complications with bivariate linear regression analysis. Also, no significant difference existed in serum TPS concentrations at different categories of HbA$_{1c}$, age, disease duration, and insulin requirements.

The results of this study indicate that serum TPS concentrations are elevated in young patients with type 1 diabetes compared with healthy control subjects and depend significantly on the metabolic control of the disease.

Rebhandl et al. (4) found that serum TPS concentrations in healthy subjects aged 8–18 years do not differ from those in adults, and no significant differences exist between male and female subjects, findings confirmed in this study also for type 1 diabetes patients. Furthermore, serum TPS concentrations do not seem to depend on the duration of the disease, but rather on its metabolic control, although the latter accounts for only 5% of TPS variance among individuals in our study.

In conclusion, the high serum TPS concentrations in young patients with type 1 diabetes—even before disease complications are evident—and the significant correlation with the metabolic control of the disease argue for further studies that include greater numbers of individuals presenting complications of type 1 diabetes in order to elucidate the underlying mechanisms and evaluate whether serum TPS concentrations could serve as a reliable marker for disease progression.

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The Effect of Qi-Gong Relaxation Exercise on the Control of Type 2 Diabetes Mellitus

A randomized controlled trial

Qi-gong relaxation exercise is one of the traditional Chinese health care self-management technique. It consists of two aspects, controlled synchronized breathing with slow body movements as an aerobic exercise, and relaxation (1). The purpose of this study was twofold: to examine the effects of Qi-gong and to identify biological and psychological characteristics associated with a positive response to therapy.

The study used a paired group design with age- and sex-matched participants randomly assigned to one of two groups. Of the 554 eligible patients, 36 type 2 diabetic subjects were randomized to the study. This study was ethically approved by the board of directors of the Science Clinic, and informed consent was obtained from all 36 patients. For a variety of reasons, 10 of these subjects were excluded from analysis, resulting in data reported on 26 participants. Group 1 (16 patients, aged 65.3 ± 7.7 years) received the initial 4-month intervention, whereas group 2 (10 patients, aged 59.1 ± 9.0 years) served as a control group. Then, the intervention was repeated for the second group. Weekly 2-h Qi-gong group sessions were held by a Chinese Qi-gong doctor, and subjects were also requested to practice Qi-gong at home. Conventional diabetes therapies, such as pharmacotherapy band dietary and exercise

treatment, were not modified during the study period.

HbA$_{1c}$ levels were measured. It changed as follows: 8.13 ± 1.73 before treatment and 7.33 ± 1.09 after treatment in group 1, and 8.29 ± 1.63 before the control period, 8.17 ± 1.30 before treatment, and 7.23 ± 0.90 after treatment in group 2. Compared with the control period of group 2, the group 1 patients demonstrated significant improvement in HbA$_{1c}$ level ($P < 0.01$) by analysis of covariance using pretreatment HbA$_{1c}$ as a covariate. In group 2, HbA$_{1c}$ levels significantly decreased by the delayed treatment, indicated by a one-way layout analysis of variance ($F = 7.26; P < 0.005$). Using Tukey's HSD multiple comparison test, no significant change was found between values before and after the control period, but a significant improvement was ascertained between values before control and after treatment ($P < 0.01$) and between values before and after treatment ($P < 0.05$). The changes in other biological and psychological factors in the combined data of groups 1 and 2 were compared using paired t tests or Wilcoxon signed-rank tests. Whereas there were no significant changes in caloric intake, caloric consumption, BMI, and lipid metabolism, significant improvements in C-peptide ($P < 0.05$) were demonstrated. Some psychological improvements were demonstrated, including the anxiety index ($P < 0.05$) and total scores ($P < 0.05$) of the Mood Inventory (2). The improvement in HbA$_{1c}$ could be predicted (total 86.3% variance; $F = 25.145; P < 0.0001$) by higher pretreatment HbA$_{1c}$ (70.8%; $P = 0.0001$), younger age (6.6%; $P = 0.002$), trend of obesity (2.2%; $P = 0.01$), stronger self-efficacy (3) (2.5%; $P = 0.08$), and weaker personality trait of alexithymia, which means difficulty in identifying and describing one's own emotions (4) (1.9%; $P = 0.04$), on multiple regression analysis.

Because obese patients benefited more and the significant decrease in C-peptide was demonstrated in this study, Qi-gong may improve insulin resistance. On the other hand, several studies described the effects of relaxation training for type 2 diabetes (5–8); thus, Qi-gong can improve glucose metabolism by the benefits of relaxation response. In conclusion, these findings suggest that Qi-gong

relaxation exercise may be a beneficial adjunctive treatment for individuals with type 2 diabetes.

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Leukocytoclastic Vasculitis Induced by Subcutaneous Injection of Human Insulin in a Patient With Type 1 Diabetes and Essential Thrombocytemia

Both local (1) and systemic immediate-type insulin allergy (2) as well as delayed-type cutaneous reactions (3) to human insulin have been reported. Histologically verified Arthus reaction to insulin has only been reported in exceptional cases in which the patient was treated with bovine/porcine insulin (4). To the best of our knowledge, no histologically verified type 3 hypersensitivity reaction has been described in a patient treated with human insulin.

We report a case of leucocytoclastic vasculitis in a 48-year-old normal-weight female patient with well-controlled (HbA$_{1c}$ 6.4, upper normal 6.4%) type 1 diabetes since 1984 who had always been treated with $\sim$0.5 units $\cdot$ kg^{-1} body wt $\cdot$ day^{-1} semisynthetic human insulin and, beginning in 1998, recombinant human insulin. The patient did not have microvascular complications (normal fundoscopy, urinary albumin, and vibration perception threshold). She presented October 1997 with monophasic tender indurations at the injection sites of both human regular and NPH insulins (Novo Nordisk) in the abdominal and femoral regions, respectively, with occurrence within 2–6 h of injection and persistence from 1 to 3 days, later (May 1998) preceded by intense itching and redness, but no wheal-and-flare immediately after injection. A macular skin redness of between 1 and 2 cm was observed, and the indurations in the subcutaneous tissue developed into nodules after 3–4 days. These lesions were independent of injection site, and switching to other insulin, insulin analogs, as well as continuous subcutaneous insulin infusion was ineffective. After 3 years, the condition had become incapacitating, requiring repeated injections of Humalog (Eli Lilly) 5–6 times a day, including one injection

at ~3:00 A.M., as the best-tolerated insulin therapy.

Intradermal insulin skin testing (insulin allergy kit; Novo Nordisk, Bagsværd, Denmark) showed reactions toward human, porcine, and bovine insulin but no reactions to protamine or other additives. IgG but not IgE insulin antibodies, with a binding capacity of 28%, were demonstrated. In vitro lymphocyte proliferation was not induced with human insulin. Skin biopsies from 5-h and 5-day-old lesions showed perivascular and interstitial infiltration with neutrophilic and eosinophilic granulocytes and with considerable amounts of nuclear dust and swollen endothelial cells, granulocytic infiltration, and fibrin deposition as well as localized extravasation of erythrocytes in the vascular walls, indicating leucocytoclastic vasculitis. Other tests included: thrombocytosis ($841 \ 10^9 \cdot l^{-1}$) and leukocytosis ($19 \ 10^9 \cdot l^{-1}$) with neutrophilia; hyperplastic bone marrow with scattered megakaryocytes (normal); and normal ultrasound scan of the abdominal region and retroperitoneum, with special attention to the spleen and lymph nodes. The following normal lab test were also normal: hemoglobin; sedimentation rate; C-reactive protein; serum creatinine; liver enzymes; 24-h urinary albumin; IgA, IgG, and IgE antibodies; eosinophil counts; M-component; cryoglobulins; antinuclear antibodies; IgM/IgA rheumatoid factor; anti-cardiolipin antibodies; and anti-neutrophil cytoplasmic antibodies.

Immunosuppressive therapy was started February 2000, with prednisolone 10 mg once daily and, initially, azathioprine 50 mg daily, which was later substituted with methotrexate 7.5–15 mg once weekly because of antral gastritis. This treatment induced complete regression of symptoms and lesions within 8 weeks, and the patient resumed work, maintaining optimal glycemic control on recombinant human regular and NPH insulin (Novo Nordisk). The differential count and IgG insulin antibodies—but not the thrombocytemia—normalized during immunosuppression. Aspirin therapy was instituted because of thrombocytosis.

Leucocytoclastic vasculitis, which exclusively or primarily involves the skin, is often seen in other systemic diseases, such as subacute bacterial endocarditis, Epstein-Barr virus infection, chronic active hepatitis, ulcerous colitis, diseases of the complement system, retroperitoneal fibrosis, primary biliary cirrhosis, or myeloproliferative diseases. In this case, essential thrombocytosis is the most likely diagnosis because thrombocytosis but not neutrophilia persisted during immunosuppressive therapy. It is therefore conceivable that the myeloproliferative disorder predisposed to a B-lymphocyte clonal abnormality, leading to antibody formation against human insulin and secondarily leukocytoclastic vasculitis.

The bone marrow findings were not discriminative as to the question of whether thrombocytosis was primary or secondary. Platelet morphology, leukocyte differentiation markers, and chromosomal studies were not carried out because these studies would not have been definitive. However, the clinical course of persistent thrombocytosis, despite complete clinical remission and elimination of insulin antibodies, speaks strongly in favor of essential thrombocytosis as the underlying disorder.

Lymphocyte proliferation toward human or analog insulin was not detected. This is in accordance with previous findings that T-cell reactivity to human insulin detected by in vitro lymphocyte transformation in patients with insulin allergy is usually much weaker than lymphocyte transformation toward beef or pork insulin in patients with immune reactivity toward these species of insulin (5). Furthermore, the antigen may be the insulin dimer rather than the insulin monomer, also contributing to explain the lack of lymphocyte proliferation to human insulin in this patient.

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Smoking and Microalbuminuria

A case-control study in African-Americans with type 2 diabetes

African-Americans are at increased risk of diabetic nephropathy (1,2). Cigarette smoking has been shown to increase the risk of microalbuminuria in Caucasian populations with type 1 and type 2 diabetes (3–6). In contrast, despite their high risk of nephropathy, the association between cigarette smoking and microalbuminuria in African-Americans with diabetes has not previously been assessed. We conducted a case-control study to examine the association between lifetime cigarette smoking history and risk of prevalent microalbuminuria in patients with recently diagnosed type 2 diabetes. Our study population was African-American patients with type 2 diabetes duration ≤2 years who had an initial visit to the Grady Diabetes Clinic in Atlanta, Georgia, between January 1994 and December 1996. The present study is partially based on secondary data from a

cross-sectional analysis of this study population, which has been previously described in detail (7). We excluded patients missing urine albumin and/or urine creatinine measurements and patients with clinical nephropathy (urine albumin-to-creatine [Alb/Cr] ratio >250 µg/mg). Serum and urine creatinine were measured in a random morning urine specimen at the first clinic visit. Patients were divided into two groups based on Alb/Cr ratios: normoalbuminuria (Alb/Cr <25 µg/mg) or microalbuminuria (Alb/Cr from 25 to 250 µg/mg) (8). All 246 microalbuminuric patients were case subjects; based on a priori power calculations, 506 control subjects were randomly sampled from the 766 normoalbuminuric patients.

Lifetime smoking history was obtained via telephone interview by three trained and blinded interviewers. Patients were classified as smokers if they had smoked at least 100 cigarettes in their lifetime and had ever smoked on a regular basis for at least 6 months, and number of pack-years smoked was estimated. Before the interview, informed consent was obtained from all participants, and the Emory University Human Investigations Committee approved the study. Multiple logistic regression was done to assess the relation between microalbuminuria status (yes or no) and pack-years of cigarettes smoked before diabetes diagnosis while controlling for other clinical variables.

The Alb/Cr ratio was calculated for 1,055 (90.4%) of the 1,167 initially eligible patients; 43 (4.1%) with evidence of clinical nephropathy (Alb/Cr >250 µg/mg) were excluded. Of the remaining 1,012 patients, 246 (23.3%) had microalbuminuria (case subjects), and 766 (72.6%) had normoalbuminuria (control subjects). We interviewed 138 (56.1%) of the case subjects and 297 (58.7%) of the control subjects. Patients interviewed were older than patients not interviewed (mean age 53.5 vs. 48.4 years, $P < 0.0001$), had slightly shorter diabetes duration (mean 0.37 vs. 0.44 years, $P = 0.04$), and had higher HDL cholesterol levels (mean 44.7 vs. 42.6 mg/dl, $P = 0.04$). The proportion of women was statistically significantly higher in the interviewed group (71.5 vs. 60.9%). There were no differences in mean arterial blood pressure or HbA_{1c}. Among the 435 case and control subjects who completed the

interview, the mean diabetes duration was just under 5 months, the mean age was 53.5 ± 13 years, the mean BMI was 33.7 ± 8.9 kg/m^2, and the mean number of years of school completed was 10.7 ± 2.9. Case subjects had significantly higher mean arterial blood pressures ($P = 0.002$) and triglycerides ($P = 0.03$) as well as trends toward fewer years of education ($P = 0.06$) and higher BMI ($P = 0.06$) than control subjects.

Pack-years of cigarette smoking was higher among case than control subjects (mean pack-years 15.1 ± 23.0 for case subjects vs. 11.1 ± 18.8 for control subjects), but this difference was not statistically significant ($P = 0.17$). Among current smokers, mean pack-years was significantly higher for case than for control subjects (34.3 ± 20.9 vs. 22.7 ± 17.7, $P = 0.007$) and was also significantly higher among case than control subjects when only looking at ever smokers (30.2 ± 24.6 for case subjects vs. 23.9 ± 21.4 for control subjects, $P = 0.03$). Forty-eight percent of our population either currently smoked or were ex-smokers.

After excluding patients with estimated creatinine clearance >250 ml/min ($n = 12$) from the multiple logistic regression analysis, the number of reported pack-years of smoking was independently associated with increased risk of prevalent microalbuminuria, controlling for HbA_{1c}, mean arterial blood pressure, age, self-reported hypertension, and diabetes duration. Estimates from the final model showed that each increase of 10 pack-years of smoking corresponded to a 14% increase in microalbuminuria risk (odds ratio [OR] = 1.14, 95% CI 1.03–1.26). An increase of 40 pack-years of smoking corresponded to an OR of 1.69 (95% CI 1.12–2.56). There was evidence of a linear dose-response, with microalbuminuria risk increasing as pack-years increased (Table 1).

This case-control study is the first to examine the relation between lifetime cigarette smoking, measured in pack-years, and microalbuminuria prevalence in African-Americans with recent-onset type 2 diabetes. Pack-years of cigarettes smoked until diabetes diagnosis was independently related to prevalence of microalbuminuria in these patients while controlling for HbA_{1c}, age, mean arterial blood pressure, hypertension, and diabetes duration.

Several limitations should be noted

Table 1—*Age-adjusted ORs for microalbuminuria by pack-years of cigarettes smoked, excluding patients with creatinine clearance >250 ml/min*

Pack-years	Case subjects	Control subjects	OR (95% CI)
Never smoked	62	155	Reference
<20	26	62	1.03 (0.59–1.80)
20–39	24	47	1.32 (0.73–2.36)
≥40	17	25	2.02 (0.99–4.12)
Total	129	289	

when interpreting our results. First, there is the potential for misclassification of both exposure and outcome. We relied on self-reported lifetime smoking histories to calculate the main exposure, pack-years. Our use of a single Alb/Cr ratio may have misclassified the microalbuminuria status of some patients. Misclassification of normo- and microalbuminura in our study is likely to be random and independent of the main exposures, biasing our ORs toward the null. Blood pressure was only measured once, so we could not assess patients' long-term blood pressure patterns. Data on the use of antihypertensive medications was incomplete in the database, and thus we relied on self-reported hypertensive status from the telephone interview. In particular, we did not have complete data on ACE inhibitor use in this population; ACE inhibitors are known to reverse the nephrotoxic effects of smoking (9). Selection bias is also a concern due to low interview response rates. It is possible that nonparticipants had on average smoked more than subjects who completed our interview.

Although response rates were low (56.1% of case subjects and 58.7% of control subjects), we feel that these data offer preliminary evidence that smoking is an independent risk factor for microalbuminuria in African-Americans with type 2 diabetes. Given the high risk for end-state renal disease in this group, clinicians should increase efforts to encourage patients with microalbuminuria to stop smoking. Further, in view of the difficulty that many smokers have in quitting, patients with type 2 diabetes and microalbuminuria who continue to smoke should be more closely monitored for progressive renal disease, and renoprotective therapies should be aggressively applied in these patients.

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COMMENTS AND RESPONSES

Frequency of Blood Glucose Monitoring in Relation to Glycemic Control in Patients With Type 2 Diabetes

We were disappointed with the conclusions of Harris (1) and the accompanying editorial (2) on self-monitoring of blood glucose (SMBG). The article is based on outdated data and reflects an era with much less SMBG capability and convenience, reimbursement, therapeutic modalities, and evidence for the benefits of improved glycemic control. Moreover, the study itself was uncontrolled, self-reported, and did not indicate whether the patients were taught about data usage. It would be unfortunate if this article and editorial were used to justify denial of appropriate reimbursement for SMBG in type 2 diabetes.

Optimal modern therapy of type 2 diabetes uses a "treat-to-target" approach, expeditiously moving patients along a sequence of therapies to achieve better diabetes control (3,4). However, to make effective and efficient decisions about therapy, patients and health care professionals should rely on appropriate data, of which SMBG is a key component (4).

The ISIS group recently (October 1996 to September 1999) assessed data from >3,000 clinic visits of 228 patients with type 2 diabetes (aged 35–65 years) who were seen by 65 doctors (assorted specialties) in four Adventist Health clinics. During this period, the average HbA_{1c} decreased by 0.8. Patients were placed into two groups based on diabetes control ($HbA_{1c} \leq 8$ for >95% of measurements during the 3-year period or $HbA_{1c} > 8$) (5). We then examined the consistency with which a health care professional documented discussing glucose monitoring and recorded the frequency of SMBG. We created "diabetes care intervals," or periods from one visit in which the primary focus was diabetes care to the next visit with the same focus. Patients were categorized as "regular SMBG performer" if, throughout the 3-year period, almost all visits documented frequency of SMBG and results. A patient was labeled "irregular SMBG performer" if there were few mentions of SMBG documented and/or if documentation did not contain the frequency of SMBG. Finally, patients were labeled "not monitored" if there was no mention of SMBG or if documentation noted that that patient was not monitoring.

Almost 21% of patients were regular SMBG performers, and 70% of these patients had $HbA_{1c} \leq 8$. For the 42% of patients who were irregular SMBG performers and the 37% of patients not monitoring, only 18 and 22%, respectively, had $HbA_{1c} \leq 8$ ($P < 0.0001$). Regularly monitoring and consistently discussing blood glucose appeared to be positively associated with a better glycemic control.

In summary, we should recognize the limitations of the Harris (1) study, not give it undo prominence or extend the data beyond its limited historical value, and consider the important and growing case for studies utilizing a treat-to-target approach. We believe that it is not the collection of blood glucose data but rather the effective use of blood glucose information for making clinical decisions that leads to improvements in diabetes control. Finally, we agree with Kennedy (2) that better studies are needed, but we believe that the studies should be large-scale observational studies of the usage of blood glucose data in normal clinical settings and stratified by therapy.

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Table 1—*Influence of health care providers' contact on clinical effect of SMBG*

	HbA$_{1c}$	
	≤8	>8
Regular SMBG peformers (21%)	70%	30%
Irregular SMBG performers (42%)	18%	82%
Not monitored (37%)	22%	78%

$P < 0.0001$.

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The Healthy Women Bias and Hormone Replacement Therapy in Women With Type 2 Diabetes

A cross-sectional study by Ferrara et al. (1), recently published in *Diabetes Care* suggests that hormone replacement therapy (HRT) is associated with a decreased HbA$_{1c}$ level in women with diabetes. The "healthy women bias" always becomes an issue to be discussed in cross-sectional studies related with HRT. It is well known that women willing to initiate and continue taking any form of HRT are usually more concerned about their health, more educated, visit their doctors more often, and have lower blood pressure and lipid levels. Furthermore, compared with the rest of women, they are physically trained and usually do not smoke tobacco or drink alcohol in excess.

The results presented by the authors clearly show that this bias may explain a large percent of the HRT-related benefit on HbA$_{1c}$ levels. Case subjects had significantly higher education and lower rates of smoking. Also, they practiced regular exercise and capillary glucose measurements more often than the control subjects. The authors tried to avoid the confounding effect of this bias by using a generalized estimating equation model. After controlling some of these variables, HRT remained as an independent predictor for the HbA$_{1c}$ levels. The "healthy women bias" results from the sum of a large number of measurable and nonmeasurable confounders (2). The only way to avoid it is the use of randomized control trials. Unfortunately, few papers had prospectively analyzed the effect of HRT on glucose control in women with type 2 diabetes. Most of them (3) had included small number of cases with a wide range in HbA$_{1c}$ levels. Also, the inclusion of a progestin may result in different conclusions.

Data published by our group (4) clearly showed that HRT might have different effects on glucose control depending on the baseline HbA$_{1c}$ level. A total of 54 postmenopausal women were included. After a 6-week run-in period on diet, case subjects were randomized to receive either placebo (HbA$_{1c}$ <8%, n = 13; >8%, n = 17) or HRT (HbA$_{1c}$ <8%, n = 11; >8%, n = 13) during 12 weeks. HRT consisted in cyclical conjugated estrogens at 0.625 mg/day plus medrogestone at 5 mg/day. At baseline and during the study, hyperglycemic cases had an HbA$_{1c}$ level significantly higher than the near-normoglycemic control subjects (baseline 10.2 ± 2.9 vs. 6.5 ± 0.7%, P < 0.01). In the normoglycemic cases, a small increase in HbA$_{1c}$ was observed (6.5 ± 0.7 vs. 7.4 ± 1%, P = 0.04). No further deterioration in glucose control resulted from HRT in hyperglycemic women (10.5 ± 2.7 vs. 10.6 ± 3.5, NS). However, the triglycerides response was significantly higher in the hyperglycemic group.

These observations are proof that randomized controlled trials (instead of cross-sectional reports) are urgently needed to assess the short- and long-term safety in women with type 2 diabetes who have a clear indication for receiving HRT.

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Hormone Replacement Therapy and Glycemic Control: Evidence from Observational Studies and Randomized Clinical Trials

Response to Dr. Aquilar-Salinas et al.

W e thank Aguilar-Salinas et al. (1) for their interest in our paper (2), and we agree that the cross-sectional associations between hormone

replacement therapy (HRT) and lower HbA_{1c} levels we reported do not establish causality. We concur with the need of long-term clinical trials among women with diabetes in order to understand whether and to what extent HRT may improve glycemic control. However, our findings are consistent with small and short-term randomized trials in women with diabetes (3–5). We demonstrated a number of differences between HRT users and nonusers in our report and went to great lengths to balance these covariates, including the use of the propensity score approach (6). As we mentioned in our discussion, HRT remained significantly associated with lower HbA_{1c} levels ($P < 0.001$) in the propensity score–adjusted Generalized Estimating Equation models.

Aguilar-Salinas et al. (1) found, in contrast with the previous randomized trial of unopposed estrogen in women with diabetes, that conjugated estrogens at 0.625 mg/day plus the cyclical medrogestone at 5 mg/day (for 10 days) may have slightly worsened HbA_{1c} levels in women with good glycemic control at baseline.

In our study (2), women using unopposed estrogen as well as women using opposed estrogen had lower HbA_{1c} levels then women not using HRT. A recent publication (7) of the results from a short-term randomized controlled cross-over study of 61 women with type 2 diabetes with acceptable glycemic control (mean HbA_{1c} 7.1%) receiving daily 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone or placebo showed that although HbA_{1c} levels were not significantly different between treatment periods, fructosamine levels were significantly lower during treatment with this HRT regime. Another recent publication (8) of a randomized placebo-controlled trial among 43 women with type 2 diabetes showed no difference in glycemic control among women assigned to continuous transdermal estradiol in combination with oral norethisterone (1 mg daily) or in women assigned to identical placebos.

Along with the data of Aguilar-Salinas et al. (1), these recent studies suggest that the type of progestin and whether treatment is continuous or cyclic may influence the effect of HRT on glycemic control in women with diabetes. It is also interesting to note that clinical trials (9,10) in women without diabetes have

shown that although fasting glucose and insulin levels decrease after estrogen therapy (with or without progestins), the addition of progestins worsens post-challenge glucose levels.

In conclusion, we strongly agree with Aguilar-Salinas et al. (1) on the need for long-term randomized trials of various HRT regimes among diabetic women with a broad spectrum of glycemic control. Results from large observational studies such as ours can provide data on the potential expected magnitude of the effect of HRT on HbA_{1c} and therefore facilitate calculations of the minimum required sample size for future randomized controlled trials.

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Potential Pharmacokinetics Interference Between α-Glucosidase Inhibitors and Other Oral Antidiabetic Agents

In the study recently reported by Chiasson et al. (1), it was concluded that miglitol, a pseudomonosaccharide α-glucosidase inhibitor, can be combined effectively with metformin therapy to give significantly greater reductions in HbA_{1c} and postprandial plasma glucose levels than metformin alone in middle-aged patients in whom type 2 diabetes is insufficiently controlled by diet alone. The combined therapy had a good safety profile, with only a trend toward an increase in the number of gastrointestinal side-effects due to miglitol acting at the small

intestine by delaying the digestion of complex carbohydrates (2).

The absorption of metformin occurs mainly in the small intestine, and it has been shown that high concentrations of the compound (10–100 times plasma levels) accumulate in the walls of the gastrointestinal tract (rev. in 3). Therefore, possible pharmacokinetic interference with drugs acting on the intestinal wall are not excluded. We previously demonstrated in six healthy subjects that acarbose (100 mg), a pseudotetrasaccharide that is currently the leading α-glucosidase inhibitor on the market, induces significant reductions in early (90-, 120-, and 180-min) serum levels, peak concentrations (C_{max} 1.22 ± 0.14 vs. 1.87 ± 0.60 mg/l; $P < 0.05$), and area under the curve for 0–540 min ($AUC_{0-540\ min}$; 423 ± 55 vs. 652 ± 55 mg·min·l^{-1}; $P < 0.05$) of metformin ingested as two tablets of 500 mg with a standardized breakfast (4).

To our knowledge, such interference of miglitol on the pharmacokinetics of metformin has not yet been studied. However, although our group did not observe any significant alteration of the glibenclamide pharmacokinetics in acarbose-treated type 2 diabetic patients (5), we observed slight modifications of the pharmacokinetic parameters of glibenclamide after ingestion of miglitol in six healthy volunteers (unpublished data). In a double-blind crossover trial, each subject was randomly allocated during two consecutive 7-day periods to either miglitol (3 × 50 mg during the first 3 days and 3 × 100 mg/day during the last 4 days) or placebo. At the 7th and 14th day of the study, the overnight-fasted subjects ingested 5 mg glibenclamide with the first bite of a standardized breakfast together with either 100 mg miglitol or placebo. Venous blood samples were taken from 0 to 540 min to measure serum glibenclamide concentrations by radioimmunoassay. Time-to-peak (T_{max}; 215 ± 40 vs. 230 ± 24 min; NS) and peak serum glibenclamide levels (C_{max}; 190 ± 33 vs. 225 ± 31 μg/l; NS) were similar after miglitol and placebo, respectively. However, the glibenclamide $AUC_{0-540\ min}$ was significantly lower after miglitol than after placebo (40,358 ± 3,203 vs. 59,950 ± 9,193 μg·min·l^{-1}; $P < 0.05$).

These observations in normal subjects suggest that a potential interference of miglitol on the pharmacokinetics of metformin cannot be excluded during combined therapy in type 2 diabetic patients. Whether this interference exists and to what extent it may influence the efficacy and/or safety of such a combined therapy remains to be investigated.

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