OBSERVATIONS

French Maritime Pine Bark Extract Pycnogenol Dose-Dependently Lowers Glucose in Type 2 Diabetic Patients

Pycnogenol, a standardized extract from the bark of the French maritime pine, consists of phenolic compounds including catechin, taxifolin, procyanidins, and phenolic acids (1).

We investigated whether Pycnogenol has a glucose-lowering effect because of personal verbal communication from patients reporting no need for insulin following supplementation with Pycnogenol.

The study was designed as an open, controlled, dose-finding study and was approved by the ethical committee of Guangnamen Hospital. Patients gave written informed consent. We recruited 18 men and 12 women among outpatients of the Guangnamen Hospital and Municipal Dental Hospital. Patients were 28–64 years of age and had a BMI 22–34 kg/m^2. Patients with type 2 diabetes were included with fasting plasma glucose between 7 and 10 mmol/l after participation in a diet and sports program for 1 month. Exclusion criteria were type 1 diabetes, manifest or malignant hypertension and any diseases requiring continuous treatment with drugs, and pregnant or lactating women.

During the first and last visit, a physical examination and assessment of demographic data, medical history, body weight, height, vital signs, blood pressure, electrocardiogram, diet, and medication was carried out. Samples for fasting blood glucose, HbA_{1c}, insulin, and endothelin-1 were taken. Blood samples were taken to measure postprandial blood glucose 2 h after breakfast.

Glucose was measured enzymatically, HbA_{1c} by high-performance liquid chromatography, and insulin and endothelin-1 by immunoassays. Statistical analysis was done with SPSS 16.0 software using one-factorial ANOVA with Fisher projected least significant difference test. Patients received in succession 50, 100, 200, and 300 mg Pycnogenol in intervals of 3 weeks. Every 3 weeks, fasting and postprandial glucose, endothelin-1, HbA_{1c}, and insulin were analyzed.

No changes were observed in vital signs, electroencephalogram, or blood pressure over the 12-week period.

Fasting blood glucose was lowered dose dependently until a dose of 200 mg Pycnogenol was administered. Increasing the dose from 200 to 300 mg did not further decrease blood glucose. Compared with baseline, 100–300 mg lowered fasting glucose significantly from 8.64 ± 0.93 to 7.54 ± 1.64 mmol/l ($P < 0.05$). Fifty milligrams of Pycnogenol lowered postprandial glucose significantly from 12.47 ± 1.06 to 11.16 ± 2.11 mmol/l ($P < 0.05$). Maximum decrease of postprandial glucose was observed with 200 mg to 10.07 ± 2.69 mmol/l; 300 mg had no stronger effect.

HbA_{1c} levels decreased continuously from 8.02 ± 1.04 to 7.37 ± 1.09%. Difference to baseline became significant after 9 and 12 weeks of treatment with 200 or 300 mg Pycnogenol ($P < 0.05$). Endothelin-1 decreased significantly after 100–300 mg Pycnogenol from 104 ± 16 to 91 ± 15 pg/ml ($P < 0.05$). There was no additional decrease with 300 mg. Insulin levels were not changed at any dosage level of Pycnogenol.

Four patients reported dizziness, two headache, two gastric discomfort, and one mouth ulcer. None of the patients discontinued the study. All unwanted effects were minor and transitory.

Stimulation of insulin secretion can be excluded as a cause for lower glucose levels because insulin secretion was not affected. Mechanistic investigations are underway to elucidate the mechanism of glucose lowering with Pycnogenol.

The decrease of endothelin-1 following supplementation with Pycnogenol points to an ameliorated function of the endothelium.

This dose-finding study encourages further mechanistic and clinical studies with Pycnogenol to explore its potential in obtaining metabolic control in patients with mild type 2 diabetes. A double-blind placebo-controlled study with 77 patients confirmed the glucose-lowering effect of Pycnogenol (2).

XIMING LIU, MD[1]
HA-JUN ZHOU, MD[2]
PETER ROHDEWALD, PHD[3]

From the [1]Guang An Men Hospital of Chinese Medical Science Research Institute, Beijing, China; the [2]Wei-Hai Stomatology Hospital of Shan-Dong Province, Wei-Hai, China; and the [3]Institute of Pharmaceutical Chemistry, University of Münster, Munster, Germany.

Address correspondence to Prof. Dr. P. Rohdewald, Department of Pharmaceutical Chemistry, University of Muenster, Hittorfstrasse 58-62, 48149 Münster, Germany. E-mail: rohdewa@uni-muenster.de.

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A Systematic Quantitative Analysis of the Literature of the High Variability in Ginseng (*Panax* spp.)

Should ginseng be trusted in diabetes?

Herbs have experienced an unprecedented surge in popularity (1). This has occurred in the absence of adequate safety and efficacy evidence, prompting calls for rigorous clinical assessments (2). Complicating these assessments is compositional variability. This is a concern with one of the most popular herbs, ginseng (3). The principal reference components, to which pharmacological effects have been attributed, are its ginsenosides (steroidal glycosides). We undertook a systematic quantitative analysis of the literature to assess the coeffi-

cient of variation (CV) in ginsenosides across species, assay technique, and ginsenoside type.

The PubMed (1966–present), EMBASE (1980–present), HealthSTAR (1975–present), Cochrane library (issue 2, 2002), and AGRICOLA (1979–present) databases were searched using "ginsenosides AND (chromatography OR HPLC OR HPTLC OR TLC OR LC OR DCC OR GC OR ELISA OR UV OR MS OR NMR OR ELSD)". One-hundred eleven articles were identified. Two reviewers applied three inclusion criteria: publication quality: peer-reviewed; end point: quantitative ginsenoside concentrations; and ginseng type: dried derivatives of panax species roots. Thirty-two articles met these criteria, reporting ginsenoside concentrations for 317 ginseng batches.

A three-factor analysis was performed to assess the independent and interactive effects of species, assay technique, and ginsenoside type on the CV of ginsenoside concentrations using ANOVA (NCSS 2000; NCSS, Kaysville, UT). The CVs of ginsenoside concentrations were calculated as CV = SD/mean × 100% in a factorial block design. A blocking principle was applied to the data such that each level of each factor was crossed with each level of the other factors for the calculation of CV. Species was comprised of 10 levels of panax species, their preparations, and their varieties: Asian (*Panax ginseng* C.A. Meyer), Asian red (*Panax ginseng* C.A. Meyer [red]), Asian wild (*Panax ginseng* C.A. Meyer [wild]), Asian extract (*Panax ginseng* C.A. Meyer [extract]), American (*Panax quinquefolius* L.), American wild (*Panax quinquefolius* L. [wild]), American extract (*Panax quinquefolius* L. [extract]), Japanese (*Panax japonicus* C.A. Meyer), Pseudo (*Panax pseudoginseng* WALL), and Sanchi (*Panax notoginseng* [Burk] F.H. Chen) ginsengs. Assay technique was comprised of six levels of different assay techniques: high-performance liquid chromatography (HPLC)-ultraviolet (UV), gas chromatography (GC)-mass spectrometry (MS), HPLC-MS, diode counter current DCC, HPLC–differential refractometry DR, and HPLC–electrospray light-scattering detection (ELSD). Ginsenoside type was comprised of 21 levels of different ginsenoside indexes: protopanaxadiol (PPD) ginsenosides (Rb_1, Rb_2, Rc, Rd, and Rg_3), protopanaxatriol (PPT) ginsenosides (Rg_1, Rf, Re, and Rg_2), and their sums (PPD, PPT, and total) and ratios (PPD:PPT, Rb_1:Rg_1, Rb_2:Rc, Re:Rb_1, Rc:Rb_1, Rd:Rb_1, Rb_2:Rb_1, Rf:Rb_1, and Rg_1:Re). The CV data calculated for each possible combination of levels from the three factors were pooled and then meaned for each level of each factor. As a result, CV data are means ± SD.

This systematic quantitative analysis of the literature demonstrated high CV in ginsenosides across species, assay technique, and ginsenoside type (26–103, 31–81, and 36–112%, respectively). These large ranges produced significant differences in each main effect (P = 0.00030, P = 0.014, and P = 0.00031, respectively), with differences in species sensitive to assay technique (P = 0.00011 for two-way interaction).

The high variability in ginseng identified by this analysis might have serious clinical sequelae. Variable pharmacological effects appear secondary to ginsenoside variability. We have shown in healthy humans that while two batches of American ginseng (cultivated *Panax quinquefolius* L.) (4–6) demonstrated similar acute postprandial glycemic-lowering efficacy, a third batch with a depressed ginsenoside profile was ineffective (4), whereas Japanese, Asian red, and Sanchi ginsengs had null effects (6) and Asian (6,7), American wild, and Siberian ginsengs (*Eleutherococcus senticosus*) (6) raised glycemia. These data suggest that the antihyperglycemic efficacy of ginseng might be as highly variable as its ginsenoside composition.

Although this makes a compelling argument for better standardization, there are mitigating factors. It is unclear which of the >30 ginsenosides or myriad of other principles should be targeted for an antihyperglycemic indication. There is also no universal ginsenoside assay. Until these issues are resolved, the reproducibility of ginseng's composition, safety, and efficacy cannot be trusted. This conclusion likely holds true for other less well-studied herbal remedies used to treat diabetes.

JOHN L. SIEVENPIPER, MSC[1,3]
JOHN T. ARNASON, PHD[2]
EDWARD VIDGEN, BSC[3]
LAWRENCE A. LEITER, MD[1,3]
VLADIMIR VUKSAN, PHD[1,3]

From the [1]Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada; the [2]Department of Biology, Faculty of Science, University of Ottawa, Ottawa, Canada; and the [3]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada.

Address correspondence to Vladimir Vuksan, PhD, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, no. 6, 138-61 Queen St. East, Toronto, Ontario M5C 2T2, Canada. E-mail: v.vuksan@utoronto.ca.

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Is a Long-Term Aerobic Plus Resistance Training Program Feasible for and Effective on Metabolic Profiles in Type 2 Diabetic Patients?

Aerobic physical activity is a major therapeutic modality for type 2 diabetes (1,2). It is well known that regular aerobic exercise produces beneficial effects on glycemic control, insulin sensitivity, lipid abnormalities, and hypertension (3,4). On the other hand, several recent studies (5,6) have demonstrated the beneficial effect of resistance exercise in diabetes, and these results should encourage its practice because of the increasing number of sedentary, older, and obese people in industrialized countries. In fact, this is particularly important in the case of individuals who may be noncompliant with aerobic exercise. To prove the effectiveness of resistance training, a recent study (7) showed the positive effects of prescribed and supervised high-intensity resistance training for 16 weeks in high-risk older adults with type 2 diabetes, resulting in improved glycemic and metabolic control. Similarly, 16 weeks of resistance plus aerobic training is reported to enhance glucose disposal in postmenopausal women with type 2 diabetes (8). Both of these studies evaluate the effect of relatively short-period physical training but neither investigates prolonged resistance exercise combined with aerobic training in diabetic people.

We therefore investigated the long-term effects (1 year) of prescribed and supervised combined aerobic and resistance training on glycemic control, cardiovascular risk factors, and body composition in type 2 diabetic patients.

Physical examination was performed to detect the presence and degree of complications as well as to determine any orthopedic limitations. After selection, 120 (60 men and 60 women) sedentary type 2 diabetic patients, aged 60.9 ± 8.9 years, with duration of diabetes 9.8 ± 7.3 years, were included in the study and randomly assigned to one of two treatments: 62 subjects (30 men and 32 women) agreed to perform the aerobic plus resistance training (ART) program, whereas 58 subjects (30 men and 28 women) asked to continue with their current diet and pharmacological therapy and formed the control group. The subjects in both groups continued to receive their standard medication. Throughout the study, diabetologists were asked to avoid nonessential changes in drugs and dosages that might affect the study outcome measures. Every essential medication change was implemented and then reported to the investigators.

The ART group performed 30 min of aerobic training at 40–80% of the heart rate reserve (based on the initial maximal graded exercise tolerance test) using treadmills, stationary bicycles, reclining bicycles, and elliptical trainers (Technogym), plus another 30-min resistance training program that included free weights, such as barbells or dumbbells, and weight machines at 40–60% of a single repetition maximal lift (1 RM), which was retested every 3 weeks. The workload was 12 repetitions each of six exercises selected for each major muscle group (i.e., legs, chest, shoulders, back, arms, and abdomen) for three sets, three times a week, for 1 year.

Blood pressure and plasma glucose levels were assessed in each patient by means of a One Touch Ultra blood glucose monitoring system (Lifescan) before and after each training setting. HbA_{1c}, BMI, waist circumference, and glycemic and lipid profiles were evaluated every 3 months. Each participant was provided with written handouts and with a notebook in which to take notes and record food diaries. A 3-day food record was obtained at baseline and every 3 months for 1 year. All nutritional information obtained from food records was analyzed by a dietitian using Winfood software (Medimatica). Body composition was measured at baseline and after 1 year by means of dual-energy X-ray absorptiometry (QDR 1000; Hologic).

This study was conducted in accordance with the Declaration of Helsinki guidelines. Each subject gave his or her informed consent before the study began.

Each group was compared using the ANOVA test with multiple comparisons and 95% CIs. A two-tailed $P < 0.05$ indicated statistical significance. All of the values are expressed as means ± SD. Subjects in the ART group attended >90% of the prescribed program sessions. The subject dropout rates were 17.7% for the ART group and 8.63% for the control group. We only included patients who completed the entire year for statistical analyses.

There were no significant differences between the two groups at baseline with respect to BMI (30 ± 5.6 vs. 30.1 ± 5.6 kg/m^2), fat mass (33 ± 9.2 vs. 35 ± 10.2%), fat-free mass (48.1 ± 10 vs. 46.8 ± 11 kg), waist circumference (104 ± 12.8 vs. 103 ± 14 cm), fasting blood glucose (163 ± 59.6 vs. 165 ± 60.6 mg/dl), total cholesterol (212 ± 31.5 vs. 212 ± 40.2 mg/dl), HDL cholesterol (45.3 ± 9.8 vs. 43.6 ± 9.1 mg/dl), LDL cholesterol (134 ± 31.6 vs. 130 ± 34.2 mg/dl), triglycerides (159 ± 80.1 vs. 187 ± 109 mg/dl), HbA_{1c} (8.28 ± 1.73 vs. 8.31 ± 1.73%), systolic blood pressure (147 ± 18 vs. 139 ± 17.1 mmHg), diastolic blood pressure (85.6 ± 7.8 vs. 85.3 ± 8.8 mmHg), and use of lipid-lowering, hypoglycemic, and antihypertensive medications (32.3 vs. 34.5, 80.8 vs. 86.3, and 48.4 vs. 50%, respectively).

After 1 year, the control group showed no statistically significant change in any measured parameters. The ART group, conversely, showed a statistically significant decrease in BMI (30.1 ± 5.6 to 28.8 ± 4.8 kg/m^2, $P < 0.0001$), fat mass (35 ± 10.2 to 32.5 ± 10.2%, $P < 0.0001$), waist circumference (103 ± 14 to 98 ± 12.7 cm, $P < 0.0001$), fasting blood glucose (165 ± 60.6 to 129 ± 37 mg/dl, $P < 0.0001$), total cholesterol (212 ± 40.2 to 195 ± 35.4 mg/dl, $P < 0.0001$), LDL cholesterol (130 ± 34.2 to 124 ± 28.7 mg/dl, $P < 0.0001$), triglycerides (187 ± 109 to 146 ± 81 mg/dl, $P < 0.0001$), HbA_{1c} (8.31 ± 1.73 to 7.1 ± 1.16%, $P < 0.0001$), systolic blood pressure (139 ± 17.1 to 135 ± 15.5 mmHg, $P < 0.04$), and diastolic blood pressure (85.3 ± 8.8 to 81.3 ± 6.7 mmHg, $P < 0.0001$) and a significant increase in fat-free mass (46.8 ± 11 to 47.2 ± 10.8 kg, $P < 0.0001$) and HDL cholesterol (43.6 ± 9.1 to 48.6 ± 12.1 mg/dl, $P < 0.0001$).

The frequency of medication changes was not significantly different between the ART and control groups. We observed a trend toward decreasing amounts of medications in all three classes of drugs (hypolipemic, hypoglycemic, and antihypertensive therapies) in the ART group

(−7.85, −3.94, and −5.90%, respectively), whereas in the control group, the opposite trend occurred (5.67, 7.55, and 5.67%, respectively).

Throughout the entire study, no adverse effects occurred in any patient. The reasonably low dropout rate in the ART group (17.7%) indicates that subjects with type 2 diabetes are willing and able to participate in a demanding intervention program if it is made available to them.

In conclusion, the combination of aerobic and resistance training is well tolerated, feasible, and safe, and it improves glycemic control, cardiovascular risk factors, and body composition in type 2 diabetic patients. Given the epidemic of diabetes and metabolic syndrome in the recent years, we stress the use of combined exercise as an adjunct to standard medical care in the management of these patients.

STEFANO BALDUCCI, MD[1]
FRIDA LEONETTI, MD[1]
UMBERTO DI MARIO, MD, PHD[1]
FRANCESCO FALLUCCA, MD[2]

From the [1]Department of Clinical Sciences, Endocrinology, La Sapienza University, Rome, Italy; and the [2]Department of Clinical Sciences, La Sapienza University II Faculty (St. Andrea Hospital), Rome, Italy.

Address correspondence to Dr. Stefano Balducci, Department of Clinical Sciences, La Sapienza University, Rome, Italy. E-mail: s.balducci@hctdiabete.it.

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A Filipino Patient With Fulminant Type 1 Diabetes

Fulminant type 1 diabetes is characterized by abrupt onset of loss of pancreas β-cell function with low initial HbA_{1c} levels and absence of autoantibodies to islet antigens (1). Initial histological examinations revealed the absence of insulitis, and it was thought that the autoimmune process did not mediate this type of diabetes. However, with an accumulation of cases, possible involvement of an immune response to islet antigens has come to light. $CD8^+$ lymphocytes infiltrating the pancreatic islets were seen in a patient who died of fulminant type 1 diabetes (2), and peripheral GAD-reactive interferon-γ–producing $CD4^+$ lymphocytes were detected in another case of fulminant type 1 diabetes (3). Thus, T-cell–mediated autoimmunity may be involved. HLA analyses also indicate that an autoimmune process similar to that in autoimmune type 1 diabetes may be involved in the development of fulminant type 1 diabetes. In his editorial comment regarding the first report of fulminant type 1 diabetes, Lernmark (4) noted that in Japanese patients most had HLA class II antigens that confer type 1 diabetes. Furthermore, Tanaka et al. (5) recently reported that fulminant type 1 diabetes is associated with specific HLA class II haplotypes, which are also associated with autoimmune type 1 diabetes in Japanese patients. Most patients reported to have fulminant type 1 diabetes were Japanese. Occurrences in other ethnicities are rare (6,7), reflecting possible immunogenetic differences. We report herein a Filipino patient with fulminant type 1 diabetes and the results of HLA analysis.

A 32-year-old Filipino woman married to a Japanese man and living in Gunma, Japan, had a low-grade fever 2 weeks before admission and visited a general practitioner, but no specific diagnosis was made. Thirst, polydipsia, polyuria, and general malaise had developed. Then abdominal pain and vomiting occurred, and she visited a clinic where severe hyperglycemia was found. She was referred to Shiroyama Hospital and was admitted for diabetic ketoacidosis. On admission blood glucose was 800 mg/dl and HbA_{1c} was 6.0%. Urinary ketone bodies were positive. Arterial blood pH was 7.11, serum amylase was 57 (IU/l), lipase was 32 (units/l), and elastase I was 344 ng/dl (all within normal range). Anti-GAD antibodies and islet cell antibodies were negative. After metabolic derangement was corrected, insulin secretion was evaluated. The fasting serum C-peptide concentration was 0.1 ng/ml; it was 0.2 ng/ml after glucagon injection. Urinary C-peptide was 1.6 μg/day. The severe abrupt-onset insulin deficiency, low HbA_{1c}, and lack of antibodies to islet antigens were compatible with fulminant type 1 diabetes. DNA typing of HLA antigens showed homozygosity for the DRB1*0405-DQB1*05031 haplotype, which is unique to the Filipino population (8). She was also HLA A24–positive.

Most Japanese fulminant type 1 diabetes patients studied carried at least one of two haplotypes, DQA1*0303-DQB1*0401 and DQA1*0302-DQB1*0303 (5), which are known to confer susceptibility to autoimmune type 1 diabetes in the Japanese population. Only 2 of 22 did not have either haplotype. Furthermore, one-third of the patients were homozygous for the DQA1*0303-DQB1*0401 haplotype. Our Filipino patient had neither haplotype. However, she had two DRB1*0405 alleles. DRB1*0405 is a risk allele for type 1 diabetes in the Japanese population. The DQA1*0303-DQB1*0401 haplotype is in close linkage disequilibrium with DRB1*0405 in Japanese and Chinese in-

dividuals. These alleles form an extended haplotype DRB1*0405-DQA1*0303-DQB1*0401. Thus it is difficult to determine whether the DQ molecule, the DR molecule, or the haplotype is responsible for the susceptibility to fulminant type 1 diabetes. In Filipino autoimmune type 1 diabetes, the risk haplotypes are DRB1*0405-DQB1*0302 and DRB1*0405-DQB1*0201, followed by DRB1*0405-DQB1*0401 and DRB1*0405-DQB1*0402 (8). The DRB1*0405-DQB1*05031 haplotype is neutral to autoimmune type 1 diabetes. Our finding of a homozygous DRB1*0405 allele without a risk haplotype in a Filipino patient suggests that this allele rather than a haplotype is associated with fulminant type 1 diabetes. Continued worldwide collection of data and HLA analysis will further clarify the involvement of immunogenetics in fulminant type 1 diabetes.

MATSUO TANIYAMA, MD[1]
RYO KATSUMATA, MD[2,3]
KANEMI AOKI, MD[1]
SEIJI SUZUKI, MD[1]

From the [1]Department of Internal Medicine, Division of Endocrinology and Metabolism, Showa University Fujigaoka Hospital, Kanagawa, Japan; the [2]Department of Internal Medicine, Shiroyama Hospital, Gunma, Japan; and the [3]Third Department of Internal Medicine, Showa University School of Medicine, Tokyo, Japan.

Address correspondence to Matsuo Taniyama, MD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Showa University Fujigaoka Hospital, 1-30 Fujigaoka, Aoba, Yokohama, Kanagawa 227-8501 Japan. E-mail: taniyama@showa-university-fujigaoka.gr.jp.

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Predictive Value of Circulating Oxidized LDL for Cardiac Events in Type 2 Diabetic Patients With Coronary Artery Disease

Oxidized LDL (oxLDL) has been shown to play an important role in the initiation and development of atherosclerosis (1). Individuals with type 2 diabetes exhibit enhanced LDL oxidizability and accelerated atherosclerosis (2,3). Past studies demonstrated the association between LDL oxidation and atherosclerosis by "indirect" methods, such as lag times and propagation rates for LDL oxidation, and antibodies against oxLDL. Recently, some groups have developed "direct" methods for measuring circulating oxLDL (4–6). Indeed, several lines of evidence have demonstrated that the level of circulating oxLDL is significantly higher in patients with type 2 diabetes, is a marker for identifying patients with coronary artery disease (CAD), and has a positive relationship with acute coronary syndromes (7,8). However, the predictive value of circulating oxLDL for cardiac events in type 2 diabetic patients with CAD has not been investigated.

Ninety-six consecutive patients, who had angiographic documentation of CAD and fulfilled the classification of the American Diabetes Association, were followed for up to 52 months. Patients with acute coronary syndrome and/or ongoing congestive heart failure were excluded. Patients with malignant disease and/or inflammatory disease were also excluded. We defined cardiac death, nonfatal myocardial infarction, and refractory angina requiring revascularization as major cardiac events. The levels of oxLDL were measured by a sandwich enzyme-linked immunosorbent assay, as previously described (9).

Thirty-five cardiac events were documented during the follow-up. Age was significantly higher in patients with cardiac events than in those without cardiac events ($P = 0.02$). The other values and

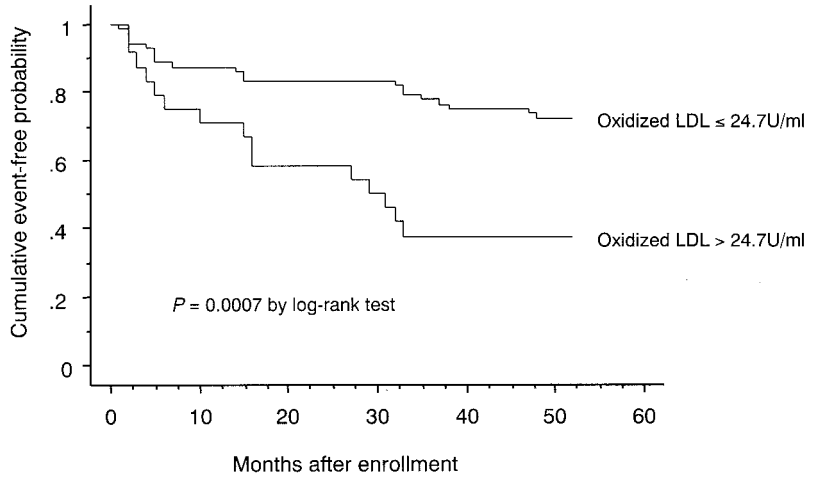

Figure 1—*Kaplan-Meier survival curves demonstrated that the prevalence of cardiac events was significantly higher in the patients with oxLDL >24.7 units/ml (event/total cases = 15/24) than in those with oxLDL ≤24.7 units/ml (event/total cases = 20/72).*

frequencies, including coronary risk factors, lipid profiles, fasting plasma glucose, and HbA_{1c}, were not significantly different between the two groups. Choice of treatment for diabetes, such as insulin, sulfonylureas, α-glucosidase inhibitors, and thiazolidinediones, was not different. The levels of oxLDL (means ± SD) in patients with cardiac events were significantly higher than in those without cardiac events (23.8 ± 14.2 vs. 18.8 ± 6.9 units/ml, $P = 0.02$). The patients were divided into two groups based on the 75th percentile (24.7 units/ml) of the distribution of oxLDL levels. Kaplan-Meier analysis demonstrated that the patients with oxLDL >24.7 units/ml had a significantly higher prevalence of cardiac events ($P = 0.0007$) (Fig. 1). After adjustment for age, sex, BMI, hypertension, smoking history, LDL cholesterol, triglyceride, HDL cholesterol, fasting plasma glucose, HbA_{1c}, number of diseased vessels, and left ventricular ejection fraction, Cox proportional analysis showed that the hazard ratio for cardiac events was 3.6 (95% CI 1.5–8.8, $P = 0.005$) times higher in patients with oxLDL >24.7 units/ml than in those with oxLDL ≤24.7 units/ml.

This study firstly, to the best of our knowledge, demonstrated that high levels of circulating oxLDL can serve as an independent and significant predictor for future cardiac events in type 2 diabetic patients with CAD. Therefore, measurement of circulating oxLDL may be helpful for identifying high-risk patients with type 2 diabetes and CAD.

KAZUNORI SHIMADA, MD
HIROSHI MOKUNO, MD, PHD
ERIKO MATSUNAGA, MD
TETSURO MIYAZAKI, MD
KATSUHIKO SUMIYOSHI, BS
ATSUMI KUME, MD
KATSUMI MIYAUCHI, MD
HIROYUKI DAIDA, MD, PHD

From the Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan.

Address correspondence to Kazunori Shimada, MD, Department of Cardiology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: shimakaz@med.juntendo.ac.jp.

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Tumor Necrosis Factor-α Is Associated With Increased Protein C Activation in Nonobese Type 2 Diabetic Patients

Tumor necrosis factor-α (TNF-α) plays a critical role in the pathogenesis of vascular injury in diabetic patients (1). Increased circulating levels of TNF-α have been reported in diabetic patients (2,3). Hyperglycemia stimulates TNF-α secreted from monocytes and endothelial cells (4,5). Moreover, TNF-α may cause vascular injury by affecting the balance between coagulation and fibrinolysis. For example, TNF-α stimulates the expression of tissue factor that is the initiator of blood coagulation activation and the secretion of plasminogen activator inhibitor-1 that inhibits fibrinolysis (1).

Activated protein C (APC) is a serine protease that inhibits activation of the blood coagulation system by proteolytically inactivating factors Va and VIIIa and by stimulating fibrinolysis (6,7). APC may indirectly promote fibrinolysis by inhibiting thrombin generation and by inhibiting the action of plasminogen activator inhibitor-1 (8). Recently, it was reported that APC has an anti-inflammatory effect and that it inhibits vascular injury induced by TNF-α (9,10). Therefore, APC may inhibit hypercoagulability and inflammatory response induced by TNF-α, which increases during hyperglycemia. However, the relationship between circulating TNF-α and APC levels has not yet been reported in diabetic patients. In the present study, we investigated the relationship between the plasma levels of TNF-α and APC in normotensive type 2 diabetic patients.

Twenty-four normotensive (<140/90 mmHg) nonobese type 2 diabetic patients (16 men and 8 women, aged 53.0 ± 2.0 years [mean ± SE], BMI 23.1 ± 0.5 kg/m^2, diabetes duration 6.7 ± 1.1 years, systolic blood pressure 131.0 ± 2.1 mmHg, diastolic blood pressure 78.1 ± 1.9 mmHg, fasting blood glucose levels 7.8 ± 0.32 mmol/l, and HbA_{1c} 8.9 ± 0.3%) enrolled in the present study. All patients had normoalbuminuria and were

being treated with diet therapy alone. Data obtained in 18 age-matched nonobese healthy subjects (14 men and 4 women) were used as control. The plasma levels of TNF-α were measured with an enzyme immunosorbent assay (EIA) kit (TNF-α EIA kit; Biosourse International, Camarillo, TX). As a marker of APC generation, APC–protein C inhibitor (PCI) complex was measured by enzyme-linked immunoassay as previously described (11). Protein C (PC) antigen was measured by solid-phase immunoassay as previously described (11). Total protein S (PS), a cofactor for activation of PC, was measured as previously reported (11). As a marker of coagulation activation, the plasma levels of thrombin-antithrombin complex (TAT) were measured by an EIA using anti-human monoclonal TAT antibody. As a marker of fibrinolysis, D-dimer was measured with a commercial EIA kit (D-dimer test F; Kokusai Shiyaku, Kobe, Japan). The plasma levels of TNF-α were significantly higher (1.60 ± 0.13 vs. 0.81 ± 0.32 pg/ml, $P < 0.05$) in diabetic patients than in normal subjects. The plasma levels of APC-PCI were significantly higher (4.63 ± 0.38 vs. 2.58 ± 0.60 pmol/l, $P < 0.005$) in diabetic patients than in normal subjects. There was a significant and positive correlation between the plasma levels of TNF-α and TAT in diabetic patients ($r = 0.46$, $P < 0.05$). There was a significant and inverted correlation between the plasma levels of TNF-α and D-dimer in diabetic patients ($r = -0.52$, $P < 0.01$). The plasma levels of TNF-α were positively and significantly correlated with the plasma levels of APC-PCI ($r = 0.42$, $P < 0.05$) in diabetic patients. There was no significant correlation between TNF-α and PC antigen ($r = 0.33$) and PS levels ($r = 0.07$).

The elevation of TNF-α in diabetic patients observed in our study is in agreement with previous data (2,3). Proportional correlation of TNF-α with TAT and inverse correlation with D-dimer suggests the occurrence of hypercoagulability and hypofibrinolysis in association with TNF-α in diabetic patients. Interestingly, the circulating levels of TNF-α were significantly correlated with APC-PCI complex, a marker of APC generation. These data suggest that APC may regulate fibrinolysis and hypercoagulability induced by TNF-α. It was reported that APC reduces vascular injury and hypercoagulability by inhibiting TNF-α production in rats treated with lipopolysaccaride (LPS) (9). APC may also inhibit production of TNF-α in LPS-treated culture cells (10). Another report (12) demonstrated that APC activates protease activated receptor-1 and induced gene expression of A20 (TNF-α induced protein 3) and tristetraprolin. A20 is cytoplasmic zinc finger protein that inhibits TNF-α–induced nuclear factor κB activity (13). Tristetraprolin inhibits TNF-α production by destabilizing its messenger RNA (14). Therefore, these mechanisms may be involved in the protective effect of APC in diabetic patients. However, the significant increase of TNF-α in diabetic patients suggests that APC may not be sufficient for regulating TNF-α expression. In brief, PC activation may be important for the regulation of TNF-α–induced coagulation abnormalities and inflammation in diabetes.

YUTAKA YANO, MD[1]
ESTEBAN C. GABAZZA, MD[1]
NAGAKO KITAGAWA, MD[1]
NELSON E. BRUNO, MD[1]
KAZUTAKA MATSUMOTO, MD[1]
KANAME NAKATANI, MD[2]
RIKA ARAKI, MD[3]
AKIRA KATSUKI, MD[1]
YUKIHIKO ADACHI, MD[1]
YASUHIRO SUMIDA, MD[1]

From the [1]Third Department of Internal Medicine, Mie University School of Medicine, Tsu, Mie, Japan; the [2]Laboratory Medicine, Mie University School of Medicine, Tsu, Mie, Japan; and the [3]Department of Internal Medicine, National Mie Hospital, Tsu, Mie, Japan.

Address correspondence to Dr. Yutaka Yano, Third Department of Internal Medicine, Mie University School of Medicine, Edobashi 2-174, Tsu, Mie 514-8507, Japan. E-mail: yanoyuta@clin.medic.mie-u.ac.jp.

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Botulinum Toxin A in the Early Treatment of Sixth Nerve Palsy–Induced Diplopia in Type 2 Diabetes

Sixth (abducent) cranial nerve palsy is a typical yet infrequent mononeuropathic complication of diabetes. It usually causes considerable diplopia, which can be debilitating and significantly impair the everyday and professional activity of afflicted individuals. In most cases, nerve function restores itself, although it usually takes several months or even over a year for the symptoms to resolve (1). No specific treatment of nerve palsy–induced diplopia in diabetic patients has been established (2,3). We report the successful use of botulinum toxin A in the early treatment of diplopia caused by sixth nerve palsy in two type 2 diabetic patients. In both patients, diplopia made it impossible for them to continue with their professional activities.

The first patient (female, computer operator, aged 52 years, with a 15-year history of type 2 diabetes and HbA_{1c} 8.2%) complained of diplopia, which occurred several days earlier. Sixth nerve palsy in the left eye was diagnosed, and her squint angle was found to be +35Δ (prism dioptries) when measured with an orism cover test. After prompt injection of botulinum toxin A (15 units) into the medial rectus muscle in the left eye, her diplopia and squint resolved completely (Fig. 1). The second patient (male, taxi driver, aged 50 years, with an 8-year history of type 2 diabetes and HbA_{1c} 8.7%) was referred with sixth nerve palsy in the left eye persisting for 3 months. His squint angle was +55Δ. The patient complained of severe diplopia, predominantly when looking left. Botulinum toxin A (15 units) was injected into the medial rectus muscle in the left eye, which resulted in the reduction of the squint angle to +15Δ. To achieve complete resolution of diplopia, prism correction was used (Fig. 2). Six months later, the vision of both patients remains stable, with no diplopia occurring while looking forward.

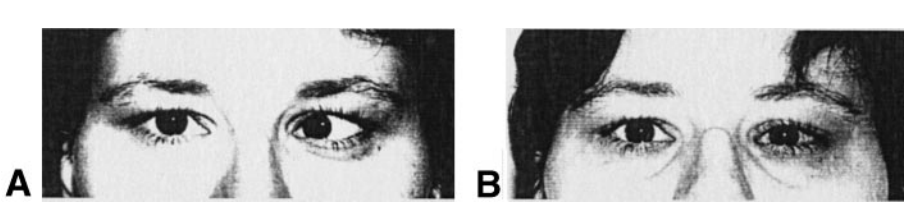

Figure 1—*The first patient before* (A) *and after* (B) *botulinum toxin A application. There is complete resolution of strabismus and associated diplopia.*

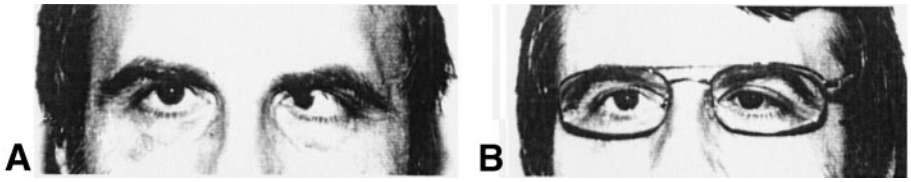

Figure 2—*The second patient before* (A) *and after* (B) *botulinum toxin A application. There is incomplete resolution of strabismus, and his diplopia resolved only upon the use of prism correction* (B).

Injections of botulinum toxin A in the treatment of sixth nerve palsy have been used since the early 1980s (4) with a success rate of 15–100%, depending on the severity and duration of the nerve palsy (5–7). In general, early botulinum toxin use is recommended, as then the resolution of diplopia can be complete (8). In long-standing cases, successful treatment inadvertently requires ocular muscle surgery, which might be also associated with botulinum toxin injections (3,9,10).

However, despite a relatively long history of botulinum toxin treatment in ocular muscle paralysis (4,6), its use and investigations of treatment with it in diabetic mononeuropathy have been less than scarce. Concomitantly, no routine treatment is offered to patients, who are often left untreated until the nerve palsy itself subsides, which actually does happen in the majority of cases. However, during this period the patient is usually unable to work and is regarded a disabled person.

Our report is, to the best of our knowledge, the first one describing the effects of the early use of botulinum toxin A in type 2 diabetic patients, in whom diplopia caused by sixth nerve palsy made them unable to work. In agreement with the recommendations mentioned above, in type 2 diabetic patients the use of botulinum toxin A at the very beginning of diplopia and nerve lesion also seems to be more effective than in patients with a long duration of symptoms. We believe that botulinum toxin A, especially if used immediately after nerve palsy occurs, offers an attractive option in the treatment of cranial nerve palsy–induced diplopia, thus saving the patient from surgical treatment and assuring that quality of life and professional activity will not suffer due to significant disturbance of vision.

ANNA BRONIARCZYK-LOBA, MD, PHD[1]
LESZEK CZUPRYNIAK, MD, PHD[2]
OLIMPIA NOWAKOWSKA, MD, PHD[1]
JERZY LOBA, MD, PHD[2]

From the From [1]Ophthalmology Department, Medical University of Lodz, Barlicki University Hospital No. 1, Lodz, Poland; and the [2]Diabetology Department, Medical University of Lodz, Barlicki University Hospital No. 1, Lodz, Poland.

Address correspondence to Leszek Czupryniak, Medical University of Lodz, Diabetology Department, Kopcinskiego 22, Lodz 90–153, Poland. E-mail: bigosik@poczta.onet.pl.

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Naltrexone Improves Blood Glucose Control in Type 1 Diabetic Women With Severe and Chronic Eating Disorders

Eating disorders are frequent causes of chronic failure of blood glucose control in young type 1 diabetic women (1) that result in a high incidence of diabetic complications (2). Moreover, severe disorders such as bulimia and binge eating are commonly associated with inappropriate compensatory behaviors to avoid weight gain, including self-induced vomiting, insulin misuse, laxative or diuretic surreptitious intake, and hyperactivity (3). Because these impulsive attitudes develop as addictions, naltrexone, an antagonist of endogenous opiates that is currently used to help weaning off alcohol, opiates, or heroin, might be considered a potentially effective therapy. Of note, recent data (4) report significant improvements obtained with naltrexone in bulimic patients, reinforcing the hypothesis of an opioid-mediated dependence.

To assess the effectiveness of naltrexone in type 1 diabetic women presenting bulimia or binge eating, we conducted an open-label, 1-year pilot trial in 10 patients affected by these eating disorders who did not respond to antidepressive drugs, behavioral therapy, and interpersonal psychotherapy. All patients volunteered and gave their informed consent to enter the trial, which was ethically approved. Mean age of the patients was 22 years (range 17–29), with type 1 diabetes history of 8 years (range 5–15). Initial BMI was 25 ± 6 kg/m^2. One patient affected by binge eating presented morbid obesity (BMI 41.5 kg/m^2). Blood glucose control at enrollment was very poor, as shown by HbA_{1c} levels (mean ± SD), which were 11.6 ± 1.6% (by high-performance liquid chromatography, normal range <5.6%). Eating disorders included binge eating in three subjects (with 14, 21, and 26 episodes per week, respectively) and bulimia in seven subjects (7–18 episodes per week) and were also associated with "purging" behavior (self-vomiting) in six subjects (7–21 episodes per week), according to the Diagnostic and Statistical Manual of Mental Disorders IV classification. No psychiatric comorbidity was diagnosed. The mean history of severe eating disorders was 6 years (range 4–11). All patients received oral naltrexone 200 mg b.i.d. (Bristol Myers Squibb, Paris, France) for 1 year. Follow-up included a monthly evaluation of the weekly occurrence of impulsive eating with or without purging episodes as the main outcome and monthly measurement of body weight and HbA_{1c} assay every 2 months as secondary outcomes. Psychological assessment by self-administered Eating Disorder Inventory 2 questionnaire was performed before and at the end of the trial.

Results after 2 months and 1 year are presented here to estimate the rapidity and maintenance of drug response. Weekly binge-eating episodes were dramatically reduced by 42, 62, and 86%, respectively, as early as in the first 2 months and remained reduced by 31, 52, and 86%, respectively, after 1 year in the three patients affected by this eating disorder. Weekly bulimic crises were reduced by 50% (range 16–88) after 2 months and by 64% (range 29–94) after 1 year, while associated purging decreased by 74% (range 50–86) and 75% (range 52–100) during the same time periods. The only patient with nonpurging bulimia reduced her weekly crises by 71% after 2 months, which was sustained after 1 year. Meanwhile, body weight decreased by 3–5% after 2 months and by 5–7% after 1 year in binge eaters, and HbA_{1c} levels moved from 11.3, 12.1, and 14.1% to 10.4, 9.8, and 10.2% after 2 months and to 9.0, 8.7, and 9.8% after 1 year, respectively. Body weight remained stable over 1 year in bulimic patients, except in the nonpurging subject, who lost 5% of her initial weight. However, HbA_{1c} levels (mean ± SD) improved from 11.6 ± 1.2 to 10.1 ± 0.6% after 2 months and to 9.0 ± 0.9% after 1 year in these patients. Scores of the Eating Disorder Inventory 2 questionnaire dramatically improved concerning "attitude toward impulsiveness" (data not shown, $P < 0.01$) and also improved at a lower level concerning "low self-esteem" (data not shown, $P < 0.05$), regardless of which eating disorder. No undesirable clinical or biological (liver enzymes and creatininemia) side effects were noted during the trial.

Similar to results obtained with naltrexone in nondiabetic subjects, our data show a dramatic improvement in impulsive eating disorders with this drug in our cohort of type 1 diabetic women. While average weekly occurrence of food intake crises was reduced by 50–64%, purging behaviors were improved even more by >70%. Most of the drug response was obtained after 2 months, but it was maintained or slightly improved further after 1 year. Only binge-eating crises slightly rebounded between the second and twelfth months in two patients, but remained much less frequent than the initial rate. The effect on body weight was modest because reduction of previous intentional insulinopenia and/or vomiting attenuates the impact on body weight. The highly significant improvement of diabetes control is shown, with an average HbA_{1c} decrease of 1.5% after 2 months and 2.5% after 1 year. If maintained for years, such reductions in HbA_{1c} levels could mean an even more impressive improvement of the incidence of diabetic complications, according to estimations from the Diabetes Control and Complications Trial (5). Beside reduction of carbohydrate intakes, psychological changes documented by the Eating Disorder Inventory 2 questionnaire likely played a role in positive behavior toward insulin treatment, which may explain the HbA_{1c} improvement. Although we cannot exclude a nonspecific "study effect," the encouraging results of this pilot trial warrant further assessment of naltrexone in controlled studies, especially as severe eating disorders associated with type 1 diabetes represent an often hopeless condition.

Isabelle Raingeard, md[1]
Philippe Courtet, md, phd[2]
Eric Renard, md, phd[1]
Jacques Bringer, md[1]

From the [1]Endocrinology Department, Lapeyronie Hospital, Montpellier, France; and the [2]Department of Psychological Medicine and Psychiatry, Lapeyronie Hospital, Montpellier, France.

Address correspondence to Eric M. Renard, MD, PhD, Endocrinology Department, Lapeyronie Hospital, F 34295 Montpellier cedex 5, France. E-mail: renard.amtim@wanadoo.fr.

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COMMENTS AND RESPONSES

Utility of B-Type Natriuretic Peptide as a Screen for Left Ventricular Dysfunction in Patients With Diabetes

Response to Epshteyn et al.

In their study recently published in *Diabetes Care*, Epshteyn et al. (1) found that plasma B-type natriuretic peptide (BNP) was able to discriminate between diabetic patients with and without left ventricular (LV) dysfunction, even among the subset without any clinical suspicion of heart failure. It is this last observation that supports the use of BNP as a screen for LV dysfunction among people with diabetes. Detection of LV dysfunction, an early feature of diabetic heart disease, presents an important opportunity for prevention of downstream morbidity and mortality (2). The question that begs to be answered is when should screening for LV dysfunction take place?

Epshteyn et al.'s (1) sample of 91 patients without clinical suspicion of heart failure did, however, contain a significant number with vascular disease. A history of hypertension, coronary artery disease, and myocardial infarction was present in 81, 23, and 18% of the sample, respectively. The study reinforced the value of screening with BNP in a high-risk diabetic population. What remains unknown is whether the utility of BNP for the detection of LV dysfunction extends to asymptomatic individuals without overt vascular disease.

We addressed this by undertaking a substudy within the large Australian Diabetes, Obesity and Lifestyle (AusDiab) study (3). A random sample of 100 adults with type 2 diabetes but free of overt cardiovascular disease and hypertension were matched 1:1:1 by age and sex to subjects with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT), who were also without overt cardiovascular disease and hypertension. In contrast to the study by Epshteyn et al. no differences were found in mean (±SE) levels of plasma N-terminal BNP across the three groups: type 2 diabetes, 155 ± 33; IGT, 172 ± 40; and NGT, 162 ± 51 pg/ml ($P = 0.96$). However, there were significant differences in urinary protein: type 2 diabetes, 102 ± 15; IGT, 64 ± 7; and NGT, 50 ± 4 mg/day ($P < 0.001$).

There are two possible explanations for the observed findings with N-terminal BNP: *1*) among diabetic patients without overt cardiovascular disease and hypertension, LV dysfunction is not more common compared with that of those with IGT and NGT, or *2*) plasma N-terminal BNP is not sensitive to its presence. Echocardiographic studies would be needed to confirm which explanation holds, but either way plasma N-terminal BNP appears to have little utility for early screening of LV dysfunction in patients with diabetes (in the absence of cardiovascular disease and hypertension). This contrasts with early screening for renal dysfunction by urinalysis.

Danny Liew, fracp[1]
Hans Schneider, fracp[2]
Joe D'Agostino, bsc[2]
Jonathan Shaw, md[3]
Henry Krum, phd[1]

From the [1]NHMRC Centre of Clinical Research Excellence in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University Medical School, Alfred Hospital, Melbourne, Victoria, Australia; the [2]Alfred Pathology Service, Alfred Hospital, Melbourne, Victoria, Australia; and the [3]International Diabetes Institute, Caulfield, Victoria, Australia.

Address correspondence to Dr. Danny Liew, Department of Epidemiology and Preventive Medicine, Monash University Medical School, Alfred Hospital, Melbourne, Victoria 3004, Australia. E-mail: danny.liew@med.monash.edu.au.

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Utility of B-Type Natriuretic Peptide as a Screen for Left Ventricular Dysfunction in Patients With Diabetes

Response to Liew et al.

Liew et al. (1) are correct in their premise that their study likely represents a different population of patients than our study (2). While their

study looked at a very early, asymptomatic population of diabetic subjects who were free of overt heart disease or hypertension, our patient population was a Veterans Administration population with many risk factors for heart disease; hence, they are a very high-risk population.

The positive predictive value of any test becomes much stronger as the prevalence of disease increases. The negative predictive value is strong in both studies. The two peptides B-type natriuretic peptide (BNP), and the inactive NH_2-terminal pro-BNP, are cleaved from the same precursor molecule, prepro BNP. Although NH_2-terminal pro-BNP has exclusive renal clearance and a longer half-life than BNP, these factors should not account for the differences. However, it is possible that the elevation of NH_2-terminal pro-BNP (and not BNP) with even small amounts of renal dysfunction might obscure the ability to detect cardiac abnormalities.

Liew et al. (1) conclude that NH_2-terminal pro-BNP has little utility for early screening of left ventricular dysfunction in patients with diabetes. This may be true in a relatively asymptomatic low-risk group, but is unlikely to be true in the majority of patients with type 2 diabetes, who have many other risk factors. It is likely that their patients had no cardiac dysfunction, whereas in our study, almost all of the patients with high BNP levels did have diastolic or systolic dysfunction, even when asymptomatic. We found a particularly high incidence of diastolic dysfunction in this group of patients.

We now have 3–4 years of follow-up data on this group of patients (V. Epshteyn, K. Morrison, P. Krishnaswamy, R. Kazanegra, P. Clopton, S. Mudaliar, S. Edelman, R.H., A. Maisel, unpublished data), and BNP turns out to be an extremely strong predictor of future cardiac events. We believe that if Liew et al. continue to follow peptide levels in these patients, they will begin to see increases in levels as the ventricle begins to either stiffen and/or fail. This may be the opportune time to maximize cardiac work-up and treatment in these patients.

Robert R. Henry, MD
Alan Maisel, MD

From the VA San Diego Healthcare System, San Diego, California.

Address correspondence to Robert R. Henry, MD, VA San Diego Healthcare System, 3350 La Jolla Village Dr., San Diego, CA 92161. E-mail: rrhenry@vapop.ucsd.edu.

R.H. holds stock in Biosite, which markets BNP.

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How to Implement Evidence Into Practice to Improve Diabetes Care

Response to Ilag et al.

In their article, Ilag et al. (1) used the Annual Diabetes Assessment Program (ADAP) as a model to improve the standard of care for patients with type 2 diabetes. Despite established guidelines for type 2 diabetes, the majority of patients in the U.S. do not reach these goals (2). Various approaches have been used, including disease management programs, physician education, nurse case management, and use of information systems to translate evidence-based recommendations into clinical practice (3).

Diabetes translation research should be conducted as an effectiveness trial, rather than an efficacy trial with loose eligibility criteria, in order to produce a heterogeneous population to enhance external validity of the intervention. Ilag et al. used comparatively strict and subjective eligibility criteria, since 284 of 584 patients were considered eligible. The study population in this trial was mainly composed of Caucasian Americans. Hispanic Americans have a higher prevalence rate of diabetes and its complications (4). The Hispanic population should be oversampled in these trials.

There was a high drop-out rate in their study group, as only 83 of 173 (48%) subjects who were enrolled returned for the year-2 visit compared with 71 of 111 (64%) in the control group. Because compliance to treatment is the major challenge faced in diabetes management, intent-to-treat analysis should be included along with protocol analysis in diabetes translation research trials.

The authors did not mention the costs and resources of implementation of this model. Certified diabetes educators (CDEs) were used for implementation of the ADAP. It was not described how many CDEs were used in relation to a certain number of patients. The use of CDEs for implementation of guidelines questions the reproducibility of this model on a mass scale due to the lack of easy availability of CDEs.

I agree with the authors' comments that lack of integration of ADAP providers in the practice and lack of continuous communication (once-a-year visit only) with both patients and physicians resulted in lower enthusiasm in providers and lack of impact on intermediate outcomes. The combined effects of a program like the ADAP, generating guideline-driven recommendations and consistent follow-up by nurse case managers, with management algorithms may prove more effective.

Tipu Faiz M. Saleem, MD

From the Division of Endocrinology, Department of Medicine, The Reading Hospital and Medical Center, Reading, Pennsylvania.

Address correspondence to Tipu Faiz M. Saleem, MD, Division of Endocrinology, Department of Medicine, Reading Health Dispensory, 430 North 2nd St., Reading, PA 19601. E-mail: tipufaiz@aol.com.

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How to Implement Evidence Into Practice to Improve Diabetes Care

Response to Saleem

We appreciate Dr. Saleem's (1) interest and comments and thank the editor for the opportunity to clarify the points raised about our study (2).

Our study was an effectiveness trial. The target population for the Annual Diabetes Assessment Program (ADAP) included all managed care members with diabetes assigned to the participating provider groups. The enrollment criteria were pragmatic, excluding those without diabetes, those who were no longer being followed by the primary care physician, and those who were deemed "unsuitable candidates for the study" by their primary care physicians. We obtained consent from both participants and their primary care physicians to comply with good clinical practice (3). The attrition in the intervention group from 173 eligible individuals to 103 enrolled subjects reflected those who did not consent to the ADAP. The decrease in sample size from year 1 to year 2 (from 103 to 83 in the intervention group and from 111 to 71 in the comparison group) was largely due to subjects' inability to come for their year 2 appointments (e.g., moved away, too ill, etc.). The drop-out rate for the intervention group was 20% (20 of 103), not 52%. We analyzed outcomes for study completers to avoid within-group and between-group bias in interpreting the results. The composition of the study population reflected the racial and ethnic composition of the health plan. We saw no reason to oversample Hispanics. Even if we had done so, we would not be able to generate a sample size sufficient to draw inferences about that population.

The intervention was added to usual care, and as a result, the ADAP was more expensive than usual care alone. Since the ADAP resulted in no improvement in outcomes, usual care dominated the experimental intervention (4). Three registered nurses/certified diabetes educators implemented the ADAP. Clearly, it was feasible to implement the ADAP with nonphysician providers. The question now is how to structure the ADAP to improve both processes of care and intermediate outcomes. Our study was limited in that the ADAP generated only patient and provider feedback. As combinations of interventions have been shown to be more effective in producing change (5,6), future studies should include the ADAP and additional interventions such as nurse case management and more effective tracking and reminder systems to impact both processes and outcomes of care.

LIZA L. ILAG, MD, MS[1]
WILLIAM H. HERMAN, MD, MPH[1,2]

From the [1]Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan; and the [2]Department of Epidemiology, University of Michigan Health System, Ann Arbor, Michigan.

Address correspondence to Liza L. Ilag, MD, MS, Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Michigan Health System, 1500 E. Medical Center Dr., 3920 Taubman Center, Box 0354, Ann Arbor, MI 48109-0354. E-mail: lilag@umich.edu.

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Use of Thiazolidinediones and Risk of Heart Failure in People With Type 2 Diabetes: A Retrospective Cohort Study

Response to Delea et al.

There is a growing concern that use of thiazolidinediones (TZDs) is associated with congestive heart failure (CHF) (1), though the causality of this relationship has not been established. Commentaries and case reports about this potential side effect have frequently appeared in the press, but peer-reviewed, large-scale epidemiologic studies have been absent. A few European nations have already limited the use of TZDs despite the absence of empirical evidence. A recently published, longitudinal observational study by Delea et al. (2) reported that initiation of TZDs was associated with an increased risk of incident CHF (hazard ratio 1.7; $P < 0.001$). While we welcome this first population-based study of TZD use and CHF, we have serious concerns regarding the methodology employed.

Our primary concern with the study by Delea et al. (2) is the potential for residual confounding by indication or severity (3). For example, this study did not measure or adjust for levels of glycemia, a

known risk factor for CHF in diabetes (4). In a time-to-event analysis, the authors compared patients who newly initiated TZDs with those who did not newly initiate TZD therapy while adjusting for other maintained diabetes therapies. Although patients may switch therapies due to side effects, most patients initiate intensified therapy because they have failed to maintain adequate glycemic control with previous regimens (5). Thus patients who initiate a new diabetes therapy, particularly a therapy not considered to be first line, would likely have poorer glycemic control and more advanced diabetes than those who maintain previous therapy and therefore may be at greater risk for CHF.

We are currently conducting a long-term study, funded by the American Diabetes Association, of TZD use and CHF in the Kaiser Permanente Northern California Diabetes Registry. In preliminary analyses, we found a substantially elevated prevalence of several markers of disease severity, including poor glycemic control (HbA_{1c} >9.5%), among patients initiating new diabetes medications relative to those not starting new therapies. Moreover, compared with those initiating other therapies, TZD initiators had a higher prevalence of many CHF risk factors, including the greatest prevalence of ischemic heart disease, hypertension, elevated urinary albumin excretion, elevated serum creatinine, microalbuminuria, and obesity; the poorest glycemic control; and the lowest mean HDL cholesterol levels. TZD initiators were those most likely to also be prescribed medications for dyslipidemia and hypertension and had the greatest outpatient and inpatient utilization. Thus, TZDs were initiated more frequently in diabetic patients with more advanced disease. Since there currently are no generic TZDs, these expensive therapies are likely being reserved for more severe or advanced cases of diabetes.

Delea et al. (2) compared CHF incidence in TZD initiators with that among all other patients, a comparison that is even more biased than the comparison of TZD initiators to initiators of other diabetes therapies. Their comparison group is primarily comprised of those maintaining rather than initiating therapies and is thus healthier. These authors acknowledge that TZD initiators were sicker than subjects in their comparison group. Substantial imbalance in disease severity between exposure groups makes observational studies particularly vulnerable to bias, especially in the absence of thorough statistical adjustment. The authors relied on adjustment for prevalent conditions reported in the previous 12 months, including concurrent medication use and processes of care. While this may seem to be adequate at first glance, the impact of residual confounding remains unclear since important clinical adjusters, such as levels of glycemic control and markers of disease severity, measured over a longer time frame were not available. Additional uncertainties remain. If TZDs confer increased risk for CHF, one might expect a dose-response effect. No such evidence was reported in the study of Delea et al.

Even the largest well-designed premarketing trials often fail to uncover serious side effects caused by new therapies (6). Spontaneous adverse drug reaction reports from postmarketing surveillance are subject to overinterpretation given the often atypical clinical characteristics of cases (confounding), unawareness of the population background rate, and exaggerating effect of media focus, underscoring the importance of large epidemiologic studies to estimate the risk of adverse events associated with drug use (7–9). Although it is well accepted that TZDs may cause volume expansion and peripheral edema (10), the association between long-term TZD utilization and increased CHF risk requires further evaluation (11). Delea et al. should be commended for taking the first step in examining the potential for TZD side effects. It is clear that these authors have conducted the best possible analysis with the available data and fully acknowledge the potential limitations of their study design. However, we cannot exclude residual confounding as an explanation for these authors' findings; any newly initiated diabetes therapy might be associated with elevated CHF risk. We therefore caution that the findings of Delea et al. should not be interpreted as causal. Changes in clinical recommendations for TZDs should be based on solid evidence; we do not think this suffices.

ANDREW J. KARTER, PHD
AMEENA T. AHMED, MD, MPH
JENNIFER LIU, MPH
HOWARD H. MOFFET, MPH
MELISSA M. PARKER, MS
ASSIAMIRA FERRARA, MD, PHD
JOE V. SELBY, MD, MPH

From the Division of Research, Kaiser Permanente, Oakland, California.

Address correspondence to Andrew J. Karter, Division of Research, Kaiser Permanente, 3505 Broadway, Oakland, CA 94611. E-mail: andy.j.karter@kp.org.

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Use of Thiazolidinediones and Risk of Heart Failure in People With Type 2 Diabetes: A Retrospective Cohort Study

Response to Karter et al.

We thank Karter et al. (1) for their comments regarding our study (2). We agree that its principal weakness is the possibility of residual confounding, and we acknowledge this limitation in our article. We also agree that comparison of patients initiating thiazolidinediones (TZDs) with all those receiving other oral antidiabetic agents (new starters plus those on maintenance therapy) may have biased our findings against TZDs. On the other hand, the alternative of comparing patients initiating therapy with TZDs with those initiating other oral antidiabetic agents could have imparted a potentially more serious bias to the study because (as Karter et al. note) the former may be more likely to be initiated later in the course of the disease than the latter. Lacking data on the duration of diabetes, we chose an approach that we hoped would minimize bias and we attempted to control for confounding using multivariate analysis and propensity matching.

Karter et al. (1) present a number of intriguing preliminary results from the Kaiser Permanente Northern California Diabetes Registry. Although the Registry provides a richer clinical picture than the claims dataset we employed in terms of patient characteristics such as glycemic control, it too has its limitations. The Registry represents a group of patients receiving treatment in a single, group practice, integrated delivery system in which processes and outcomes of care for diabetes patients may differ substantially from those among the more diverse group of patients represented in our study. In Kaiser Permanente Northern California, TZDs may be more likely to be reserved for the "sickest" patients. Also, the effects of TZDs on risk of heart failure may be less pronounced in settings where patients are monitored more frequently and edema is therefore less likely to progress to overt heart failure before arousing clinical suspicion and action.

Thus, although we eagerly await the results of the analysis by Karter et al., we suspect that it may not provide a definitive answer with respect to the effects of TZDs on risk of heart failure because their analysis will suffer from the same fundamental weakness (i.e., possibility of residual confounding) that they correctly identified in ours, although perhaps to a lesser degree. Moreover, their study may suffer from the additional potential limitation of lack of generalizability to the overall population of patients receiving TZDs. As we note in our study, definitive conclusions must await the results of long-term, randomized, controlled trials (although these too may suffer from problems of generalizability).

So where does this leave us? While awaiting the results of ongoing studies, clinicians must make use of the best available data to guide their decisions. We agree with Karter et al. that the results of our study do not warrant changes in clinical practice guidelines. Our recommendation that physicians use these drugs with caution in patients with heart failure is entirely consistent with warnings set forth in U.S. Food and Drug Administration–approved labeling for rosiglitazone and pioglitazone (3,4). Our recommendation that physicians seek alternatives for patients with shortness of breath is only common sense in light of the strength and consistency of the association that we observed, the known physiologic effects of these agents, and published reports of TZD-induced heart failure and pulmonary edema resolving after discontinuation of such therapy (5).

Unfortunately, even well-established treatment guidelines are not consistently followed in typical clinical practice, as demonstrated by a recent study (6) that found that patients hospitalized for heart failure frequently receive TZDs despite explicit warnings against this practice. We hope that our study will increase physician awareness of the potential risk of heart failure associated with the use TZDs so that it may be weighed against the potential benefits of these agents in improving clinical outcomes in patients with diabetes (7–8).

THOMAS E. DELEA, MBA[1]
JOHN S. EDELSBERG, MD, MPH[1]
MAY HAGIWARA, PHD[1]
GERRY OSTER, PHD[1]
LAWRENCE S. PHILLIPS, MD[2]

From [1]Policy Analysis, Inc. (PAI), Brookline, Massachusetts; and the [2]Division of Endocrinology, School of Medicine, Emory University, Atlanta, Georgia.

Address correspondence to Thomas E. Delea, MBA, Policy Analysis, Inc. (PAI), 4 Davis Ct., Brookline, MA 02445. E-mail: tdelea@pai2.com.

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