

## OBSERVATIONS

## Eating Disorders in 12- to 16-Year-Old Diabetic and Nondiabetic Adolescents From Barcelona, Spain

Although eating disorders are common in late adolescent diabetic patients, the occurrence in younger populations, particularly male diabetic patients, is not well documented (1,2). The prevalence was studied in 60 boys and 38 girls ( $13.78 \pm 1.05$  years of age, range 12–16) with diabetes duration  $1.5 \pm 3.35$  years and in 321 boys and 254 girls as nondiabetic peers ( $13.73 \pm 0.63$  years of age, 12–16).

Patients and peers completed the Spanish validated version of the Eating Attitudes Test (EAT-40) (3). The semi-structured Eating Disorder Examination (EDE) interview (4) was held for those with an EAT-40  $>30$  (13 diabetic patients and 57 nondiabetic peers) and an additional randomly selected population (24 diabetic patients and 57 nondiabetic peers) with an EAT-40 score  $<30$ . Eating disorders were classified as clinical (5) and subthreshold (1). SPSS version 9.0 was used for statistical analysis.

No cases of anorexia or bulimia were found. Eating disorders not otherwise specified (EDNOS) were more prevalent in diabetic patients than in peers: boys (1.7 vs. 0.9%, odds ratio 1.7, CI 95% 0.2–17.6) and girls (5.3 vs. 1.6%, 3.2, 0.62–17.2). Subthreshold eating disorders were more prevalent in male diabetic patients than in nondiabetic peers (10 vs. 4.4%, 2.4, 0.9–6.6), with no differences between female diabetic patients and nondiabetic peers (10.5 vs. 9.9%, 1.1, 0.4–3.2). Male diabetic patients had 2.4 times increased risk for subthreshold eating disorders than nondiabetic peers. No eating disorders were observed in the 24 diabetic patients and 57 nondiabetic peers with EAT-40 scores  $<30$ . Glycated hemoglobin values were higher in diabetic patients with eating disorders ( $9.8 \pm 0.42$  and  $5.63 \pm 2.76\%$ ,  $n = 13$ )

than in those without ( $8.4 \pm 1.5$  and  $5.09 \pm 2.73\%$ ,  $n = 85$ ) ( $P = 0.049$ ).

Although no cases of anorexia or bulimia were found, EDNOS and subthreshold eating disorders were detected in younger diabetic patients of both sexes. The higher glycated hemoglobin levels found in diabetic patients with eating disorders suggest poor metabolic control and increased risk for later vascular complications (6). Further studies including large series of patients are necessary to confirm these preliminary results; however, our data underline the need for careful surveillance in young diabetic patients of both sexes in order to promptly detect and prevent these incipient eating disorders.

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insulin-dependent diabetes mellitus. *N Engl J Med* 336:1849–1854, 1997

## Can Cranberry Supplementation Benefit Adults With Type 2 Diabetes?

Cranberries (*Vaccinium macrocarpon*) are a rich source of phytochemicals, including anthocyanins and other flavonoids that may decrease lipid oxidation and protein glycosylation (1). Anthocyanins inhibit aldose reductase in vitro (2). Red wine anthocyanins improved urine and serum glucose levels and free radical control in streptozotocin-injected rats (3). Daily consumption of 200 ml chokeberry (*Aronia melanocarpa*) juice for 3 months lowered fasting blood glucose, HbA<sub>1c</sub>, and lipid levels in people who had been diagnosed with type 2 diabetes for 6–17 years (4). Cranberry juice may decrease the side effects of diabetes and increase the quality of life for people with diabetes.

Adults controlling their type 2 diabetes through diet alone were recruited from the Bangor, Maine, community. Fourteen subjects (aged  $57.9 \pm 10.6$  years, 6 women, 8 men, duration of diabetes  $6.0 \pm 8.5$  years) were randomized to the cranberry group; 13 subjects (aged  $52.6 \pm 13.7$  years, 6 women, 7 men, duration of diabetes  $4.1 \pm 4.9$  years) were assigned to the placebo group. Subjects consumed six capsules filled with either cranberry juice concentrate powder or a placebo daily for 12 weeks. Six capsules were equivalent to a 240-ml serving of cranberry juice cocktail. The artificially colored placebo mimicked the cranberry powder in all respects but flavonoid content. Subjects were asked to discontinue use of dietary supplements, but no other diet and lifestyle changes were made during the study.

More than one-half of the subjects had good control of blood glucose levels ( $<7.0$  mmol/l) at the beginning of the study. No differences were found between the treatment groups in fasting serum glucose, HbA<sub>1c</sub>, fructosamine, triglyceride, or HDL or LDL levels after 6 and 12 weeks. Placebo subjects had higher insulin values throughout the

study ( $160 \pm 167$  vs.  $86 \pm 51$  pmol/l at week 12,  $P < 0.05$ ). Different effects might be seen in subjects with poor glucose control, individuals with type 1 diabetes, or people who use medications to control their type 2 diabetes.

Although the National Kidney Foundation recommends drinking one glass of cranberry juice per day to prevent urinary tract infections, people with diabetes may need to consume greater quantities to improve their health. Since most commercial cranberry juice cocktails contain only 27–31% cranberry juice, more concentrated products might improve compliance. The additional heat processing necessary to convert the cranberry juice to a shelf-stable powder may have altered bioactivity. Despite the lack of significant findings in this small study, the role of cranberries and other flavonoid-rich fruits should be investigated further.

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## –429T/C and –374T/A Polymorphisms of RAGE Gene Promoter Are Not Associated With Diabetic Retinopathy in Chinese Patients With Type 2 Diabetes

The interaction between advanced glycation end products (AGEs) and the cellular receptor of AGE (RAGE) could result in cellular activation and inflammation (1). In vitro and in vivo studies indicate that RAGE plays an important role in the pathogenesis of diabetic vascular complications (2). It is plausible that genetic differences in the RAGE gene could alter expression and function to affect disease development. Many polymorphisms in the RAGE gene have already been identified (3) and show no association with macro- or microvasculopathy of diabetes (4,5). However, Hudson et al. (6) have detected two polymorphisms, –429T/C and –374T/A, in RAGE gene promoters. They reported that the –429T/C polymorphism is associated with diabetic retinopathy in type 2 diabetic patients, but found no association between the two polymorphisms and macrovascular diseases (7).

We screened the –429T/C and –374T/A polymorphisms among 212 unrelated Chinese nondiabetic subjects and 357 type 2 diabetic subjects (205 with and 152 without diabetic retinopathy). Type 2 diabetes was diagnosed according to 1999 World Health Organization criteria. Retinopathy was defined by an ophthalmologist. Genotyping was performed by PCR fragment-length polymorphism assay. Primers were designed according to the method of Hudson et al. (6).

There were no differences in allele frequencies between diabetic subjects with (–429T 90.1%, C 9.9%; –374T 86.4%, A 13.6%) or without (–429T 87.8%, 12.2%; –374T 87.3%, 12.7%) diabetic retinopathy. No differences were found between the diabetic and nondiabetic subjects (–429T 87.3%, 12.7%; –374T 86.1%, 13.9%). The –429C and –374A allele frequencies (12.7 and 13.9%, re-

spectively) are lower than those in Caucasians (18 and 20%) (7).

Our study indicates that the –429T/C and –374T/A polymorphisms in RAGE gene promoters are not associated with diabetic retinopathy in Chinese patients with type 2 diabetes. However, further studies on large populations are still required to evaluate whether these polymorphisms and other polymorphisms in RAGE genes are related to diabetic vascular complications.

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## High Frequency of Type 1B (Idiopathic) Diabetes in North Indian Children With Recent-Onset Diabetes

Islet antibody-negative or type 1B (idiopathic) diabetes constitutes 5–10% of Caucasian diabetic subjects with recent-onset type 1 diabetes (1). A study from Italy (2) failed to show clinical differences between these patients and those with antibodies. In contrast, a fulminant form of type 1B diabetes with associated exocrine pancreatic involvement, possibly secondary to viral infection, has been described in Japanese (3). There is little information on type 1B diabetes in other racial groups. Therefore, we studied the frequency and characteristics of type 1B diabetes in children of north Indian origin.

We studied all 55 children (32 male and 23 female) with recent-onset type 1 diabetes who presented at our diabetes clinic over a 10-year period. Subjects had an age at onset <20 years ( $9.7 \pm 5.0$  years [mean  $\pm$  SD]), duration of diabetes <3 months ( $33 \pm 20$  days), severe hyperglycemia (plasma glucose  $20.7 \pm 8.6$  mmol/l), and required insulin continuously after diagnosis. Chronic pancreatitis was ruled out by abdominal ultrasonography. GAD and insulinoma-associated protein 2 (IA-2) antibodies (GADAs and IA-2As) were determined by immunoprecipitation of recombinant <sup>35</sup>S-labeled human antigen, as described previously (4). The antibody assays were included in all workshops and Immunology of Diabetes Society serum exchanges, and they have proven sensitivity and specificity. HLA typing for 12 DR antigens was performed using sequence-specific oligonucleotide probes.

GADAs were present in 23 subjects (42%), and IA-2As were only found in 18 subjects (33%). Both antibodies were absent in 25 children (45%). When compared with control subjects, the only HLA genotype associated with type 1 diabetes

was DRB1\*03/03 (8/41 [19.5%] vs. 1/105 [1%], odds ratio [OR] 26.4,  $P < 0.001$ ). When children with GADAs or IA2As (type 1A diabetes) were compared with those in whom neither was present (type 1B diabetes), there were no differences in their clinical features (age at onset, duration of symptoms before diagnosis, frequency of ketosis, or BMI) or metabolic profile (plasma glucose, HbA<sub>1c</sub>, or fasting plasma C-peptide). The frequency of the HLA-DRB1\*03/03 genotype, when compared with control subjects, was increased in the type 1A (7/24 [29%] vs. 1/105 [1%], OR 44.8,  $P < 0.001$ ) but not in the type 1B (1/17 [6%]) diabetic subgroup. No patient with fulminant type 1B diabetes (duration of symptoms <1 week and elevated serum trypsin) was detected. In fact, patients with type 1B diabetes had lower serum trypsin levels compared with the levels in those with type 1A diabetes ( $19.4 \pm 11.9$  vs.  $29.1 \pm 16.6$   $\mu$ g/l,  $P = 0.03$ ; normal range 10–57  $\mu$ g/l).

We found a far higher frequency of type 1B diabetes (45%) among children and adolescents with recent-onset type 1 diabetes than previously reported in other Caucasian populations (1). This may be related in part to the low frequency of IA-2A in the current study. This finding has also been reported earlier (4,5) and may be due to the low prevalence of HLA-DR4 in type 1 diabetic subjects in this racial group (5). Alternatively, an increase in diabetes from “nonautoimmune” causes such as viral infections, toxins, mutations in transcription factors, or subclinical pancreatitis is possible. The association of the high-risk genotype DRB1\*03/03 with only type 1A diabetes suggests that different pathogenetic mechanisms may exist for type 1A and 1B diabetes in this study population. In view of the absence of the type of fulminant type 1B diabetes found in Japanese subjects in both the current study and earlier reports in other Caucasian groups (2), it is likely that type 1B diabetes will be heterogeneous in its etiology.

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## Glyceryl Trinitrate Patches as an Alternative to Isosorbide Dinitrate Spray in the Treatment of Chronic Painful Diabetic Neuropathy

In the October 2002 issue of *Diabetes Care*, we reported (1) the benefit of isosorbide dinitrate (ISDN) in the treatment of painful diabetic neuropathy. This stance was based on the speculation that the impaired nitric oxide (NO) generation might play a role in the pathogenesis of neuropathic pain through defects in local vasodilatation. This was a double-

blind, randomized, placebo-controlled, two-period, crossover design study of 22 diabetic patients. The ISDN spray reduced overall neuropathic pain ( $P = 0.02$ ) and burning sensation ( $P = 0.006$ ). Fifty percent of the patients reported improvement in their quality of life and wanted to continue the ISDN spray. Since then, this publication has received considerable interest, with numerous inquiries from clinicians and patients wishing to try ISDN spray but unable to obtain it. Unfortunately, the company who provided with spray and placebo material has stopped manufacturing the ISDN spray. Nevertheless, we believe the following information regarding the use of glyceryl trinitrate (GTN) patches may be of interest and helpful for those who would like to try this therapy.

We had originally intended to use GTN patches to test our hypothesis after finding benefit in a small number of index cases with chronic painful neuropathy. In this pilot study the majority (four of six subjects) reported improvement in the pain. Based on this observation, we designed a placebo-controlled study, but were unable to obtain placebo patches from any of the manufacturers of GTN patches. It was the availability of placebo material that led us to explore our hypothesis using ISDN spray as the NO donor.

Since publication and the unavailability of ISDN, we have reverted to using GTN patches. A total of 18 patients (10 men, 15 with type 2 diabetes, age  $57 \pm 2.3$  years [mean  $\pm$  SD]) have now been treated. We present the following observations from our experiences with these patients. However, it should be stressed that this is not a placebo-controlled study.

Our clinical practice is to prescribe a 5-mg patch to be applied to the dorsum of one foot in the early evening, which is to be replaced with a new patch by the patient the following evening. The rationale behind this was to avoid headaches from prescribing too large a dose at the outset. If no headache occurred after several days we recommended the patients to use one 5-mg patch on each foot. If this produced headaches, then the patients are instructed to halve the patch and apply 2.5 mg to each foot.

Among the 18 patients, 8 (44%) reported reduction in pain and wished to continue using the patches. Of the subjects who noted an improvement, it occurred with the first or second application

or within the first week. Two patients had to discontinue using the patches; one because of headache and the other due to a skin rash, but both had reported definite benefit. There were no other systemic adverse events reported. Thus, similar to the ISDN spray, GTN patches are helpful in some patients with painful diabetic peripheral neuropathy.

It is of interest that during the initial period, when only one patch was used, most patients reported a reduction in pain solely in the leg to which the patch was applied. This suggests a local mechanism rather than a systemic effect.

Thus, further placebo-controlled studies with larger patient numbers are required to confirm the potential of GTN patches in alleviating sensory symptoms associated with painful diabetic neuropathy. The mechanism remains speculative, and the apparent local effect, if confirmed, is intriguing.

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## Heart Rate Response During Positive Exercise Stress Test Predicts Coronary Artery Disease and Its Severity in High-Risk Type 2 Diabetic Patients With Silent Ischemia

**D**agnosis of coronary artery disease (CAD) before symptoms appear can reduce mortality in diabetes (1). ST depression at exercise stress test (EST) independent of angina is a hallmark of CAD

(2); however, if a positive EST is characterized by the lack of angina, a second test to better stratify the risk of ischemia is recommended (3). Heart rate response at EST with ST depression can improve risk stratification in the general population (4), but no such data are available in diabetic patients.

We studied the relationship between heart rate response and CAD in 33 consecutive patients with type 2 diabetes and silent ischemia at EST (i.e., horizontal or downsloping ST depression  $\geq 1$  mm at 0.08 s after J point, without angina). Patients (22 men and 11 women, age  $59 \pm 7$  years, BMI  $30 \pm 4$  kg/m<sup>2</sup>, duration of type 2 diabetes  $11 \pm 6$  years, and HbA<sub>1c</sub>  $8.3 \pm 1\%$ ) with no symptoms or resting electrocardiogram signs of ischemia were considered at “high risk” for CAD due to peripheral vascular disease and/or two additional atherogenic factors according to guidelines criteria (1). Cardiovascular drugs were stopped 48 h before the EST. Coronary angiography was considered positive if stenosis  $\geq 70\%$  was observed in a major epicardial artery or its main branches.

Maximal heart rate at the moment of ST depression was lower in 13 patients with three-vessel disease (7 of whom did not reach the 85% of predicted maximal heart rate) than in 20 patients with less than or equal to two- or no-vessel disease (4 of whom did not reach the 85% of predicted maximal heart rate) ( $127 \pm 12$  vs.  $140 \pm 13$  bpm,  $P = 0.009$ ).

Maximal heart rate  $< 136$  bpm (mean and median value) predicted three-vessel disease with an odds ratio (OR) of 7.7 (95% CI 1.5–38,  $P < 0.05$ ) independent of both age and sex, or of each of the following potential confounders: BMI, diabetes duration, hypertension, smoking, and diabetes complications, including peripheral vascular disease (stenosis  $\geq 40\%$  at ultrasound doppler), nephropathy (urinary albumin excretion rate  $> 20$   $\mu$ g/min), retinopathy (at fundoscopy), and neuropathy (at electromiography).

Heart rate reserve (i.e., maximal heart rate at the moment of ST depression minus resting heart rate) was lower in 13 patients with three-vessel disease than in 20 patients with less than or equal to two- or no-vessel disease ( $48.6 \pm 12$  vs.  $61 \pm 16$  bpm,  $P = 0.01$ ).

Heart rate reserve  $< 56$  bpm (mean and median value) predicted three-vessel disease with an OR of 5.0 (95% CI 1.1–

24,  $P < 0.05$ ) independent of both age and sex or each previously mentioned confounder.

Maximal heart rate and heart rate reserve were lower in 17 patients with ejection fraction  $<60\%$  (mean value) than in 16 patients with ejection fraction  $>60\%$  ( $126 \pm 12$  vs.  $143 \pm 13$  bpm,  $P = 0.001$  for maximal heart rate and  $49 \pm 12$  vs.  $63 \pm 17$  bpm,  $P = 0.01$  for heart rate reserve).

Maximal heart rate  $<136$  bpm (OR 10.9, 95% CI 1.8–66) and heart rate reserve  $<56$  bpm (6.7, 1.3–33) predicted ejection fraction  $<60\%$ , independent ( $P < 0.05$ ) of both age and sex or each previously mentioned confounders but not of three-vessel disease.

In conclusion, maximal heart rate and heart rate reserve predict CAD severity and ejection fraction in “high risk” diabetic patients with silent ischemia at EST. The Coronary Artery Surgery Study (CASS) (5) showed that coronary artery bypass surgery improves the prognosis in silent diabetic patients with three-vessel disease and impaired ventricular function. Our present data suggest that maximal heart rate and heart rate reserve might serve the function of identifying these patients who could, therefore, undergo coronary angiography with no need of a second test, thus reducing time and cost of diagnosis.

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## Haptoglobin Type and 30-Day Mortality in Diabetic Individuals Presenting With Acute Myocardial Infarction

There are two major classes of alleles for the haptoglobin (Hp) gene, denoted 1 and 2 (1). We have recently reported evidence that Hp is a major susceptibility gene for cardiovascular disease in the diabetic state (2,3). Moreover, we have provided a mechanism for this differential susceptibility conferred by the Hp type by demonstrating striking differences in the antioxidant protection afforded by the protein products of the different Hp alleles (4).

Mortality after myocardial infarction in the diabetic patient remains alarmingly high. Increased oxidative stress leading to increased ischemia-reperfusion injury may play a major role in explaining this poor outcome (5). Accordingly, we proposed that the Hp type would be predictive of mortality and major adverse cardiac events after acute myocardial infarction (AMI) in individuals with diabetes. We sought to prospectively test this hypothesis by determining the association between the Hp type and major adverse cardiac events occurring within 30 days of AMI in a consecutive series of 601

patients (224 diabetic subjects). We found a significantly increased mortality rate in the diabetic cohort in individuals with the Hp 2 allele (30-day mortality rate of 0% for Hp 1-1, 23% for Hp 2-1, and 25% for Hp 2-2,  $P = 0.014$ ). The composite major adverse cardiac events rate (death, reinfarction, and revascularization) at 30 days was 11% in Hp 1-1, 51% in Hp 2-1, and 55% in Hp 2-2 ( $P < 0.0001$ ). After multivariate analysis, using the Cox model, Hp type was significantly associated with the risk of adverse cardiac events in diabetic patients in the first 30 days after AMI (odds ratio 4.9, 95% CI 1.5–15.7,  $P = 0.007$ ). There was no significant difference in the mortality rate or composite primary end point rate among nondiabetic patients segregated by Hp type.

The elevated mortality risk after AMI associated with diabetes appears to be restricted to those individuals with the Hp 2 allele. Determination of the Hp type may be of use in the evaluation of therapies to reduce cardiovascular mortality after AMI in diabetic individuals.

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## Unilateral Edema Due to a Thiazolidinedione

**A** 51-year-old African-American man with type 2 diabetes (anti-GAD antibody negative and C-peptide positive) of 7 years duration was controlled (A1c 7.0%) on a combination of 1 g metformin, 2 mg glimeperide, and 4 mg rosiglitazone all twice daily and 40 units Glargine insulin at bedtime. He had been taking rosiglitazone for 26 months and troglitazone for 13 months before changing to rosiglitazone.

The patient suddenly developed painful swelling of the right leg. On examination there was no edema in the left leg and pitting edema to just below the knee in the right leg, which had an increased temperature. However, no tenderness was found on deep palpation of the calf, popliteal, and femoral areas or in the adductor canal. Two venous ultrasounds 5 days apart showed no evidence of a deep vein thrombosis, and furosemide self-administered by the patient had no effect on the edema. In addition, the neck veins were not distended, hepatojugular reflux was negative, chest was clinically clear, and there was no hepatomegaly or added heart sounds. Serum albumin and liver profile were normal, and there was no albuminuria.

The patient's wife, having consulted

the *Physicians Desk Reference*, felt that the edema was due to rosiglitazone and insisted that her husband discontinue the medication. Within 3 days of discontinuing rosiglitazone the edema disappeared. On rechallenge the edema reappeared within 5 days and the thiazolidinedione was permanently discontinued with resolution and no recurrence of edema.

Dependent edema is a side effect of thiazolidinediones due to increased plasma volume, insulin-induced vasodilatation, and increased production of vascular endothelial growth factor (1–4). However, the distribution of the edema is almost invariably bilateral. Because of unilateral edema in this case, the diagnosis of thiazolidinedione-induced dependent edema was not considered. Since the edema resolved with withdrawal of the thiazolidinedione and reappeared on rechallenge and disappeared after withdrawal, never to return, it was the obvious cause of this unilateral edema. There was no anatomical reason, such as venous insufficiency from varicose veins, or a neurological cause, such as a previous stroke, childhood poliomyelitis, or previous trauma to the leg to explain this unilateral edema. Why an edema with systemic involvement should present unilaterally is not known or gleaned from this case.

In conclusion, practitioners need to be aware that dependent edema due to thiazolidinediones can present with unilateral edema, which will disappear with discontinuation of the thiazolidinedione.

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## COMMENTS AND RESPONSES

### Should postprandial glucose be routinely measured and treated to a particular target? Connecting the two sides of the debate

I would very much appreciate the opportunity to clarify the purpose of my article regarding the role of postprandial glucose (1) and the fact that it was not written as a stand-alone commentary.

Much to the contrary, the piece was submitted after invitation to continue the debate that Dr. Jaime Davidson and I started at the American Diabetes Association Scientific Session in June 2002. The manuscript was intended as a counterpoint to a second piece written by Dr. Davidson (2).

On its own, the counterpoint article lacks fair balance and does not represent the full discourse required for the reader to make reasonable judgments. It was not intended as a review, but as a point of view developed as part of a scholarly exercise. It is unfortunate, even though inadvertently, that the pro and con points were published in consecutive issues of *Diabetes Care* (May and June), rather than simultaneously, as they will most likely be more often read out of context. It is my hope that this letter will serve as glue to draw the two halves of the debate back together, at least when they are accessed as part of an electronic literature search.

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## Preventing, Delaying, or Masking Type 2 Diabetes With Metformin in the Diabetes Prevention Program?

The secondary analysis of the Diabetes Prevention Program (DPP) showed that withdrawal of metformin for 1–2 weeks resulted in a trend to a higher conversion rate from impaired glucose tolerance to diabetes as compared with the placebo group (1). This resulted in a reduction by 26% of the so-called prevention effect of metformin, i.e., from 31% in the primary analysis (2) to 25% in the secondary analysis, a reduction in the incidence of diabetes that, however, remained highly significant as compared with placebo. The same trend was observed in the Study to Prevent (STOP)-NIDDM trial with acarbose after a longer washout period of 3 months (3). As previously discussed (4) and emphasized in a previous *Diabetes Care* Editorial (5), one key question is to know whether the positive results with metformin in the DPP (2) or with acarbose in the STOP-NIDDM trial (3) could be interpreted as a real prevention of the disease or only as a delay in its progression, or even simply as a masking effect due to the metabolic effect of the drug. It was astonishing that a possible direct effect of metformin was not discussed in the original paper of the DPP, despite the fact that the results were ini-

tially presented without any washout period (2). Indeed, a significant improvement of insulin sensitivity and glucose metabolism was consistently demonstrated in placebo-controlled randomized clinical trials after only 48 h treatment with metformin (850 mg twice daily), both in insulin-resistant normoglycemic first-degree relatives of diabetic patients during a euglycemic insulin clamp (6) and in hyperglycemic patients with type 2 diabetes with the isotope dilution technique to measure hepatic glucose production (7).

Using the frequently sampled intravenous glucose tolerance test and the minimal model approach, we also reported such acute favorable effect of metformin in a population similar to that of the DPP, i.e., in subjects with impaired glucose tolerance with a significant increase of the insulin sensitivity index after only 48 h metformin therapy (+50%;  $P = 0.03$ ) (8). That part of the overall effect seen in the DPP may be accounted for by a pure pharmacological effect of metformin that did not persist when the drug was stopped (1) is in agreement with those experimental results (6–8). Furthermore, the rather short washout period of only 1–2 weeks may be questionable. First, it did not allow a sufficiently high number of new cases of diabetes, which limited the statistical power of the analysis (5)—the  $P$  value was 0.098 despite a difference of 49% in diabetes rates between placebo and metformin groups during the washout period. In addition, while the washout period was beyond the classically requested period of five times the plasma half-life of the drug (9), it did not completely exclude the persistence of any biological effect of metformin, which has a particularly complex cellular mechanism of action. Thus, in our opinion and in agreement with Buchanan (5), the question remains open as to whether the results of the DPP with metformin correspond to preventing, delaying, or partially masking effects of type 2 diabetes.

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## Preventing, Delaying, or Masking Type 2 Diabetes With Metformin in the Diabetes Prevention Program?

Response to Scheen

I agree with the fundamental point made by Dr. Scheen (1) in this issue of *Diabetes Care*. It is unclear whether the effect of metformin to reduce the incidence of diabetes during the Diabetes Pre-

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vention Program (DPP) (2) was true prevention or simply a masking of diabetes. The posttrial washout period was very short for testing that distinction. The data cited by Dr. Scheen regarding a very rapid effect of metformin to increase insulin sensitivity suggests that dissipation of any such effect in the DPP could have been rapid as well. Thus, acute effects of metformin on insulin sensitivity could have been gone 2 weeks after the drug was stopped. It seems unlikely that we will ever know for sure because direct measures of insulin sensitivity were not made in the DPP. Additionally, we will never know whether glucose levels had stabilized or were still rising 2 weeks after metformin was stopped. The Study to Prevent (STOP)-NIDDM trial (3) included a more convincing washout period of 3 months before retesting for diabetes. During the washout, the jump in new cases of diabetes in the former acarbose group (twice as many as in the former placebo group) was even more striking than the analogous jump in the former metformin group in the DPP (49% more cases than in the placebo group). Whether this greater jump in the STOP-NIDDM trial reflects the more meaningful washout period used in that trial or a greater component of masking rather than prevention of diabetes compared with metformin can't be determined from the published data.

We have provided strong evidence from the Troglitazone in the Prevention of Diabetes (TRIPOD) study (4), conducted in Hispanic-American women, that lowering endogenous insulin requirements can slow or stop the loss of  $\beta$ -cell function, which leads to type 2 diabetes. If this effect occurs in other ethnic groups (still a big "if"), then any effect of metformin or acarbose to lower glucose levels or enhance insulin sensitivity could have had an analogous, albeit probably weaker, effect in the DPP and STOP-NIDDM trials. Given the known effects of metformin and acarbose on carbohydrate metabolism, I suspect that portions of the reductions in diabetes rates observed in the metformin arm of the DPP and in the STOP-NIDDM trial were due to  $\beta$ -cell protection. The posttrial washouts in the two studies demonstrate that some of the apparent protection from diabetes was simply masking caused by acute glucose-lowering effects of the drugs.

We will never know precisely how much prevention and how much masking

of diabetes occurred in the DPP and the STOP-NIDDM trials. Nonetheless, discourse on this issue can be helpful. It can focus diabetes prevention research on the real disease of type 2 diabetes—progressive  $\beta$ -cell failure—rather than on the glucose thresholds that currently define diabetes. Those thresholds are clearly important for assessing the risk of microvascular and neuropathic complications of diabetes. However, they are not very useful for tracking the underlying  $\beta$ -cell disease. That disease progresses for a long time before patients cross the glucose threshold to diabetes, and it continues after they have crossed that threshold. When the discussion turns to prevention (or even to initial treatment) of type 2 diabetes, the goal should become stability of glucose levels and  $\beta$ -cell function.

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## Response to Scheen and Buchanan

We appreciate the comments of Drs. Scheen (1) and Buchanan (2) regarding our article (3), which described the effects of withdrawal of metformin on diabetes status in the Diabetes Prevention Program (DPP). As Dr. Scheen comments, and as we pointed out in our article, clearly part of the effect of metformin was due to an acute pharmacological effect of metformin, but the great majority of the effect persisted beyond this period of washout. As he notes, the washout period of 1-2 weeks was indeed beyond the usual required period of five times the plasma half-life of the drug. The duration and nature of metformin's effects beyond that time frame are not well established. However, there are no data to support Dr. Scheen's conjecture that waiting for an additional time would "allow a sufficiently high number of new cases of diabetes," which he feels limited the statistical power of the analyses. The data are what they are. Within the DPP, the investigators felt that it would not be ethical to withhold such an efficacious treatment for a prolonged period of time to answer these questions. Furthermore, pharmacological treatment of many other chronic diseases, such as hypertension and dyslipidemia, is generally given continuously. We don't expect drugs treating these conditions to work after they are discontinued. Similarly, we shouldn't expect drug treatment of impaired glucose regulation and other risk factors for type 2 diabetes to be effective after the drugs are discontinued.

We agree that whether drug therapy with metformin, acarbose, troglitazone, estrogens, ACE inhibitors, or angiotensin II receptor blockers truly prevent diabetes or delay its onset cannot be determined completely by the existing studies. However, delaying the onset of diabetes is clearly an important goal with major individual and public health implications. From a practical standpoint, there is little difference between delay and prevention of a disease such as type 2 diabetes with variable and late onset. If an intervention could delay the onset of diabetes long enough such that a person ultimately dies without developing the disease, delay would be equivalent to prevention. Un-



