

## OBSERVATIONS

## Diabetes Screening Practices Among Individuals Aged 45 Years and Older

In 1997, the American Diabetes Association (ADA) adopted new recommendations for screening the general population aged  $\geq 45$  years for diabetes every 3 years with an emphasis on those at high risk for undiagnosed diabetes (1). Few studies have examined the extent to which this screening has been adopted. This report describes the results of a telephone survey of Montana residents aged  $\geq 45$  years to assess the diabetes screening practices in this population.

From October to December 1998, the Montana Department of Public Health and Human Services conducted a random household telephone survey of Montana residents aged  $\geq 45$  years living in 18 counties. Respondents indicated whether they ever had been told by a physician that they had diabetes, the number of visits they made to a health care provider during the past year, their family history of diabetes, whether they had ever been told they had high cholesterol and/or high blood pressure, and their height and weight. Respondents were asked the following question to identify whether they had ever been screened for diabetes: "Glucose or sugar is a substance found in your blood. Have you ever had your blood glucose or sugar checked to see if you have diabetes?" When respondents responded "yes" to this question, they were asked to identify when screening was completed ("When was the last time your blood glucose or sugar level was measured by a health care professional?"). The response categories for this question included within the past year, within the past 3 years,  $>3$  years ago, do not know/not sure, and refused to answer. Pearson  $\chi^2$  tests were used to assess associations between diabetes screening and risk factors for diabetes. Logistical regression analyses were conducted to identify independent variables associated with screening for diabetes during the past year. Odds ratios (95% CIs) were calculated.

Of the 1,204 respondents, 92 (7.6%) reported that they had diagnosed diabetes.

The remaining 1,112 respondents reported that they did not have diagnosed diabetes and are included in the following analyses. Of the respondents, 39% reported a family history of diabetes, 32% reported a BMI  $\geq 27$  kg/m<sup>2</sup>, 28% reported having hypertension, and 28% reported having high cholesterol. Excluding age, 34% of respondents had one risk factor for diabetes, and 40% had two or more risk factors. Of the 1,112 respondents without diagnosed diabetes, 39% reported that they had been screened for diabetes during the past year, 14% reported screening from 1 to 3 years ago, and 47% reported screening  $>3$  years ago or having never been screened.

Respondents who reported being screened for diabetes during the past year were more likely to be age  $\geq 65$  years and to have a family history of diabetes, two or more visits to a health care provider during the past year, hypertension, and high cholesterol levels (Table 1). We found no association between recent screening and sex (40% men vs. 38% women), American Indian ancestry (41% yes vs. 38% no), or BMI (42%  $\geq 27$  kg/m<sup>2</sup> vs. 37%  $< 27$  kg/m<sup>2</sup>). Respondents with three or more risk factors (e.g., aged  $\geq 45$  years, American Indian ancestry, family history of diabetes, hypertension, high cholesterol, or BMI  $\geq 27$  kg/m<sup>2</sup>) were more likely to be screened for diabetes compared with

respondents with only one risk factor (46 vs. 28%, respectively). However, 48% of individuals with two risk factors for diabetes and 37% of individuals with more than three risk factors had not been screened during the past 3 years.

Based on logistical regression analysis, three factors were associated with screening for diabetes during the past year: two or more visits to a health care provider during the past year (2.34 [95% CI 1.76–3.11]), high cholesterol level (1.37 [1.03–1.82]), and family history of diabetes (1.45 [1.12–1.89]). Respondents aged 45–54 years were less likely to report recent screening than those aged  $\geq 65$  years (0.62 [0.46–0.84]).

A limitation of this assessment is that these data are self-reported. Previous studies, however, have found that self-reports of conditions such as diabetes and hypertension are reliable (2,3). In addition, the survey was conducted by telephone and does not reflect the experience of individuals in Montana homes without telephones.

The findings suggest that diabetes screening is being adopted by physicians for individuals aged  $\geq 45$  years at risk for diabetes and that the ADA recommendations are being implemented in the general community. However, these data also indicate a need to develop strategies to encour-

Table 1—Characteristics of respondents aged  $\geq 45$  years reporting screening for diabetes in Montana in 1998

	Screening for diabetes		
	Past year	1–3 years	$>3$ years or never
n	430	160	520
Age (years)			
45–54	155 (32)	80 (17)	251 (52)
55–64	95 (39)	41 (17)	108 (44)
$\geq 65$	180 (47)*	39 (10)	163 (43)
Family history of diabetes			
Yes	192 (45)*	74 (17)	162 (38)
No	235 (35)	85 (13)	352 (52)
Visits to a health care provider during the past year			
$\geq 2$	317 (47)*	84 (12)	275 (41)
$< 2$	100 (24)	74 (18)	237 (58)
Hypertension			
Yes	149 (48)*	41 (13)	122 (39)
No	281 (35)	119 (15)	400 (50)
High cholesterol			
Yes	148 (47)*	43 (14)	123 (39)
No	280 (35)	116 (15)	396 (50)

Data are n (%). \*P  $< 0.001$ .

age screening among all individuals at high risk for diabetes.

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## HbA<sub>1c</sub> Is Not Recommended as a Screening Test for Diabetes in Cystic Fibrosis

In the June 1999 issue of *Diabetes Care*, Hunkert et al. (1) recommend the use of HbA<sub>1c</sub> for early detection of cystic fibrosis-related diabetes (CFRD). Their recommendation is based on the finding that mean HbA<sub>1c</sub> is slightly higher in cystic fibrosis (CF) patients requiring insulin therapy, compared with CF patients with

impaired or normal glucose tolerance. However, no data on the validity of this approach for the diagnosis of asymptomatic diabetes in patients with cystic fibrosis are presented.

Our group has a long-standing interest in the early diagnosis of CFRD, comparing fasting blood glucose levels with oral glucose tolerance test results (2). In our series, we have now 13 CF patients with newly diagnosed diabetes based on a 2-h venous plasma glucose value >200 mg/dl (11.1 mmol/l), and simultaneous determination of HbA<sub>1c</sub> (high-performance liquid chromatography method [Pharmacia, Erlangen, Germany], normal range 3.5-5.7%). Only 4 out of 13 CF patients (31%) diagnosed as diabetic according to the American Diabetes Association and World Health Organization criteria (3) had an HbA<sub>1c</sub> value above the normal range (individual values 5.9, 6.0, 6.3, and 6.6%). In nine diabetic CF patients with normal HbA<sub>1c</sub>, values between 4.6 and 5.7% were encountered (mean ± SD, 5.1 ± 0.4%). The mean 2-h blood glucose value after ingestion of oral glucose was not significantly different between diabetic CF patients with normal HbA<sub>1c</sub> (263 ± 36 mg/dl, mean ± SD) and diabetic CF patients with elevated HbA<sub>1c</sub> (298 ± 34 mg/dl, Student's t test). These data clearly demonstrate that the determination of HbA<sub>1c</sub> is not able to substitute for the oral glucose tolerance test in the early diagnosis of CFRD. Our findings are in agreement with several reports in the literature (4-6) as well as the 1998 consensus conference on CFRD (7). In addition to its low sensitivity when used as a diagnostic tool for the detection of CFRD, the measurement of HbA<sub>1c</sub> has the disadvantage of considerable interassay variability and lack of standardization. Therefore, we strongly advise against the use of glycosylated hemoglobin as a screening test for the early diagnosis of diabetes in patients with cystic fibrosis.

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## Pro115Gln Peroxisome Proliferator-Activated Receptor-γ and Obesity

Ristow et al. (1) reported an activating mutation in the peroxisome proliferator-activated receptor-γ gene (Pro115Gln PPAR-γ), which was present in 3% (4 of 121) of obese and 0% (0 of 238) of nonobese German Caucasians. These findings may have profound implications, particularly if the presence of this variant and its association with obesity are confirmed in other populations.

We performed polymerase chain reaction-restriction fragment length polymorphism analysis for the Pro115Gln PPAR-γ variant as described (1) on DNA samples from several independent populations, including lean and obese Caucasians from the Baltimore, Maryland, region; African-

Table 1—Characteristics of subjects screened for Pro115Gln PPAR- $\gamma$ 

Population	n (alleles typed)	Age $\pm$ SD (years)	Female (%)	BMI $\pm$ SD (kg/m <sup>2</sup> )
Caucasians				
Baltimore Longitudinal Study on Aging	105 (210)	58.7 $\pm$ 15.3	53.3	24.8 $\pm$ 5.3
Johns Hopkins Weight Management Center Amish, Lancaster, PA	285 (570)	42.8 $\pm$ 12.0	65.3	38.8 $\pm$ 10.0
Amish, Lancaster, PA	173 (346)	45.7 $\pm$ 14.2	51.4	27.4 $\pm$ 8.9
African-Americans				
Atherosclerosis Risk in Communities Study	228 (456)	54.8 $\pm$ 5.9	60.0	31.4 $\pm$ 5.5
Pima Indians				
Arizona	192 (384)	47.5 $\pm$ 14.8	—	32.6 $\pm$ 6.5

All non-Amish subjects were unrelated; Amish subjects were not first-degree relatives of each other.

Americans from Jackson, Mississippi, and Forsyth County, North Carolina; Pima Indians from Arizona; and Old Order Amish from Lancaster County, Pennsylvania (Table 1). A PCR fragment corresponding to gastric insulinotropic peptide, which has two known restriction sites for HindII, was mixed with each sample as a positive control. Among a total of 983 subjects (1,966 alleles), the Pro115Gln variant was not detected in a single subject.

These findings were unexpected because there is substantial overlap of gene pools of Caucasians from Central Europe and the Baltimore and Amish Caucasians studied (2). The German Caucasians studied by Ristow et al. were said to be unrelated and recruited from the Nordrhein-Westfalen region, but they may be a genetic isolate whose gene pool does not reflect that of other Caucasian populations. Alternatively, if the individuals carrying the mutation were related, the true frequency of the Pro115Gln PPAR- $\gamma$  variant may have been overestimated. The absence or very low frequency of this variant has also been documented in Danish (3) and German (4) populations. This study is the first, to our knowledge, to examine American populations for this variant.

In summary, the study by Ristow et al. demonstrating that the Pro115Gln PPAR- $\gamma$  variant is activating and can influence body weight in people is important. However, this variant appears to be absent or very rare in the American populations studied. Additional studies are required in other regions of Europe and the U.S. to further define the relevance of this interesting genetic variant to susceptibility to obesity.

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## Insulin Secretion, Insulin Sensitivity, and Glucose Effectiveness in Nonobese Individuals With Varying Degrees of Glucose Tolerance

**A**lthough it is well known that insulin secretion, insulin sensitivity, and glucose effectiveness are impaired in type 2 diabetic patients (1–5), little is known about the role of each of these factors individually on the evolution of type 2 diabetes. In this context, a major issue is that hyperglycemia per se impairs insulin secretion and insulin sensitivity and that obesity observed in type 2 diabetic patients per se causes insulin resistance (6,7). To overcome this problem, we studied 37 untreated nonobese subjects classified as having normal glucose tolerance (NGT) ( $n = 14$ ; BMI  $21.0 \pm 0.5$  kg/m<sup>2</sup> [range 18.1–23.6], mean  $\pm$  SEM), impaired glucose tolerance (IGT) ( $n = 12$ ; BMI  $21.3 \pm 0.8$  kg/m<sup>2</sup> [17.0–26.9]), and type 2 diabetes ( $n = 11$ ; fetal bovine serum  $7.0 \pm 0.5$  mmol/l [range 5.2–9.9], BMI  $20.0 \pm 0.9$  kg/m<sup>2</sup> [13.6–24.5]), based on the criteria of the World Health Organization (8). They were normotensive and had normal renal, hepatic, and thyroid function. Insulin sensitivity and glucose effectiveness were estimated by the minimal model approach (1–4). Insulin secretion was expressed as the area under the insulin curve between 0 and 10 min after an intravenous glucose injection (2). After the data were analyzed by one-way analysis of variance, Bonferroni correction was used to evaluate the differences between any two of the three groups we studied (9). No significant difference was observed in BMI among the three groups. Compared with the subjects with NGT, the subjects with



drug was being taken only intermittently after the first 6 months, and the estimated total load presented to the liver would be equivalent to the exposure at 8 months in a compliant patient? We doubt this, since troglitazone's hepatic effects are thought to be idiosyncratic and therefore the total exposure should be irrelevant.

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## Glyburide-Induced Hemolysis in Myelodysplastic Syndrome

Glyburide, also known as glibenclamide, is a widely used sulfonylurea to treat patients with type 2 diabetes. Hemolytic anemia is an extremely rare side effect of which there have been only a few reports (1-3). We describe a patient with myelodysplastic syndrome who presented with glyburide-induced hemolysis.

A 68-year-old man with a long history of type 2 diabetes presented with left foot cellulitis of 1 week's duration. This patient was known to have slowly progressive pancytopenia for 2 years, for which no work-ups had been performed. His medications included the following: glyburide, 5 mg per day, which he had taken for more than 1 year; buformine, 150 mg per day; and boglibose, 0.6 mg per day. He was afebrile, and the physical examination was normal, except for localized cellulitis on his left foot, for which he was started on intravenous antibiotics.

The laboratory studies revealed a white blood cell count of  $3.3 \times 10^9/l$ , hemoglobin 8.4 g/dl, platelet count  $138 \times 10^9/l$ , reticulocyte count 3.7%, mean corpuscle volume 96 fl, moderate anisocytosis, fasting plasma glucose 89 mg/dl, HbA<sub>1c</sub> 5.2%, lactate dehydrogenase 192 IU/l, total bilirubin 0.9 mg/dl, and haptoglobin <11 mg/dl. Red cell glucose-6-phosphate dehydrogenase level was adequate. Cold agglutinin test, Ham's test, and sugar water test were normal. Both direct and indirect Coombs' tests were negative. Red cell resistance to osmolarity was mildly low (Parpart's method). Urinalysis demonstrated no urobilinogen. Endoscopic studies did not reveal gastrointestinal bleeding. Ultrasonography of the abdomen showed no splenomegaly. The result of bone marrow aspiration was equivocal. On the basis of presumptive glyburide-induced hemolysis, glyburide was discontinued and the patient was switched to subcutaneous insulin on the seventh day. Thereafter, his hemoglobin level increased to 11.1 g/dl, reticulocyte count decreased to 1.3%, and anisocytosis disappeared promptly. He was discharged with insulin therapy after 1 month in the hospital, which is when the cellulitis resolved.

Three months later, his hemoglobin level was ~10.0 g/dl and his haptoglobin remained low. Repeated bone marrow aspiration confirmed the diagnosis of myelodysplastic syndrome.

We conclude that this patient developed glyburide-induced hemolysis superimposed on red cell fragility secondary to an underlying bone marrow disorder. There have been several reports of hemolysis caused by sulfonylureas, most of which have been considered immune-mediated (1,2,4). Our case points to the possibility that glyburide could cause hemolysis by a non-immune-mediated mechanism. It is important to be aware of this potential side effect of glyburide in light of this medication's widespread prescription, even though such a side effect is rare.

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## Effects of Exposure at an Altitude of 3,000 m on Performance of Glucose Meters

Self-monitoring of blood glucose is mandatory for type 1 diabetic patients who participate in sports to adjust insulin dose and carbohydrate ingestion (1). Sports also include activities performed at moderately high altitudes, such as hiking or skiing. Capillary blood glucose monitors (BGMs) have been shown to underestimate blood glucose values at an altitude of 2,244 m (2) and at a simulated altitude of >2,000 m with temperature and humidity kept constant (3). The aim of the present study was to assess the accuracy of two BGMs at a moderately high altitude in which changes in temperature, humidity, and pO<sub>2</sub> can result in errors in blood glucose determination (2).

Two BGMs, the LifeScan One Touch II (OT) (Ortho Diagnostics, Milpitas, CA) and the Glucometer Elite II (GE) (Bayer Diagnostics, Brussels, Belgium), were tested during a study on the effects of acute exposure at an altitude of 3,000 m and exercise on blood pressure and albumin excretion rate in six type 1 diabetic patients.

All subjects (four men and two women) were free of disease-related complications and in good and stable glycemic control (GHb  $6.8 \pm 1.1\%$ ). All subjects gave their informed and written consent to participate in the study protocol. All subjects were investigated both at

sea level and after ascent by car and cable car to the Angelo Mosso Institute at Col d'Olen (2,950 m altitude), Gressoney La Trinité, Italy.

At sea level and at a moderately high altitude, BGM reliability at different blood glucose levels was tested, and blood glucose was assessed in fasting and resting conditions at 7:00 A.M.; at 10:00 A.M. before an in-field exercise test; and immediately, 5 min, and 15 min after the exercise stopped. Capillary glucose was simultaneously assessed with the OT and the GE. Both of these BGMs measure capillary blood glucose through the glucose oxidase-peroxidase reaction. BGMs were calibrated at the beginning of each test session. A venous blood sample was simultaneously drawn from the contralateral antecubital vein in a sodium fluoride tube, centrifuged, and stored at  $-20^{\circ}\text{C}$ . Plasma glucose was assayed with the glucose oxidase method (GO) within 3 days. This last assessment was taken as a reference method. Statistical analysis compared BGM capillary glucose values and GO plasma glucose values for each blood collection time. Measurement linearity was tested with Pearson's correlation coefficient. The mean of the differences between the BGM and GO results represents the mean bias between the methods with accuracy expressed as percent error (PE):

$$\text{PE (\%)} = \frac{\text{BMG} - \text{GO}}{\text{GO}} \times 100\%$$

The level of statistical significance was considered to be  $P < 0.05$ .

The GE and OT measurements had a good correlation with plasma glucose both at moderately high altitude and at sea level. Pearson's correlation coefficients were 0.960 and 0.981 for the GE and 0.946 and 0.985 for the OT at sea level and at moderately high altitude, respectively. Biases between plasma glucose and BGM measurements were as follows: for the GE,  $-5.9 \pm 27.3$  at sea level and  $4.9 \pm 21.6$  at moderately high altitude; for the OT,  $4.5 \pm 32.3$  at sea level and  $-13.3 \pm 22.7$  at moderately high altitude. At sea level, both the GE and the OT tended to underestimate glucose values (NS); at moderately high altitude, the GE tended to overestimate and the OT tended to underestimate glucose values (NS). Mean PEs between plasma glucose and BGM measurements were 0.5 (OT) and 4.1 (GE) at sea level and 6.4 (OT) and 8.1 (GE) at moderately high altitude. PE tended to be higher for both BGMs at moderately high

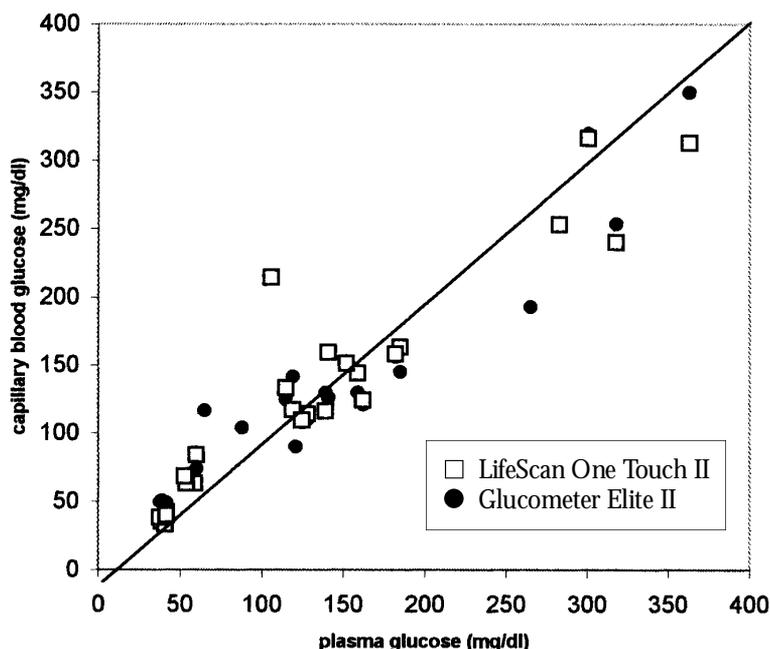


Figure 1—Relationship between plasma and capillary glucose at sea level.

altitude (NS). Figures 1 and 2 show the bias between the single measurements with both devices at sea level and at moderately high altitude, respectively. At moderately high altitude (Fig. 2), the tendency of the GE to overestimate was more evident for low ( $<100$  mg/dl) and intermediate (100–200 mg/dl) blood glucose values, whereas the OT tended to underestimate mainly high blood glucose values (NS).

In our study, BGM performance was similar and good at sea level. At a moderately high altitude, a tendency to overestimate blood glucose for the GE and to underestimate for the OT was observed. The overestimation for the GE involved mainly low ( $<100$  mg/dl) and intermediate (100–200 mg/dl) blood glucose values. This could present a problem in the presence of symptoms suggesting hypo-

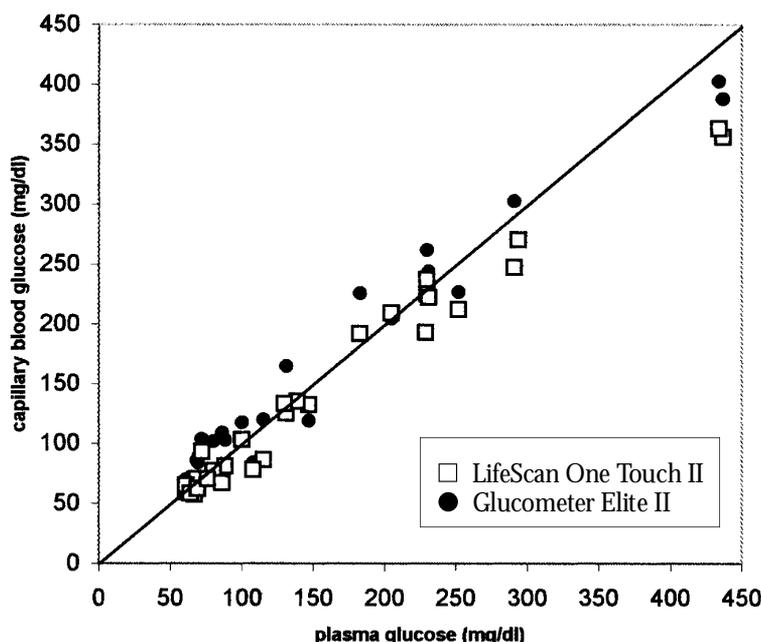


Figure 2—Relationship between plasma and capillary glucose at moderately high altitude.

glycemia and normal blood glucose values. The OT tended to underestimate mainly high blood glucose values, although its performance with low to intermediate values was good. The present study assessed the accuracy of two BGMs at a moderately high altitude in which changes in temperature, humidity, and  $pO_2$  can result in errors in blood glucose determination (2). Our results are consistent with previous studies (2,3). The decrease in  $pO_2$  could alter the second phase of the chromogen reaction and underestimate blood glucose values (4); on the other hand, an increase in atmospheric pressure could overestimate blood glucose values (5). In our study, minimal overestimation by the GE at low intermediate blood glucose values at moderately high altitude cannot be explained by the altered  $pO_2$ . An increase in hematocrit, which is known to alter blood glucose measurements with BGMs (6), may also occur after prolonged exposure to high altitude or as a consequence of dehydration. Although our study did not determine hematocrit, the exercise test was short, and the patients were instructed to drink according to their thirst during the 3,000-m exposure; therefore, dehydration was not likely to have occurred. In conclusion, BGM performance is similar and good at sea level. At a moderately high altitude similar to that experienced during winter skiing or summer hiking, a tendency to overestimate low to normal blood glucose values for the GE and to underestimate high blood glucose values for the OT was observed. The bias is not clinically meaningful for either BGM, both of which can be safely used by diabetic patients during exposure to moderately high altitudes. Some care in the evaluation of low and intermediate blood glucose values measured with the GE is nevertheless recommended.

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## COMMENTS AND RESPONSES

### Deterioration of Glycemic Control After Long-Term Treatment With Troglitazone in Nonobese Type 2 Diabetic Patients

Troglitazone is an oral antidiabetic drug used to treat type 2 diabetic patients with insulin resistance. Troglitazone improves overall insulin sensitivity in the liver and skeletal muscles, which are the largest consumers and metabolizers of glucose in the body (1-3). Recent reports showed that troglitazone is also effective in nonobese type 2 diabetic patients whose hyperglycemia could not be controlled with sulfonylurea therapy (4,5). However, we aware that in some patients in whom adequate glycemic control is obtained during the first several months of troglitazone treatment, their glycemic control deteriorates several months later. We assume that two distinct groups of type 2 diabetic patients exist

who respond differently to long-term administration of troglitazone, one group that maintains a steady response and another group that has a decreasing response after certain periods. In this study, we retrospectively examined 20 patients with type 2 diabetes who were treated with troglitazone for  $\geq 12$  months and whose  $HbA_{1c}$  levels had improved by  $\geq 1\%$  with troglitazone by month 6.

In 8 of the 20 patients (40%),  $HbA_{1c}$  levels increased by  $\geq 0.5\%$  after 6-9 months despite continuous troglitazone treatment (group P). In contrast, the rest of the patients experienced steady glycemic control with  $< 0.5\%$  of  $HbA_{1c}$  fluctuation (group G). During the first 5 months,  $HbA_{1c}$  levels decreased from means  $\pm$  SEM  $9.1 \pm 0.9$  to  $7.3 \pm 0.8\%$  in group P and from  $8.5 \pm 1.2$  to  $6.8 \pm 0.8\%$  in group G, respectively. No significant differences were evident between the two groups regarding the decrease in  $HbA_{1c}$  during the first 5 months (Fig. 1). From month 6 onward,  $HbA_{1c}$  levels in group P climbed gradually by 0.2% a month up to the baseline level at month 12, but  $HbA_{1c}$  levels were stable in group G throughout the treatment period. A significant difference in  $HbA_{1c}$  levels was evident during months 6-12 ( $P < 0.05$ ).

Among clinical characteristics, group P had a significantly lower BMI ( $22.5 \pm 3.2$  vs.  $26.7 \pm 4.1$  kg/m<sup>2</sup>,  $P < 0.05$ ) and significantly lower fasting insulin levels ( $4.9 \pm 3.6$  vs.  $9.3 \pm 4.9$   $\mu$ U/ml,  $P < 0.05$ ). Of the 10 patients with a BMI of  $< 25$  kg/m<sup>2</sup> (80%), 8 exhibited deterioration of glycemic control.

In this study, we report a group of patients who showed a renewed decline in glycemic control after long-term treatment with troglitazone. These results seemed to suggest a secondary failure of troglitazone. Our study demonstrates that this drug is indeed useful for a long-standing obese insulin-resistant diabetes but not for a nonobese type 2 diabetes.

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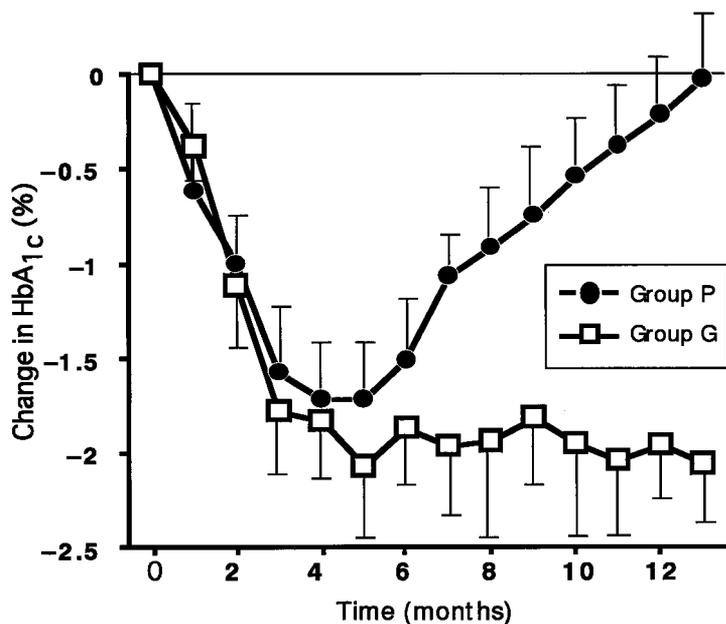


Figure 1—Change from baseline in HbA<sub>1c</sub>. Values are means ± SEM.



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