The Diagnosis of Preexisting Diabetes Associated With Acute Myocardial Infarction

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hun et al. (1) reported an increased risk of death among patients with first myocardial infarction in a population-based study of coronary disease morbidity and mortality. They comment that some misclassification bias was possible for patients who died, which may have led to an underestimation of the impact of diabetes on subject fatality. Further, they lightly dismissed the phenomenon of stress hyperglycemia because they classified all hyperglycemic patients diagnosed for the first time during hospitalization for myocardial infarction as undiagnosed diabetes. Such misclassification would lead to further distortion of the study results. We have shown that hyperglycemia after acute myocardial infarction is common, and that in most patients it is a temporary phenomenon (2) and is associated with activation of the pituitary adrenal axis (3). However, stress hyperglycemia is likely to have been underreported in the study of Chun et al. because it was population based.

The diagnosis of preexisting diabetes when associated with acute myocardial infarction, especially when transient, should be based on additional evidence of hyperglycemia, such as a diabetic glucose tolerance test response or raised HbA1c level.

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References


How Well Do Patients With Type 1 Diabetes Measure Their Blood Glucose in Daily Life?

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umerous publications are available that address the technical aspects of blood glucose monitoring. However, the practical aspects of self-monitoring the actual metabolic control are less well studied. We have investigated how well patients with type 1 and type 2 diabetes can monitor their blood glucose immediately after participation in a structured treatment and teaching program and some years thereafter (1–3). In a recent population-based public health study aiming at assessment of the degree of diabetes care and education in the geographic area of Northrhine, Germany, we have had the opportunity to evaluate how well and with which technique randomly selected adult individuals with type 1 diabetes self-monitor their blood glucose (4).

Patients were recruited from a random sample of 630 primary care practices by means of a biometrical selection procedure. All patients were examined at their homes using a mobile ambulance as described previously (5). More than 60% of the patients had participated in a structured group treatment and teaching program for intensification of insulin therapy.

Of the 684 patients, 402 (59%) were men, and 282 (41%) were women (age 36 ± 11 years, duration of diabetes 18 ± 11 years, HbA1c 8.0 ± 1.5% [mean ± SD]). A capillary blood sample was obtained by the patients, using their own method. The accuracy of blood glucose self-measurements was assessed by comparing the value obtained by the patient using his or her own method with a laboratory method. Plasma glucose was measured immediately in the van with the Reflotron (Boehringer Mannheim, Mannheim, Germany). Data from parallel measurements are available from 538 patients (79%). Reasons for the missing parallel measurements in 146 patients (21%) include the following: 54 patients did not have their glucose monitor with them (8%), 33 patients did not perform self-monitoring (5%), in 17 cases the patients’ glucose monitor was defective (3%), 9 patients declined to perform parallel measurements (1%), in 9 cases no special reasons were given (1%), and in 24 cases the laboratory system was defective (4%).

Of the patients, 88% used a glucose monitor, and 9% used test strips. 579 patients (85%) reported that they measured their blood glucose at least twice daily, 463 (68%) reported that they measured it at least three times daily.

The parallel measurements resulted in an absolute difference of 0.5 ± 1.4 (−6.0–8.2) mmol/l (mean ± SD [range]; percentage difference of 8 ± 20% [−54–181%]). The systems used by the patients measured blood glucose, whereas the laboratory system measured plasma glucose. This systematic difference can be assumed to explain the deviation in the results. Error grid analysis showed that 90% of the measurements were in zone A, with deviations that were clinically not relevant, and 9% were in zone B, with clinically acceptable deviations.

This study shows that nearly all patients had the appropriate material available for self-monitoring of blood glucose. This is in contrast to the results of the Wisconsin study that included 750 type 1 diabetic patients at the 10-year follow-up (6). More than 21% of the participants of that study did not perform self-monitoring, and 24% performed less than one measurement per day. At least two measurements per day were done by only 42% of the patients, in contrast to 85% in our study. In the present study, the vast majority of the diabetic patients used a glucose monitor for self-monitoring.

The results of this study with a single parallel measurement of blood glucose by the patients and a laboratory method showed that randomly selected diabetic patients with type 1 diabetes do measure their blood glucose with sufficient reliability.

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A Word of Caution on the Use of Lispro

Kotsanos et al. (1) point out that lispro appears to have a measurably beneficial impact on lifestyle for patients with type 1 diabetes.

No doubt, insulin analogs are already contributing to better diabetes care and an improved quality of life for patients with type 1 diabetes. Lispro obviously is offering at least these two important characteristics.

Nevertheless, we would like to share observations on the use of lispro in intensive regimens (three daily premeal injections combined with Ultralente administration before going to bed) in 12 adolescents (14–17 years) of these 12 patients, five had to return to their previous intensified insulin regimen of three injections of Regular or Actrapid plus Ultralente within 7–10 days of treatment because of the elevation of their blood glucose 2 h postprandially (180–240 mg/dl).

Because blood glucose levels were perfect (70–110 mg/dl) 1 h after lispro administration and meal ingestion, we thought that dosage increase could be helpful, but this resulted in hypoglycemia.

Therefore, we assumed that the Mediterranean diet, containing large amounts of fiber and nutrients with low glycemic indexes and slower absorption, may probably be the cause of hyperglycemia. We should wait for an analog with a longer action to use in such cases.

It should be added that by returning to their previous intensified regimens, patients succeeded in having their previous good control.

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References


Medicine and the Media

The B. case

In a March 1997 murder trial in Vienna, Austria, a 66-year-old woman, Mrs. B., was accused of having lethally poisoned a friend by use of glibenclamide tablets. Numerous media reports of the careful planning and ruthless execution of the murder and of Mrs. B.'s possible involvement in several other unsolved murder cases soon made the B. case well known throughout Austria. While investigations were ongoing and witnesses were examined, three patients were admitted to our hospital with problems related to the case.

Case 1: A 70-year-old man came into the emergency room feeling weak and complaining of polydipsia during the previous days. A history of diabetes since about 2 years and an actual fasting blood glucose of 218 mg/dl explained his condition. He had stopped taking glibenclamide for fear of diabetic hypoglycemia after the media campaign surrounding the B. case. The patient was immediately treated with insulin and discharged from the hospital taking metformin twice a day after stabilization of his diabetes.

Case 2: A 69-year-old woman was admitted with a fever of 40°C. The results of medical history, physical examination, and laboratory tests led to the diagnosis of a urinary tract infection. Her blood glucose was 458 mg/dl. Fearing death, she had stopped taking glibenclamide 3 weeks earlier after hearing the latest news on the B. case. The patient was treated with insulin but could be dismissed again on twice-daily glibenclamide after 8 days in the hospital.

Case 3: A 17-year-old girl was brought to our intensive care unit with reported recurrent seizures during the 2 previous weeks. At admission, her blood glucose was 12 mg/dl. There was no history of diabetes or antidiabetic medication, but blood glucose stayed low during the following days and continuous intravenous glucose was necessary. Though the girl denied having taken tablets, a serum sample was found definitely positive for glibenclamide by the same forensic pathologist who was consultant in the B. case. Psychiatric therapy was introduced after suicide attempts in previous years were revealed. Presently, the patient is free from seizures, and blood glucose values have remained in a normal range throughout follow-up.

Health care personnel, as well as the media, should be aware of the influence that nationwide announcements of medical reports have on the public. The B. case is an example of the misuse of medical information on a broad public basis that has led to treatment errors, under- or overuse of recommended drugs, and unnecessary health damage, hospitalization, and cost. The media should be cautious about giving detailed information on the use of drugs in suicidal or homicidal attempts. Misinterpretation and misuse by patients and the public could be unintentional consequences.

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Genetic Variation in Promoter (4G/5G) of Plasminogen Activator Inhibitor 1 Gene in Type 2 Diabetes

Absence of relationship with microangiopathy

Recently, Nagi et al. (1) have reported the presence of the plasminogen activator inhibitor (PAI)-1 4G allele to be associated with a higher risk of diabetic retinopathy in Pima Indians with type 2 diabetes. We have studied the PAI-1 gene (4G/5G) polymorphism in 177 Caucasian Mediterranean type 2 diabetic patients. The sample was composed of 96 women and 81 men with a mean age of 58.9 ± 10 years. Retinopathy was present in 46.3% of the patients, 9% of them having proliferative retinopathy. Nephropathy in the microalbuminuric stage was present in 25% of type 2 diabetic patients, and 13.2% had macroalbuminuria. PAI-1 mutation was analyzed by polymerase chain reaction amplification according to Mansfield et al. (2). The allelic and genotypic frequencies obtained in our population were similar to those described in Pima Indians (4G/4G 20.3%; 5G/5G 26.6%, and 4G/5G 53.1%). Clinical characteristics of diabetic subjects according to PAI-1 genotype showed no differences (Table 1). The prevalence of either retinopathy or nephropathy did not differ significantly in the three genotype groups and remained not significant after controlling for age, sex, BMI, duration of diabetes, and glycated hemoglobin in a logistic regression analysis.

We did not measure PAI-1 activity in our type 2 diabetic patients; however, Nagi et al. (1) failed to show differences between the three obtained genotypes and circulating PAI-1 levels, suggesting a local action in retinal circulation to explain the association between PAI-1 genotype and retinopathy. In view of our results and the previous published works (3), we believe that the conclusions obtained by Nagi et al. must be restricted to Pima Indians because of the variability of the genetic association studies explained, in part, by differences in the ethnic origin, the population analyzed, and environmental factors that can alter the phenotypic expression of the genes.

We conclude that it is somewhat early to confer on PAI-1 a role in the susceptibility to retinopathy, at least in Caucasian populations.

**Table 1—Clinical characteristics of diabetic subjects by PAI genotype**

<table>
<thead>
<tr>
<th></th>
<th>4G/4G</th>
<th>4G/5G</th>
<th>5G/5G</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>94</td>
<td>47</td>
<td>—</td>
</tr>
<tr>
<td>Age (M/F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.4 ± 9.3</td>
<td>58.5 ± 10.3</td>
<td>59.3 ± 10.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>13/23</td>
<td>47/47</td>
<td>21/26</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetes (years) (range)</td>
<td>6.0 (0–25)</td>
<td>7.0 (1–27)</td>
<td>7.0 (1–24)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.7 ± 4.6</td>
<td>28.6 ± 5.9</td>
<td>30.0 ± 6.0</td>
<td>NS</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>149.0 ± 22.4</td>
<td>144.6 ± 19.9</td>
<td>149.9 ± 21.4</td>
<td>NS</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>88.4 ± 13.3</td>
<td>83.1 ± 9.6</td>
<td>84.2 ± 10.4</td>
<td>NS</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.7 ± 2.5</td>
<td>7.7 ± 2.0</td>
<td>7.5 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Total triglyceride (mmol/1)</td>
<td>2.3 ± 1.1</td>
<td>1.9 ± 1.2</td>
<td>1.8 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mmol/1)</td>
<td>6.0 ± 1.4</td>
<td>5.9 ± 1.2</td>
<td>5.9 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>21.0</td>
<td>56.5</td>
<td>22.5</td>
<td>NS</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>17.3</td>
<td>53.9</td>
<td>28.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SD or %.

Acknowledgments—This study has been supported in part by a grant from the Comision Interministerial de Ciencia y Tecnologia, CICYT SAF 95–0214.

References


Uremia and HbA₁c Measured by High-Performance Liquid Chromatography

Carbamylation of hemoglobin is increased in uremic patients (1). The letter by Hansen et al. (2) indicates that HbA₁c values in uremic patients are overestimated by the Variant (Bio-Rad, Hercules, CA) ion-exchange high-performance liquid chromatography (HPLC) method and that immunoassays should be used instead. Overestimation of HbA₁c by ion-exchange chromatography (HPLC or minicolumns) is a well-known problem (1,3,4). However, with a recent HPLC analyzer, carbamylated hemoglobin does not interfere with the measurement of HbA₁c. The A₁c 2.2 device (Eurogenetics-Tosoh, Orleans, France) is a fully automated HPLC analyzer that uses a nonporous cation-exchange polymer that can separate the stable and labile fractions of HbA₁c. The A₁c 2.2 analyzer samples directly from the primary sample tube, while the Variant and Diamat devices require blood to be prediluted and incubated at 37°C to eliminate the labile Schiff fraction.

We compared HbA₁c values measured by the Diamat, Variant, and A₁c 2.2 devices in a healthy volunteer before and after in
vivo hemoglobin carbamylation. The carbamylated hemoglobin fraction was prepared by incubating washed red blood cells (RBC) isolated from EDTA-anticoagulated blood with 5 mmol/l cyanate solution for 1 h (3) to obtain carbamylated hemoglobin at a final concentration of ~5%. Before RBC treatment, the HbA1c levels were 5.4% (Variance), 5.4% (Diamat), and 5.2% (A1c, 2.2). After in vitro carbamylation, the HbA1c levels were 10.4, 12, and 5.4%, respectively. In the A1c 2.2 analyzer, carbamylated hemoglobin coelutes with the labile fraction, while the Diamat and Variant devices do not distinguish HbA1c from carbamylated hemoglobin, which is not eliminated during the preincubation step at 37°C.

Because the carbamylated hemoglobin level can reach 3% in uremia (1,4), we conclude that HbA1c can be measured accurately in uremic patients with the A1c 2.2 HPLC analyzer. Other methods, like immunosassay and affinity chromatography, can also be used for samples from these patients.

**Letters**

**Cost-Effectiveness of Treatment of Type 2 Diabetes**

In a recent publication on the cost-effectiveness of treating type 2 diabetes with the goal of normoglycemia (1), intensive intervention became progressively less cost-effective in those who developed diabetes later in life. This conclusion might have left the reader with the impression that treatment of geriatric patients with type 2 diabetes is not cost-effective. It should be emphasized, as it is in the publication (Ref. 1, p. 42, column 3, 2nd paragraph), that the analysis was of patients with newly diagnosed diabetes that developed at a more advanced age and not of patients who had survived diabetes until an older age. This is an important distinction. Newly diagnosed patients have low rates of complications, while patients surviving with diabetes have a high prevalence of early complications that are amenable to intervention.

To quantify the relationship of attained age and prior duration of diabetes, analyses were done on a cohort representative of 85% of the incident cases of type 2 diabetes in the U.S. Standard care (HbA1c 10%) was compared with intensive care implemented immediately at the time of diagnosis (as in the original study [1]) or delayed 3–18 years and implemented in those surviving with diabetes. As in the original study, intensive treatment was assumed to reduce HbA1c to 7.2% at an incremental cost of ~$2,000 per person-year. For the average person aged 51 years (range 19–74) at the time of clinical diagnosis, implementation of intensive care was therefore delayed to age 54–69 years (age range at implementation of intensive care was 77–92 for the oldest patients in the cohort).

Under these assumptions, the cost-effectiveness (C-to-E) ratio was similar whether intensive care was implemented immediately or delayed 12 years ($12,000–20,000 per quality-adjusted life-year [QALY] gained). The ratio increased to ~$28,000 per QALY gained when implementation was delayed 15 years and then increased to $32,000 per QALY gained after 18 years. Intensive treatment was most effective at reducing complications and increasing quality and quantity of life if implemented at the time of clinical diagnosis of diabetes but was also the most costly. The benefits and costs both decreased with delayed implementation, although there was still a modest benefit and a small incremental cost after a delay of 18 years.

These analyses show that intensive treatment of patients who survive with diabetes remains cost-effective. This is in sharp contrast to the previously published analyses. For example, the C-to-E ratio for a patient newly diagnosed with clinical diabetes at age 65 years is ~$60,000 per QALY gained (Ref. 1, Fig. 2). (In the published version of the model, it was rare for patients to live beyond age 95 years. Because there is no data on mortality for patients over age 95 years, the model has been programmed to limit survival to age 95 years. This improves the cost-effectiveness of treating diabetes diagnosed at age 65 years [range 60–70] over the value published [~$100,000 per QALY gained].) However, the ratio is ~$28,000 per QALY gained for a 65-year-old person who has lived with diabetes for 14 years.

These findings have important implications for health care policy related to the treatment of type 2 diabetes. They suggest that decisions about the intensity of diabetes treatment at a given point in the natural history of the disease should take into account the prior duration of diabetes, the status of complications, and the patients’ life expectancy (2). Attained age, per se, cannot alone be used to determine the benefits and cost-effectiveness of intervention.

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Different Effects of Acarbose and Voglibose on Serum 1,5-Anhydroglucitol Concentrations

Serum 1,5-anhydroglucitol (1,5-AG) concentrations are widely used as clinical markers of glycemic control in NIDDM patients (1). Recently, Yoshioka et al. (2) reported that serum 1,5-AG concentrations improve rapidly after administration of the α-glucosidase inhibitor voglibose and concluded that 1,5-AG is superior to HbA1c for evaluating current glycemic status. We evaluated the clinical usefulness of 1,5-AG using another α-glucosidase inhibitor, acarbose, which is currently being prescribed for NIDDM patients with postprandial hyperglycemia (3).

Thirty-one patients with NIDDM (20 men and 11 women; mean age 66 ± 9 years; BMI 22.4 ± 3.3 kg/m²) who were receiving diet therapy of 25–30 kcal/kg ideal body wt were studied. Subjects were divided into the acarbose (300 mg) or voglibose (0.6 mg) group and received the respective drugs three times a day before each meal because of postprandial hyperglycemia.

After 2 weeks of treatment, 1,5-AG concentrations in the voglibose group rapidly improved, consistent with the previous study (2), while those in the acarbose group did not improve (Table 1). After 4 weeks, in both groups, the fasting plasma glucose and HbA1c concentrations were significantly improved, but contrary to our expectations, 1,5-AG concentrations in the acarbose group were slightly decreased.

The mechanism of paradoxical decrease in 1,5-AG concentrations after treatment with acarbose is unclear. However, because acarbose, being different from voglibose, inhibits not only maltase, α-dextrinase, and sucrase but also α-amylase (4), this agent may inhibit the absorption of foods (vegetables, fruits, grains, meat, and milk) containing 1,5-AG, which may have resulted in the observed discrepancy between 1,5-AG and HbA1c. Furthermore, metabolites of acarbose (5) might inhibit reabsorption of 1,5-AG in renal tubules. Further examinations are needed to clarify these points.

References

Table 1—Effects of acarbose and voglibose on fasting blood glucose, HbA1c, and 1,5-AG levels

<table>
<thead>
<tr>
<th></th>
<th>Acarbose</th>
<th>P value</th>
<th>Voglibose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M/F)</td>
<td>16 (10/6)</td>
<td>—</td>
<td>15 (10/5)</td>
<td>—</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>8.9 ± 1.8</td>
<td>—</td>
<td>8.7 ± 2.1</td>
<td>—</td>
</tr>
<tr>
<td>2 weeks</td>
<td>8.3 ± 1.0</td>
<td>0.134</td>
<td>8.2 ± 1.4</td>
<td>0.148</td>
</tr>
<tr>
<td>4 weeks</td>
<td>7.8 ± 0.8</td>
<td>0.003</td>
<td>7.8 ± 1.4</td>
<td>0.041</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>7.5 ± 0.8</td>
<td>—</td>
<td>7.3 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td>2 weeks</td>
<td>7.5 ± 0.8</td>
<td>0.480</td>
<td>7.3 ± 0.7</td>
<td>0.110</td>
</tr>
<tr>
<td>4 weeks</td>
<td>7.2 ± 0.9</td>
<td>0.001</td>
<td>7.1 ± 0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>1,5-AG (µg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>5.4 ± 3.4</td>
<td>—</td>
<td>5.5 ± 2.6</td>
<td>—</td>
</tr>
<tr>
<td>2 weeks</td>
<td>5.0 ± 3.0</td>
<td>0.115</td>
<td>7.2 ± 2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>4 weeks</td>
<td>4.8 ± 3.3</td>
<td>0.179</td>
<td>9.6 ± 3.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are means ± SD. Wilcoxon’s test was performed. P values are versus before treatment.

Response to Sakane et al.

Serum 1,5-anhydroglucitol (1,5-AG) concentration is a new clinical marker of short-term glycemic control in diabetes (1). Sakane et al. (2) have reported the different effects of acarbose and voglibose on serum 1,5-AG concentrations. We agree with their results, which are consistent with our previous study (3), showing that the serum 1,5-AG concentrations rapidly improved in the voglibose group while those in the acarbose group did not improve even when HbA1c level was corrected 4 weeks after administration of acarbose. The results presented by Sakane et al. are consistent with the recent report by Hotta et al. (4). They showed that serum 1,5-AG concentrations did not change significantly during 1-week acarbose therapy, when serum fructosamine levels and 24-h urinary glucose excretion decreased significantly compared with that before administration of acarbose, but increased markedly 1 week after discontinu-
using acarbose, when serum fructosamine levels and 24-h urinary glucose excretion did not change compared with that during acarbose therapy. 1,5-AG is actively absorbed in the intestine (5) and actively transported in the renal reabsorption process (6). Daily 1,5-AG balance in nondiabetic subjects is constant (7), but serum 1,5-AG concentration is dominantly affected by the amount of urinary glucose (1). On the basis of the above information, and as mentioned by Sakane et al., different effects of acarbose on serum 1,5-AG may be due to reduction of absorption of 1,5-AG in the intestine via inhibiting α-amylase, although this point remains to be clarified. On the other hand, it is unlikely that metabolites of acarbose might inhibit reabsorption of 1,5-AG in renal tubules because only 1–2% of the orally administered dose of acarbose is absorbed in active form (8). Serum 1,5-AG is useful for evaluating current glycemic control in short-term response to voglibose (3). During acarbose therapy, however, it is underestimated for monitoring the glycemic status and should be used in cooperation with other markers, such as fructosamine.

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References


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Revised Etiologic Classification of Diabetes

The recently published comprehensive Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1) is most welcome and timely because it reflects progress in the understanding of the etiology and pathogenesis of diabetes. I would like to comment on section III.A of Table 1, which addresses other specific types of diabetes and the genetic defects of β-cell function, and the accompanying text on p. 1187. While correct, the statement in the second sentence that “these forms of diabetes are frequently characterized by onset of mild hyperglycemia at an early age (generally before age 25 years)” may perpetuate the misconception that maturity-onset diabetes of the young (MODY) is generally characterized by mild hyperglycemia. This pertains to the nonprogressive diabetes or impaired glucose tolerance associated with mutations of the glucokinase gene on chromosome 7 (MODY2) (2). On the other hand, diabetes associated with either mutations of hepatocyte nuclear factor (HNF)-1β on chromosome 12 (MODY3) or mutations of HNF-4α on chromosome 20 (MODY2) are forms of the disease associated with fasting hyperglycemia at diagnosis or on follow-up in up to 80% of patients, with insulin requirement in up to 30% of patients, with need for oral hypoglycemic agents in the majority of the remaining patients, and with microvascu-}

lar complications in a frequency similar to that seen in type 2 diabetes (3–5). If “mild hyperglycemia” refers to the state at “onset,” the same pertains to type 2 diabetes if the diagnosis is made at an early stage in the natural history of the disease.

In an etiologic classification, the use of chromosome number and gene give scientific precision to the loci of the mutations. In referring to the phenotypic expression of the various forms of these mutations of β-cell function, or to the group of these disorders (excluding mitochondrial DNA or other defects), the identification of the specific types by the repetitive use of chromosome and gene may be cumbersome, while the present designations of MODY1, MODY2, MODY3, etc., or MODY, respectively, may be more convenient. Thus, in Table 1, elimination of “formerly” within the parentheses would be appropriate.

Similarly, the designation of “type 1 diabetes,” as used in Table 1 and text, is more convenient than the more exact scientific and etiologic term “Diabetes due to immune-mediated β-cell destruction.”

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Response to Fajans

Drs. Fajans (1) raises relevant and important issues with regard to maturity-onset diabetes of the young. His suggestions are well taken, and in the next printing of the Expert Panel Report (January 1998), the appropriate changes in the document will be made.

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References

Response to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus

The landmark report of the American Diabetes Association’s Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1) is welcomed. It recommends a shift from the present phenotypic classification to one based on etiology and emphasizes earlier detection and possible prevention.

The diagnosis of undifferentiated gestational diabetes mellitus (GDM) is reviewed in detail and included as a single diagnosis in group IV of the proposed classification. Pregnancy provides a free stress test for latent diabetes, but it is the underlying mechanism that determines the type for the individual patient. Since there are two definite etiologic types of GDM, each of which carries different implications for the prevention and for the management of diabetes, we suggest that they be recognized in the classification as the following:

IV. Gestational Diabetes Mellitus (GDM)
A. Type 1 associated, leading to absolute insulin deficiency
B. Type 2 associated, with predominantly insulin resistance

A wide range of islet cell and anti-GAD antibodies has been reported in patients during and after pregnancy complicated by GDM, varying with population and geography (2,3). The timing of the test may be important. However, the reliability of autoantibody testing in pregnancy remains unknown because of the alterations in maternal immune status to prevent rejection of the fetus and placenta. The timing of the test may be important, and testing after the pregnancy may prove more reliable. However, long-term (2–11 years) clinical studies (4) have reported that in specific populations, up to 20% of women with previous GDM have type 1 diabetes because of markedly decreased plasma C-peptide response to glucose infusion. Further work is clearly needed in this area. Thus, general screening with tests for anti-islet antibodies may not be cost-effective for all pregnant women with GDM. However, a case can be made for testing those subjects with risk factors for this type of diabetes, particularly a family history of type 1 diabetes or autoimmune disease, and without those for type 2. Methods of arresting type 1 diabetes are effective in mice, but not yet in humans. There are now, however, ongoing trials of prevention to which patients may be referred. These issues and other recommendations for women with GDM are discussed in more detail in the report of the recent 4th International Workshop Conference on Gestational Diabetes to be published shortly in Diabetes Care.

It seems equally important to recognize GDM associated with type 2 diabetes. Presumptive diagnosis may be made on the basis of risk factors such as a family history, central obesity, particularly visceral abdominal, and the various aspects of the metabolic syndrome of insulin resistance. Measurement of the insulin/glucose (I/G) ratio may be useful in differentiating from type 1-associated GDM.

Thus, all in all, it seems reasonable to us to include the distinction of the two etiologic types of GDM, even though we do not yet have all the answers.

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Response to Sims and Catalano

Drs. Sims and Catalano (1), who have contributed much to our understanding of the pathophysiology of gestational diabetes mellitus (GDM), have proposed that the classification for GDM include two separate types, indicating whether the woman who has had GDM is more likely to go on to develop type 1 or type 2 diabetes later in life. Certainly, most women with GDM are at greatest risk for the development of type 2 diabetes. The detection of autoantibodies during and after pregnancies complicated by GDM seems to be associated with an increased risk for type 1 diabetes in the years following pregnancy, as shown in several studies, including the recent publication by Fuchtenbusch et al. (2). However, as implied by Drs. Sims and Catalano, this body of knowledge is still evolving. Hopefully, increasing information
in this important field will allow us to better understand processes leading to GDM.

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References

Screening for Diabetes in Obese Patients Using the New Diagnostic Criteria

The introduction of the new diagnostic criteria for diabetes, recently proposed by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association (ADA) (1) may considerably affect prevalence estimates. The proposed classification of diabetes and related metabolic abnormalities also includes a new category, impaired fasting glucose (IFG), the prevalence of which is unknown.

A consecutive series of 350 obese patients (BMI >30 kg/m²), aged ≥25 years and with no previous history of diabetes, who attended the Outpatient Clinic of the Section of Metabolic Diseases and Diabetology of the University of Florence (Florence, Italy) after 1 September 1996 was studied. The patients (286 women, 64 men) had an age of 45.8 ± 11.9 years (mean ± SD), a BMI of 37.3 ± 7.1 kg/m², and a waist-to-hip ratio of 0.85 ± 0.05 for women and 0.92 ± 0.06 for men. In all patients, fasting plasma glucose (FPG) was determined at 8:00 a.m. after an overnight fast. On the following day, FPG was measured again, and a standard oral glucose tolerance test (OGTT) was performed, determining plasma glucose 30, 60, 90, and 120 min after the administration of a 75-g oral glucose load (2).

Using the previous (1979) criteria of the National Diabetes Data Group (3), 69 patients (55 women, 13 men) could be classified as being affected by diabetes and 54 patients (41 women, 13 men) by impaired glucose tolerance (IGT). Applying criteria issued by the World Health Organization (WHO) in 1985 (2), the number of cases of diabetes did not change, while the number of patients classified as affected by IGT increased to 100 (79 women, 21 men).

Using the new diagnostic criteria proposed by the ADA (1), 83 cases (67 women, 16 men) of diabetes and 92 cases (72 women, 20 men) of IGT were identified. The prevalence of diabetes was 23.7 vs. 19.7% with WHO criteria (an increase of 20.3%), while the prevalence of IGT was 26.2 vs. 28.5%. The diagnosis of IFG (without IGT or diabetes at the OGTT) could be established in 17 patients (14 women, 3 men), with a prevalence of 4.8%. The overall prevalence of diabetes and related abnormalities was 48.2% using WHO criteria (diabetes plus IGT), and 54.7% using the new criteria (diabetes plus IGT and IFG), with a relative increase of 59.0%. If the results of the OGTT had not been considered, the diagnosis of diabetes could have been established in only 47 patients (13.4%) who had a FPG ≥126 mg/dl at both determinations instead of 83 patients (23.7%).

Although this clinical sample of obese patients is not representative of the general population, the present results allow some considerations about the impact of the new diagnostic criteria and screening methods proposed (1). The adoption of the new criteria determines a substantial rise in the estimates of prevalence of diabetes, which could have a relevant impact on management of resources for health care. In fact, the classification of a patient as being affected by diabetes has legal consequences on reimbursement issues in several countries, and a rise of >20% in the number of diabetic individuals can modify considerably provisions of public expenditures.

To simplify screening procedures, it has been recommended that FPG be used for diagnosis of diabetes in unaffected individuals in clinical settings (1). It should be observed that only 56.6% of cases can be identified with this procedure; the standard OGTT could therefore retain its relevance as a screening method in high-risk groups. If the OGTT is applied, the prevalence of IFG appears to be substantially lower than that of diabetes and IGT.

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References

Response to Mannucci et al.

The observations of Mannucci et al. (1) are important and appreciated. They highlight some of the difficulties of defining precise cutoff points for the diagnosis of a clinically heterogeneous disease in which the damaging effects of the offending etiologic agent (glucose) occur along a continuum.

It should be noted that the new recommendations do not presume to “considerably affect prevalence estimates.” In fact, should there be more widespread use of a single test (i.e., fasting plasma glucose [FPG] ≥126 mg/dl, with confirmation) rather than multiple tests, overall prevalence rates of newly diagnosed disease might decrease (1). However, the use of a single simpler test might indeed greatly increase the number of high-risk individuals tested and result in
earlier diagnosis when such risks and increased screenings are identified. Earlier diagnosis and intervention, including appropriately increased follow-up, would be expected to lessen, not increase, the economic burden of this disease.

Finally, the authors confirm the assertion that the use of multiple testing procedures in an at-risk population will indeed increase the detection and the prevalence estimates. The Expert Committee fully acknowledged that, in some instances, the use of the oral glucose tolerance test might confer benefit for diagnostic purposes. Thus, its retention as a tool has been recommended. However, it is not likely to be very useful as a widely used, reliable, user-friendly clinical tool for the broad cross-section of individuals with diabetes in the U.S. and the world. With respect to the concern about missing individuals with diabetes because of the inability of the recommended FPG cutoff point to identify 100% of cases at any point in time, it is crucial to remember that the diagnosis of the disease should be made in the context of the total patient, with appropriate consideration of all the risks associated with this disease, including family history, ethnicity, body weight and lifestyle, age, and others. With the use of such a comprehensive approach in determining risk for diabetes, the less reliance we must place on the value of any single number at specific points in time. Rather, the patient receives the benefit of earlier, more frequent assessment, with the numbers, however obtained, serving to confirm where in the dynamic spectrum of glucose tolerance a given patient may be.

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References

New Classification of Diabetes

The devastating health consequences of diabetes accrue from its degenerative complications. Without these, treatment of diabetes would be directed solely at avoidance of symptoms of hyperglycemia and hypoglycemia. There is convincing evidence for type 1 diabetes and compelling evidence for type 2 diabetes that restoration of blood glucose concentrations to, or close to, normal ameliorates the microvascular complications of diabetes.

The proposal by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1) to reclassify diabetes using a system based on disease etiology has considerable intrinsic appeal. Such an approach inherently implies knowledge of the pathophysiologic of the various subtypes of diabetes, the availability of clinical tests to identify these mechanisms, or, at least, the identification of clinically reliable surrogates for these mechanisms and therapeutic modalities to intervene in the pathophysiologic mechanisms. Unfortunately, such information was completely lacking from the Report.

In lieu of achieving its primary goal, the Committee could have taken a fallback position by providing guidance on the determination of degrees of insulin secretory reserve and insulin resistance, the proximal contributors to hyperglycemia of diabetes.

Because they were unwilling to establish C-peptide criteria for the former, despite abundant published data, it is not surprising that the Committee shied away from recommending even rudimentary assessments of the latter. In what amounts to a complete intellectual retreat in the classification of diabetes, the Committee comes full-face back to the National Diabetes Data Group’s (NDDG) (2) clinical and treatment-based criteria, references to which liberally pepper the Report. The Committee provides tacit acknowledgment of the continued primacy of the NDDG classification and an abnegation of the purpose of the proposed classification in the Report: “Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively” (1).

For whom then, if not clinicians and patients was the classification created: academic exercise, political document? Doubtless, this enterprise was underwritten by funds generated by American Diabetes Association volunteers (patients and physicians) who have a right to be disappointed by this use of their hard-earned volunteer dollars.

For my part, I will continue to classify patients and characterize research subjects with diabetes according to NDDG criteria and will insist on the same for manuscripts that I review.

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Response to Service

The concerns raised in Dr. Service’s letter (1) merit thoughtful response. The core element of his disappointment in the Expert Committee’s efforts appears to be that the committee did not provide recommendations for the determination of degrees of insulin secretory reserve and insulin resistance, both of which are acknowledged as proximal contributors to hyperglycemia of diabetes.

Indeed, to have attempted the establishment of such criteria may have exceeded the committee’s charge. As he implies in his letter, the reason for our concern and the basis for our diagnosis of diabetes is hyperglycemia. The Expert Committee confirmed levels of hyperglycemia at which the degenerative effects of diabetes begin and the etiology and/or pathogenesis of that hyperglycemia in the various subtypes of diabetes. To have cited that immune-mediated diabetes is, in its later stages, characterized by low or undetectable levels of plasma C-peptide without attempt-
The recent article by Morris et al. (1) once again raises the important issue of whether the use of ACE inhibitors is associated with an increased risk of severe hypoglycemia (2). The interpretation of some of the results presented in the paper can, however, be queried. The number of patients admitted to the hospital who experienced an episode of severe hypoglycemia while taking an ACE inhibitor was very small (7 of 64 patients were admitted with severe hypoglycemia). As a result, the adjusted and unadjusted 95% CIs for the odds ratios (ORs) associating the use of ACE inhibitors with severe hypoglycemia were very broad, making it difficult to determine reliably the overall effect size. Also, the data for several of the most important confounding factors were strikingly incomplete. For example, <50% of the patients’ serum creatinine values were available, which suggests that for some parameters only a proportion of subjects were included in the logistic regression analysis. In addition, the regression analysis showed that after adjustment for serum creatinine concentration, the OR linking ACE inhibitor use with risk of severe hypoglycemia was not statistically significant. We would accept that this latter OR could become significant in a larger study, but we feel that overall, the authors have provided interesting, but not convincing, evidence linking the use of ACE inhibitors with severe hypoglycemia.

It is important to emphasize, as do the authors of the article, that any potential increase in the risk of severe hypoglycemia that may be associated with the use of an ACE inhibitor is greatly outweighed by the other benefits of ACE inhibition in the treatment of heart failure and diabetic nephropathy, and by the fact that there are many other, more important risk factors for severe hypoglycemia, such as impaired hypoglycemia awareness (3). In addition, the authors are correct in asserting that their findings cannot be applied directly to the overwhelming majority of cases of severe hypoglycemia managed in the community or in hospital emergency departments. Further studies are required to provide a definitive answer to this important question.

**References**


ment for this variable substantially reduced the risk of hypoglycemic events associated with ACE inhibitors. Hospital care can act as a proxy for several important factors, such as disease severity, and there must therefore be a degree of residual confounding. We could hypothesize that those patients under hospital care had a previous history of poor glycemic control; attempts to improve control under the aegis of hospital care may at the time of the study have had the desired effect of normalizing glycated hemoglobin, but at the cost of increased hypoglycemic events. This situation would have little to do with ACE inhibitor therapy. Furthermore, data on key confounders, such as glycemic control and diabetes duration, were missing for 25–50% of patients.

The only way to address the issue of ACE inhibitors and hypoglycemic risk satisfactorily is to use data from clinical trials in people with diabetes. We have recently published findings from the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) study (3), a placebo-controlled randomized trial of the effects of the ACE inhibitor lisinopril on albumin excretion rate in 530 patients with IDDM (265 patients randomized to each group). This is the largest trial of an ACE inhibitor conducted in people with diabetes. We clearly show that there was no difference in glycemic control between the treatment and placebo groups at any time during the study. A hypoglycemic event was defined as that requiring the assistance of another person. There were 10 reports of these events in 8 people administered placebo, and 12 such reports in 12 people administered lisinopril. These findings do not require statistical testing to confirm that there are no group differences in hypoglycemic event rates.

We conclude that evidence indicating a role for ACE inhibitors in the causation of hypoglycemic events is weak and based on studies with biased methodology. We clearly show in a properly designed randomized controlled trial that ACE inhibitors do not cause hypoglycemic events in people with diabetes.

**References**


**Response to Strachan and Frier and to Chaturvedi and Fuller**

We welcome Drs. Strachan’s and Frier’s interest in our article on the association between ACE inhibitor use and hospitalization for severe hypoglycemia (1). In their letter, they suggest that our study was too small to reliably measure the size of the association between ACE inhibitors and hospitalization for severe hypoglycemia (2). They point out that the CIs for the unadjusted odds ratio (OR) of 3.2 are wide (i.e., 1.2–8.3). Although it is true that our results are based essentially on seven exposed cases, it should be remembered that our study included 504 subjects of a population of 6,649. This number represents a high sampling fraction of 8%, which means that the OR of 3.2 is probably more reliable than the CIs may suggest. A better question than “How reliable is our estimate?” would be “How typical is Tayside of other populations?” The fact that our findings are comparable to those of Herings et al. (3) suggests that our results may well be typical.

Strachan and Frier claim that “the data for several of the most important confounding factors were strikingly incomplete,” and they particularly emphasize that only 49% of serum creatinine values were available. In fact, serum creatinine was not a confounding factor. In order for it to be a confounder, the OR for exposure must change after adjustment. In our study, serum creatinine was not even associated with hypoglycemia. Thus, given that serum creatinine was not a confounding variable, it is not surprising that the OR remained at 3.2 after adjustment. A possible weakness of our study, however, was that one of the true confounding variables was only 74% complete, namely, duration of diabetes. Reassuringly, this variable was one that actually increased the OR from 3.2 to 3.6. Strachan and Frier also point out that the association between ACE inhibitors and hypoglycemia was not statistically significant after adjustment for serum creatinine. We do not consider this point to be relevant because the point estimate remained unchanged. The concept of confounding is important but is difficult to understand at times. We therefore described the phenomenon carefully in our article.

Chaturvedi and Fuller (4) also make several valid comments about our work. To answer their specific comments, our study was an electronic nested case-control study. It was not subject to the recall bias often seen in case-control studies. The biases may be similar to an electronic observational cohort study. We stated clearly in the METHODS section that conditional logistic regression analysis was used, which explains why the ORs presented in our article differ from calculated unmatched ORs.

We note with interest Chaturvedi and Fuller’s comment that the only way to address the question of ACE inhibitor–associated hypoglycemia is from clinical trials in people with diabetes. They are quite right to state that since publication of our work, reassuring data have emerged from the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) study (5). In this randomized placebo-controlled study of lisinopril in 530 patients (median age, 33 years) with type 1 diabetes, there was no treatment difference in hypoglycemic events or glycemic control throughout the study. We would argue, however, that clinical trials, which often enroll selected “low-risk” patients, are not always good at examining the unintended effects of drugs. The OR of 1.5 for the risk of severe hypoglycemia associated with ACE inhibitors in the EUCLID study is certainly an interesting one.
Observation. We suggest that important questions remain regarding community-based hypoglycemia, especially in patients with type 2 diabetes.

Our study did indeed have weaknesses, which we have detailed in the article. However, we do not accept that our interpretation of the results was questionable. We believe that our discussion was a fair, reasonable, and accurate representation of the data. We emphasize that our findings cannot be applied directly to the overwhelming majority of cases of hypoglycemia that are managed in the community or hospital emergency departments, but as such, our results could represent the “tip of the iceberg” of this drug interaction. We agree that further studies are indeed required to provide a definitive answer to this important question. We reiterate that the benefits of ACE inhibitors should not be denied patients with diabetes; rather, care should be exercised, as with any intervention that may improve insulin sensitivity.

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References