## OBSERVATIONS

# Are there Different Effects of Acarbose and Voglibose on Serum Levels of Digoxin in a Diabetic Patient With Congestive Heart Failure?

α-Glucosidase inhibitors (α-GI), such as acarbose and voglibose, are widely used in diabetic patients to suppress postprandial hyperglycemia by interfering with carbohydrate-digesting enzymes, thus delaying glucose absorption (1). Recently, acarbose and voglibose were reported to have different effects on the absorption of digoxin; acarbose has been shown to decrease the absorption of coadministered digoxin, whereas voglibose has been demonstrated to have no such effect (2–5). We describe here a diabetic patient with congestive heart failure whose serum digoxin concentration responded differently to acarbose and voglibose.

An 82-year-old man with type 2 diabetes and congestive heart failure was treated with voglibose (0.9 mg/day) and digoxin. The serum level of digoxin remained within the therapeutic range (0.8–2.0 ng/ml). However, we decided to administer acarbose (300 mg/day) in place of voglibose because of high levels of $HbA_{1c}$. The decision to switch from voglibose to acarbose was prompted by data from our earlier study, which demonstrated that acarbose (300 mg/day) has a stronger effect than voglibose (0.9 mg/day) on suppressing postprandial hyperglycemia (Y.N., T.H., unpublished data). Thereafter, the $HbA_{1c}$ level was improved by acarbose without flatulence and abdominal distention. However, subtherapeutic levels of digoxin (0.2–0.4 ng/ml) were found without changing the digoxin dosage. The patient showed no sign of worsening congestive heart failure. The patient asserted that he was taking the medications regularly according to the instructions, so compliance to the regimen did not appear to be the problem. We suspected the occurrence of a pharmacokinetic drug-drug interaction between acarbose and digoxin, a phenomenon previously described in earlier reports (2–4); therefore, we switched from acarbose back to voglibose (0.9 mg/day). Contrary to our expectations, the serum level of digoxin 1 month after voglibose readministration remained within the subtherapeutic range (0.3 ng/ml).

Miura et al. (3) reported that administering acarbose reduces the absorption of digoxin. In a report on two patients who showed subtherapeutic levels of digoxin induced by acarbose, Ben-Ami et al. (4) proposed the following mechanisms to explain the phenomenon: *1*) coadministration with acarbose increases gastrointestinal motility, leading to decreased absorption of digoxin, and 2) acarbose interferes with the hydrolysis of digoxin before its absorption, thereby altering the release of the corresponding genine and affecting the reliability of the digoxin laboratory test. However, another type of α-GI voglibose was shown not to reduce the level of digoxin (5), casting doubt on the hypotheses from Ben-Ami et al. The most interesting finding in our case is that the level of digoxin was essentially unchanged after switching back from acarbose to voglibose. We have no knowledge of the mechanism behind this phenomenon; further studies are needed to clarify it. Although the precise mechanism of acarbose-induced reduction of digoxin levels remains unknown, voglibose should be recommended for diabetic patients with digoxin coadministration. If acarbose is needed, the dosage of digoxin and the timing of its administration should be considered.

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# Effect of Chitosan on Plasma Lipoprotein Concentrations in Type 2 Diabetic Subjects With Hypercholesterolemia

Hypercholesterolemia is a well-known major cardiovascular risk factor in patients with type 2 diabetes (1). Step I of the National Cholesterol Educational Program (2), the restriction of fat and cholesterol intake, is usually recommended as the initial treatment to lower blood cholesterol. Therefore, dietary intervention is the first-line treatment, and, in addition to traditional hypolipidemic agents, there is the emerging role of dietary fiber in the hypolipidemic effect. Chitosan, the main component of crab and shrimp shells, is a polymer containing glucosamine units that have high positive charge densities in acidic solutions. The positive charge of chitosan interacts with negative surfaces, such as lipids. We studied the effects of chitosan on the plasma lipoprotein concentrations in subjects with type 2 diabetes who had hypercholesterolemia.

We recruited 40 subjects with type 2 diabetes and hypercholesterolemia, of which 33 completed the study. All subjects had received oral hypoglycemic agents for at least 1 year and were in stable condition. Glycemic control was kept constant, and the subjects maintained their routine eating habits throughout the course of the study. The inclusion criterion was having a fasting plasma glucose level of ≤10 mmol/l with hypercholesterolemia. Subjects were recruited if their LDL cholesterol level remained >3.36 mmol/l after dietary control for 4–6 weeks. In experiment A, 19 subjects underwent a mixed

meal test for 8 h. Patients received chitosan (Kio Tek, Hsin Chu, Taiwan), which was derived from shrimp shells with 97% deacetylate, in doses of 450 mg three times per day ($n$ = 10) or placebo ($n$ = 9). Blood samples were drawn hourly for determination of glucose and triglyceride concentrations. In experiment B, 33 of 40 subjects completed a randomized, double-blind, placebo-controlled, crossover clinical trial with a total duration of 16 weeks. Patients were randomly assigned to receive either 450 mg chitosan three times per day or placebo and were crossed over to the other treatment after 8 weeks. The subjects visited our center once before the trial and at weeks 4, 8, 12, and 16. Their compliance was followed by counting the remaining capsules after each visit. Possible adverse events were monitored by questioning the subjects during each visit.

In experiment A, the ambient plasma glucose and triglyceride concentrations did not differ significantly between the chitosan and placebo groups. In experiment B, the respective plasma total cholesterol (TC) and LDL cholesterol concentrations in the chitosan group were 4.4 ± 1.8% ($P$ = 0.039) and 6.5 ± 2.9% ($P$ = 0.045) lower than those in the placebo group. There was no significant difference in triglycerides, HDL cholesterol, ratio of TC to HDL cholesterol, $HbA_{1c}$, and fasting glucose values.

Our results confirm the findings of Sharma et al. (3), Yihua and Binglin (4), and Wuolijoki et al. (5), who showed that chitosan can specifically lower LDL cholesterol and does not affect the plasma triglyceride concentration. Chitosan did not affect triglyceride levels probably because triglyceride is an electrically neutral fat. The positive charge of chitosan cannot interact with the triglycerides of diet and bile acid in the intestine.

The major sources of cholesterol in the intestinal lumen are dietary lipids and bile, which contain negatively charged surfaces of phospholipids and unesterified cholesterol. A possible mechanism is that chitosan is positively charged in gastric acid; thus, the positive charge of chitosan interacts strongly with negative surfaces of cholesterol and bile. The chitosan-cholesterol complex is transferred to the intestines (in an alkaline environment) and changes into an insoluble gel form that cannot be hydrolyzed by pancreatic or intestinal enzymes (6) and is excreted in the feces, thereby interrupting the cholesterol enterohepatic circulation and accelerating its loss in stools. The effects of chitosan on fecal steroid excretion have been reported in animal and human studies (7,8). Consequently, the absorption of cholesterol is decreased, the hepatic bile acid pool is depleted, and more hepatic cholesterol is diverted to the production of bile acids. As hepatic cholesterol demands increase, hepatic cholesterol synthesis increases and LDL receptor apolipoprotein (apo)B/E activity is stimulated. Stimulation of LDL receptor apoB/E activity then increases the catabolism of LDL cholesterol and reduces plasma LDL cholesterol levels (9). The present study demonstrated that chitosan can effectively lower plasma cholesterol, possibly by binding dietary lipids, cholesterol, and cholesterol-containing bile acids.

In conclusion, our results suggest that chitosan could effectively lower plasma total cholesterol and LDL cholesterol concentrations without affecting plasma triglyceride levels and blood glucose control in subjects with type 2 diabetes who have hypercholesterolemia. No serious adverse events were reported.

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# Prevalence of Diabetes in Canadian Adults Aged 40 Years or Older

The prevalence of diabetes, mainly type 2 diabetes, in adults is believed to be higher in women than in men (1,2). However, some population-based studies have recently demonstrated that men are as likely or more likely to have the disease than women (3,4). These studies may suggest a changing pattern of sex-related distribution of type 2 diabetes in Western countries.

This analysis was based on the data from the second cycle of the National Population Health Survey conducted in 1996–1997. The survey used multistage sampling techniques to select subjects from all provinces of Canada (5). A total of 39,021 adults, aged 40 years or older, who answered the question on diabetes were included in this analysis. The subjects considered to be diabetic were those who positively answered the question of having diabetes diagnosed by a health professional. Prevalence estimates were weighted to the Canadian population. A logistic regression was used to calculate adjusted odds ratios. The Rao-Wu bootstrap tech-

**Table 1—*Prevalence and adjusted odds ratio for diabetes in relation to age and resident area among Canadian men and women***

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | *n* | Prevalence (95% CI) | Adjusted* OR (95% CI) | *n* | Prevalence (95% CI) | Adjusted* OR (95% CI) |
| Age (years) | | | | | | |
| 40–49 | 6,067 | 2.2 (1.6–2.9) | 1.0 | 6,232 | 2.4 (1.6–3.1) | 1.0 |
| 50–59 | 4,433 | 6.6 (4.8–8.5) | 2.9 (1.9–4.4) | 4,947 | 3.7 (2.8–4.6) | 1.2 (0.7–2.0) |
| 60–69 | 3,655 | 9.8 (7.9–11.8) | 4.2 (2.5–6.9) | 4,324 | 8.1 (6.4–9.7) | 2.3 (1.3–3.8) |
| 70–79 | 2,613 | 13.1 (10.2–16.0) | 5.5 (2.9–10.6) | 3,889 | 9.7 (7.6–12.0) | 2.5 (1.3–4.8) |
| 80+ | 962 | 14.4 (6.5–22.3) | 6.0 (2.4–14.7) | 1,899 | 7.2 (5.4–9.0) | 1.8 (0.9–3.4) |
| Resident area | | | | | | |
| Rural | 13,421 | 6.5 (5.6–7.5) | 1.0 | 16,674 | 5.08 (4.5–5.7) | 1.0 |
| Urban | 4,301 | 7.1 (5.2–9.0) | 1.1 (0.8–1.5) | 4,606 | 5.39 (4.4–6.4) | 1.0 (0.8–1.3) |
| Total | 17,730 | 6.6 (5.8–7.5) | — | 21,291 | 5.13 (4.6–5.7) | — |

*Adjusted by income adequacy, education level, employment status, BMI, and physical activity. OR, odds ratio.

nique was used to take the design effect into consideration (6).

The overall prevalence (95% CI) was 6.6% (5.8–7.5%) for men and 5.1% (4.6–5.7%) for women. The prevalence increased with increasing age in both sexes, and leveled off for women aged 80 years or older (Table 1). The odds ratio (95% CI) for men compared with women was 1.60 (1.33–1.91) after adjusting for covariates. Men and women living in rural and urban areas had similar prevalences of diabetes.

In the last two decades, type 2 diabetes had been profoundly studied in specific populations, especially aboriginal people, in Canada. This analysis was based on data from a representative sample of the Canadian population and demonstrated a difference in distribution of diabetes between men and women nationally. The reasons for the increased risk of diabetes in men are not known. Obesity is one of the major risk factors for type 2 diabetes (1). The prevalence of overweight (BMI $\geq$25 kg/m$^2$) is higher in men than in women in Canada (60 vs. 40%) (7), which may be a partial explanation. Men visited their dietitians less frequently (8), and less than half of men compared with almost two-thirds of women with a BMI >27 kg/m$^2$ were trying to lose weight (9). A similar prevalence in rural and urban areas may indicate there is not much difference in determinants of the disease between two areas.

The prevalence of diabetes has been steadily increasing in Canada (10). The prevalence of diabetes in aging men is increasing more rapidly than that in aging women. This suggests that senior men should be given more attention in terms of disease control and prevention.

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**Acknowledgments —** This research was supported by a National Health Research and Development Program Grant (6606–06–1998/2640023).

We thank Ms. Colette Koeune of Statistics Canada for her assistance in remote access to the NPHS data.

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# Prevalence of GAD Autoantibodies in Women With Gestational Diabetes

## A retrospective analysis

Autoantibodies to GAD (GADa) have been the source of considerable attention because of their association with the development of type 1 diabetes. As a consequence, several groups have been interested in the relationship between GADa in women with gestational diabetes and the subsequent occurrence of permanent diabetes. Interestingly, publications on this subject, emanating primarily from Europe, have been notable for their lack of unanimity concerning the rates of autoantibody positivity. These rates have ranged from 0% GADa positivity in gestational diabetic women from northern Italy (1) to a high of 10% in gestational diabetic women from a German multicenter study (2). A study in Denmark reported an incidence of 2.2% GADa positivity in sera from gestational diabetic women (3). In all likelihood, such discrepancies can be attributed in whole or in part to distinct population characteristics and differences in laboratory methodology.

In view of the experience of the European investigators vis-à-vis the aforementioned rates of GADa positivity, we thought it would be of interest to deter-

mine the incidence of GADa in North American women. To have a reasonable basis for comparison, we elected to measure GADa in women during the time of their pregnancy rather than postpartum. Therefore, we undertook a pilot retrospective study in which GADa were assayed in sera that had been collected from women during a defined period of pregnancy.

Since 1978, the Foundation for Blood Research has routinely tested sera for α-fetoprotein between 15 and 18 weeks of gestation from ~60% of the pregnant women in Maine. Aliquots of sera were retrieved from 100 women with gestational diabetes and 100 matched nondiabetic control subjects. These sera had been collected from 1990 to 1992 and stored in the frozen state at −20°C. With the exception of the diagnosis of gestational diabetes, no information regarding treatment was available.

GADa were measured using a highly sensitive radioimmunoassay kit for serum (Kronus, Boise, ID) according to the manufacturer's instructions. Briefly, sera, calibrators, and controls were incubated for ≥2 h with human recombinant $^{125}$I $GAD_{65}$ in polystyrene tubes. Protein A was added, followed 1 h later by a wash solution. The tubes were centrifuged, after which the supernatants were discarded. Residual radioactivity was counted, and a standard curve was automatically constructed by online data reduction, which generated values for the sera.

To account for systematic differences among assay runs, individual results were divided by the median control value for each run. The normalized results, expressed in multiples of the median (MoM), were transformed logarithmically, thereby generating a Gaussian distribution. Samples with antibody values above the geometric mean +3 SD (6.2 MoM) were considered positive. None (0%) of the 100 control specimens was positive (the highest value was 5.0 MoM). In contrast, six (6%) of the 100 women with gestational diabetes were autoantibody-positive (values ranged from 6.3 to 31.0 MoM).

The GADa positivity of 6% in our gestational diabetic cohort essentially falls midway between the 0% reported from northern Italy and the 10% prevalence found in the German multicenter study. As mentioned earlier, these discrepancies in the rates of GADa positivity may be a reflection of differences in both methodology and population characteristics. In regard to the latter, the determination of whether our findings are unique to the women in Maine will have to await additional retrospective or prospective studies from other areas of North America.

The potential value for assaying GADa in gestational diabetic women was demonstrated in the follow-up of patients in the German multicenter study. The data indicated that there was a significant correlation between the number of antibodies (among insulin antibody 2, islet cell antibody, and GAD antibody) and the probability of developing type 1 diabetes. Testing for GADa and other islet cell antibodies should prove useful in population screening when methods become available to arrest or prevent type 1 diabetes.

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M.L.M. received research support from Kronus.

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# School Attendance of Children With Type 1 Diabetes

Regular school attendance is important for a child's academic achievement, formation of peer relationships, and self-esteem (1). Studies have shown that children with chronic illnesses have greater school absenteeism rates than their healthy peers (1–3). Although diabetes is one of the most common chronic disorders of childhood, most children with the condition are otherwise healthy. To date, there has been very little focus specifically on school attendance in children with diabetes (4).

In this pilot study, we recruited 56 families from the diabetes clinic at the Hospital for Sick Children in Toronto, Canada. Parents who participated in the study were contacted by telephone and asked to report the number of missed school days, as detailed on their child's report card. Absenteeism data for the 1997–1998 academic year was collected for both the diabetic children and each child's closest sibling. The school absenteeism rate for the diabetic children was compared with both the nondiabetic siblings' records and published school attendance data of a control group from the Toronto School Board (5).

Diabetic children were absent 6.1 more school days than their siblings (11.4 ± 10.9 vs. 5.3 ± 5.8, respectively, $P < 0.01$). When school absences caused by diabetes clinic appointments were subtracted from total absences, diabetic children were still found to be absent 3.6 more school days than their siblings (8.9 ± 10.1 vs. 5.3 ± 5.8, $P < 0.01$). Although diabetic children also had higher absenteeism rates than the control group, this difference was not statistically significant. There was a trend for young children with diabetes (grades 1–3) to have higher rates of absenteeism than older children with diabetes ($P = 0.06$); however, a similar trend was not found among the siblings. Neither metabolic control, as measured by $HbA_{1c}$ levels, nor the duration of diabetes correlated with absenteeism. For children in the same family, there was a highly significant correlation in absenteeism between those with and those without diabetes ($r = 0.53$, $P < 0.01$). Family unit function was not assessed quantitatively in this study; however, some interesting observations were noted. It was our distinct impression that in families well adjusted to dealing with diabetes, the children missed very little school. Similarly, in the families that had significant difficulties coping with the practical aspects of diabetes care, both the diabetic children and their siblings appeared to have much higher rates of absenteeism.

This pilot study showed that diabetic children miss, on average, a little more

than 1 week per school year than their nondiabetic siblings. The close correlation in absenteeism between diabetic children and their nondiabetic siblings suggests that family attitudes may be a major factor in determining school attendance. Factors contributing to differences in school attendance may include parental overprotection, parental philosophy regarding academics, and the quality of communication between parents and teachers. To gain greater insight into this issue, a more extensive study that attempts to quantify family attitudes and family unit function is needed.

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# "Lady-like"

## Is there a latent autoimmune diabetes in the young?

Latent autoimmune diabetes in adults is often characterized by a mild manifestation and a long period of preserved β-cell function (1). In contrast, autoimmune diabetes in childhood is normally seen as a rapid progressive disease with immediate insulin deficiency at diagnosis. Longer periods of remission after initial insulin therapy for up to several years have been described. In a series of 747 children with newly diagnosed type 1 diabetes (2), only 3.4% of the autoantibody-positive children had clinical remissions 18 months after diagnosis (defined as a daily insulin dose $<0.5$ U · kg$^{-1}$ · day). This statistic suggests that insulin independence $>1$ year after initial diagnosis of diabetes is a rather rare event in children with type 1 diabetes.

We have studied two newly diagnosed type 1 diabetic children with multiple and high-titer autoantibodies and typical high-risk HLA haplotypes for autoimmune diabetes. Nevertheless, the children have been insulin independent for up to one year. In both children, stable residual β-cell function without insulin therapy was preserved. The study of these patients questions the concept of rapidly progressive type 1 diabetes in autoimmune diabetes during childhood and adds a point of caution for the interpretation of ongoing trials for diabetes prevention in so-called high-risk prediabetic patients (3).

Patient 1, a girl aged 8 years 7 months, was diagnosed with diabetes in April 1999 with a fasting blood glucose of 7 mmol/l and an $HbA_{1c}$ level of 8.0% (upper limit in our laboratory 6.2%). She had no polyuria or polydipsia and no weight loss at this time. Furthermore, no ketonuria or ketoacidosis was present. Basal C-peptide was measured at 0.76 nmol/l and could be stimulated by 1 mg glucagon intravenously to reach 1.47 nmol/l. Family history revealed type 2 diabetes in both grandparents on the maternal side, who had been diagnosed at 46 and 60 years, respectively, and treated by oral hypoglycemic drugs. The girl herself was overweight at diagnosis (BMI 28 kg/m$^2$). Therefore, type 2 diabetes or maturity-onset diabetes of the young was suspected at this time, and a calorie-reduced diet and physical exercise were prescribed. Surprisingly, high-titer autoantibodies were detected in the patient's serum (ICA $>40$ Juvenile Diabetes Foundation units [JDF-U], GADA 101 U, and IA2A 28 U) (methods and workshop data of assays in [4]). In addition, the HLA type of the patient was DRB1*0301/0401-DQB1*0201/0302. This represents the highest association for autoimmune type 1 diabetes. We found no other autoantibodies typical for polyendocrine autoimmunity. In July 1999, the girl had lost 6 kg of weight, her $HbA_{1c}$ had normalized to 5.9%, and all blood glucose levels (fasting and postprandial) were in the normal range. In August 1999, we measured a postprandial C-peptide level of 2.86 nmol/l. This level suggests complete recovery of β-cell function. In April 2000, 12 months after initial diagnosis, the girl was still insulin-free with normal values for fasting blood glucose and $HbA_{1c}$, but the 2-h blood glucose level of the oral glucose tolerance test (OGTT) was 11.9 mmol/l, again in the diabetic range. The islet cell–specific autoantibodies were consistently positive (islet cell antibody, GAD, and IA2) throughout this period.

Patient 2 was a girl aged 8 years 5 months who was diagnosed in January 1999 with a blood glucose level of 17.6 mmol/l from an OGTT and an $HbA_{1c}$ of 6.4%. In the family history, the grandmother on the paternal side had type 2 diabetes. The girl was also overweight with a BMI of 22.1 kg/m$^2$. She was treated with diet and released from the hospital after weight reduction without further therapy. Five months later, she was admitted to a diabetes rehabilitation clinic. There, she was still insulin-free and was considered not to have diabetes afterall. But after 3 months, in September 1999, she was again admitted to the hospital with a fasting blood glucose level of 11.8 mmol/l. Her blood glucose level increased to 22.8 mmol/l during an OGTT. The $HbA_{1c}$ level was then 8.6%. She had type 1 diabetes–associated HLA haplotype DR3/4, DQ*0201/0302, and high-titer autoantibodies in her serum (ICA $>40$ JDF-U, GAD 7 U, and IA2 37 U). Therefore, the diagnosis of type 1 diabetes was made according to the criteria of the American Diabetes Association and the World Health Organization (5). The C-peptide level from the OGTT was basal 0.61 nmol/l and increased to 0.76 nmol/l after glucose load. Therefore, insulin deficiency has been recognized and insulin therapy started 9 months after the first diagnosis with 0.15 U · kg$^{-1}$ · day. Three months later, her $HbA_{1c}$ was 6.5%, and insulin doses were reduced to 0.05 U · kg$^{-1}$ · day.

Both cases demonstrate that the autoimmune destruction of islets can also be slowly progressive in childhood diabetes. Even insulin independency may be observed for up to 1 year. Others have reported nonprogression of subclinical β-cell dysfunction in relatives of type 1 diabetic patients and called this phenomen

"silent diabetes" (6). We found that even overt diabetes in children may be seemingly reversible for some months. Furthermore, being severely overweight may add some kind of insulin resistance to the pathogenesis and suggests a combination of type 1 and type 2 diabetes. This problem will be seen more often in the future because of the increasing frequency of overweight children in many countries and may complicate diagnoses. These patients show how heterogeneous the natural history of autoimmune diabetes may be in so-called high-risk prediabetic patients (multiple autoantibodies of high-titer and HLA alleles associated with high risk for type 1 diabetes) currently studied in diabetes prevention trials (3). We suggest allowing for such slow progression when case ratios are calculated in prevention trials.

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# Relevance of the Treatment Facility for Disease-Related Knowledge of Diabetic Patients

The treatment of diabetes is predominantly a form of self-treatment carried out by patients. For this reason, being sufficiently informed is considered to be a prerequisite for a patient's successful management of his or her blood glucose levels (1–3). It is a known fact that structured training courses can improve treatment-related knowledge, at least in the short term (4), whereas the physician's qualification and the quality of the physician–patient relationship is more likely to be of fundamental importance for the procurement of knowledge on the part of the patient (5–7). However, the ultimate decisive factor is the amount of information patients have managed to acquire under routine conditions. We examined whether the degree of specialization at the facility where diabetic patients receive treatment has any relevance for patients' level of knowledge (8).

The present study examines a sampling of 625 diabetic patients. A total of 174 patients were recruited from the diabetes outpatient center at the Charité University Polyclinic, 264 patients were recruited from three specialist practices, and 187 patients were recruited from 28 general practitioner practices. The three specialist practices and 194 general practitioners were contacted randomly using the Medical Handbook for Berlin (9) until 3 specialists and 30 general practitioners were recruited in the Berlin metro area. Two general practitioners later refused to take part in the study. The record was compiled consecutively over a period of 3 months; the near-complete registration of patients treated at the polyclinic required a period of 9 months. Sociodemographic variables (e.g., age, sex, and school education) were equally distributed, except for a slight predominance among men in specialized facilities. All patients were asked to fill out a standardized questionnaire to test their knowledge (10) while waiting to meet with their physician. The 90-item questionnaire is based on comparable Anglo-American questionnaires (11,12) and assesses knowledge in the following areas: causes/pathophysiology, insulin/effects of insulin, insulin injection/storage, nutrition, physical activity, personal control over metabolic functions, hyperglycemia, hypoglycemia, illnesses, insulin adaptation, and consequential damages. Patients who did not have insulin therapy were given an adapted version that excluded questions on insulin treatment.

In terms of treatment-related knowledge dependent on the facility where they received treatment, the mean values, corrected for age, sex, and education, showed hardly any disparity between type 1 diabetic patients and non–insulin-requiring type 2 diabetic patients, even when the impact of structured training was eliminated in the calculation (Table 1). Conversely, insulin-dependent type 2 diabetic patients treated in specialized facilities had a significantly higher level of knowledge (~16% more correct answers) than those treated by a general practitioner. This difference can be partially explained by the fact that specialized facilities apply more intensified forms of therapy (intensified conventional insulin treatment and/or continuous subcutaneous insulin infusion) and frequent structured training programs; these two characteristics, independent of each other, were associated with a higher level of knowledge. If these effects are excluded, differences still exist between treatment facilities, but they are not significant.

To summarize, in terms of acquiring extensive knowledge of diabetes, type 1 and non–insulin-dependent type 2 diabetic patients do not benefit from a degree of specialization in the therapeutic facility. However, insulin-requiring type 2 diabetic patients treated in specialized clinics have a much higher level of knowledge due to the enhanced utilization of intensified forms of therapy and structured training.

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**Table 1—*Diabetes-specific knowledge of patients in different treatment facilities***

| | % Correct answers | | | Differences between providers [*F* (*P*)] |
|---|---|---|---|---|
| | Polyclinics | Specialist clinics | General practitioners | |
| Type 1 diabetic patients | | | | |
| *n* | 95 | 108 | 21 | |
| Controlled and adjusted for age, sex, and education | 65.9 ± 2.02 | 62.5 ± 2.09 | 65.7 ± 4.78 | NS* |
| Controlled and adjusted for age, sex, education and use of training program, and type of therapy | 64.3 ± 2.02 | 63.7 ± 2.08 | 67.9 ± 4.75 | NS† |
| Insulin-requiring type 2 diabetic patients | | | | |
| *n* | 72 | 115 | 58 | |
| Controlled and adjusted for age, sex, and education | 49.3 ± 2.95 | 40.3 ± 2.19 | 33.0 ± 3.08 | 7.219 (0.001)‡ |
| Controlled and adjusted for age, sex, education and use of training program, and type of therapy | 44.6 ± 3.25 | 40.7 ± 2.12 | 37.2 ± 3.15 | NS§ |
| Non–insulin-requiring type 2 diabetic patients | | | | |
| *n* | 7 | 41 | 108 | |
| Controlled and adjusted for age, sex, and education | 58.7 ± 10.2 | 44.9 ± 3.48 | 47.6 ± 2.13 | NS‖ |
| Controlled and adjusted for age, sex, education and use of training program, and type of therapy | 58.1 ± 10.3 | 45.1 ± 3.50 | 47.5 ± 2.14 | NS¶ |

Data are means ± SEM unless otherwise indicated. Whole-corrected models: *F* (*P*) *9.03 (0.000); †8.47 (0.000); ‡5.66 (0.000); §7.56 (0.000); ‖2.91 (0.017); ¶2.25 (0.038).

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# The Met$^{416}$ → Val Variant in the Glycogen Synthase Gene

## The prevalence and the association with diabetes in a large number of Japanese individuals

Muscle glycogen synthase (GYS1) is a key enzyme catalyzing glucose storage in skeletal muscles during insulin stimulation (1) and seems a promising candidate gene for type 2 diabetes. The *Xba*I polymorphism of the GYS1 gene was shown to be associated with type 2 diabetes (2). Mutational analyses in the coding region of the GYS1 gene detected four amino acid polymorphisms (3–6). Among them, the allele frequency of the Met$^{416}$ (ATG) → Val (GTG) variant in exon 10 was much higher compared with three other mutations. In type 2 diabetic Japanese individuals, this variant was shown to be associated with decreased insulin sensitivity evaluated by minimal model analysis (5), although the subsequent study in Finnish subjects did not reach the same result (6).

In this study, we organized a multiinstitutional study and investigated the prevalence and significance of the Met$^{416}$ → Val polymorphism in a large number of Japanese individuals. All study subjects (1,529 diabetic and 901 control subjects) were unrelated, and they gave their written consent after being informed of the nature of the study. The diagnosis of diabetes was based on the criteria of the World Health Organization. The normal control subjects were selected according to the following criteria: no past history of urinary sugar or glucose intolerance and having an $HbA_{1c}$ level <5.6%, an age of >60 years, and no family history of diabetes. With the use of previously reported polymerase chain reaction–restriction fragment-length polymorphism analysis (5), we determined the Met$^{416}$ → Val variant genotypes.

The allele frequency of the Met$^{416}$ → Val variant was 0.108 in diabetic subjects (Met/Met was 1,221, Met/Val was 285, and Val/Val was 23 of 1,529 subjects) and 0.102 in control subjects (Met/Met was 723, Met/Val was 172, and Val/Val was 6 of 901 subjects). There was no statistical difference in allele frequency of the Met416Val variant between the diabetic and control groups (the odds ratio for the association of the Val allele with type 2 diabetes was 1.1067 [95% CI 0.882–1.291], $P$ = 0.50233 vs. normal control group [$\chi^2$ test]). In diabetic subjects, there were no differences in age, sex, age at onset of diabetes, and the $HbA_{1c}$, fasting plasma glucose, and serum lipid levels between the groups with or without the Met$^{416}$ → Val substitution. Among the clinical parameters related to insulin resistance, BMI, maximum BMI, waist-to-hip ratio, and insulin resistance measured by the homeostasis model assessment (HOMA-IR) (7) also showed no significant differences.

These results suggest that the Met$^{416}$ → Val variant is not likely to be a single-nucleotide polymorphism associated with susceptibility to type 2 diabetes. Moreover, this polymorphism does not affect the insulin sensitivity assessed by HOMA-IR in the present study, although the previous study showed the association between this variant and decreased insulin sensitivity evaluated by the minimal model analysis (5).

**STUDY GROUP FOR THE IDENTIFICATION OF TYPE 2 DIABETES GENES IN JAPANESE**

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**Acknowledgments —** The Study Group for the Identification of Type 2 Diabetes Genes in Japanese is supported by Health Sciences Research Grants (Research on Human Genome and Gene Therapy) from the Ministry of Health and Welfare in Japan.

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# Venlafaxine in Treatment of Severe Painful Peripheral Diabetic Neuropathy

Venlafaxine is an antidepressant that was recently demonstrated to be an effective remedy for painful diabetic neuropathy (1). This report is on a 26-year-old woman who has had type 1 diabetes since the age of 13 years. She was a nonsmoker and had no long-term diabetic complications. In association with bulimia and high blood glucose levels, she developed burning pains and pronounced tenderness in her legs and arms, particularly in the distal part of her left leg. There was also distal edema in both legs, mostly on the left side.

The patient received the following ambulatory treatment at our department of medicine: paracetamol and dextropropoxifen for 7 months; amitriptylin, klonazepan, gabapentin, and diclofenak for 4 months; and tramadol and buprenorfin for 3 months. She then had eight different analgesics at the upper level of the recommended doses, but they had no effect on her pains. She could only find relief when she put her legs in buckets of cold water for most of the night and day; otherwise, she was bedridden. When she took her legs out of the buckets, the pain returned. After 7 months, she developed pronounced orthostatism and was entirely dependent on her family. During the period of severe pain, she developed preproliferative retinopathy and moderate signs of distal sensory, autonomic, and motor neuropathy.

Her pains increased despite taking the eight analgesics, and her health deteriorated. The only pharmaceutical left to try was mexiletinhydrochloride (2), but her pronounced orthostatism was a contraindication. However, I had recently read the report on venlafaxine (1); when her health further deteriorated, there was no alternative, and a rapid decision was necessary. During her first week on venlafaxine depot at 75 mg/day (later increased to 3 × 75 mg/day), an improvement was noticed, including an improvement in her visual analogue scale tests. Now, 7 months later, her health is continuously better. She still has distal pains, but she regards them as controllable. There have been some setbacks, such as when she walked too much and severe pain in the feet returned for some days, or when she had bulimia for a short time. The number of her analgesics could have been continuously reduced. However, we noted that apart from venlafaxine, the only pharmaceutical that was not possible to reduce was gabapentin; the patient experienced a return of pain both times it was reduced.

In conclusion, we found that, when no other analgesics helped in a diabetic patient with severe distal painful neuropathy, venlafaxine had a good results from the start of the treatment and possibly in combination with gabapentin. In future studies, these factors associated with venlafaxine should be validated.

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# Evaluating Clinical Accuracy of Systems for Self-Monitoring of Blood Glucose by Error Grid Analysis

## Comment on constructing the "upper A-line"

Error grid analysis for the evaluation of systems for the self-monitoring of blood glucose (SMBG) was developed in the late 1980s (1,2) and, since then, has been applied by many scientists (3). To construct an error grid plot for our own purposes (Fig. 1), we screened the respective studies and were surprised to find that the upper A-line was often incorrectly constructed (4,5). Whereas the correct upper A-line corresponds to a clinically acceptable +20% deviation of a SMBG from the reference, those authors showed a line that corresponds to a +25% deviation, resulting in an overoptimistic interpretation of SMBG.

The reason for this error might be the following. Most authors use an error grid plot with an equally scaled *x*- and *y*-axis and start its construction by drawing the lower A-line (−20% deviation) using the formula $y = 0.8 \cdot x$. Thus, in Fig. 1, the lower A-line extends from the (*x*,*y*) pair (3.9,3.12) to (25,20). Then, one may be tempted (because of the *y*-scale limitation) to construct the upper A-line by simply reversing the *x*/*y* coordinates (4,5), which would result in the points (3.12,3.9) and (20,25) (represented by the bold broken line in Fig. 1). However, this line represents a +25% deviation from the reference. Correctly, one needs to calculate the respective points with the formula $x = y/1.2$. Thus, in our case, the correct upper A-line extends from (3.25, 3.9) to (20.83, 25) (represented by the full bold line in Fig. 1). A correct construction has been demonstrated previously by Brunner et al. (6).

In view of this observation, we investigated whether the original article by Clarke et al. (1) would contain the same error (i.e., an upper A-line that represents a +25% deviation). To this purpose, we graphically superimposed a self-constructed analog of the Clarke et al. figure with the original one and read the highest point of the upper A-line from the original (~[330,410] in original units [milligrams per deciliter]; the correct point should be [330,396]). Both indicated that the original figure might be erroneous. However, the quality of the graph in the original articles (1,2) made the reading of the point difficult. Definitive proof of the erroneous upper A-line (coordinates of the upper point [330,412], which equal $y = 1.25 \cdot x$) was found in a more detailed figure published later by the same group (7).

From the above, readers should be aware that error grid plots published in the past may contain an erroneous upper A-line, and conclusions taken from such graphs should be interpreted with caution.

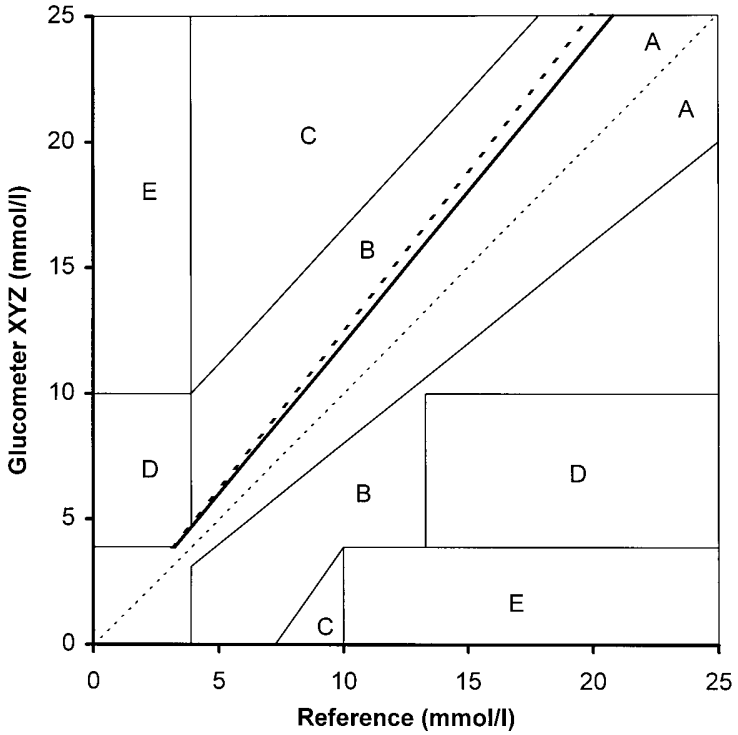


**Figure 1**—*Error grid analysis according to Clarke et al. (1). The original upper A-line is indicated by – – – and the correct upper A-line by ——. Detailed interpretations of the different zones* (A–E) *have been published previously (1–3).*

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# Moderate-Intensity Physical Activity and Fasting Insulin Levels in Women

From a cross-sectional study, Irwin et al. (1) concluded that increasing moderate-intensity physical activity (PA) reduced fasting insulin levels among 142 African-American, Native American, and Caucasian women aged 40–83 years. While interesting, this study contains a perplexing statement and a paradoxical result.

The authors' perplexing statement is "to encourage increased participation in moderate-intensity PA, it is necessary to intervene on activities in which women report participating" (1). The authors did not detail the singular contributions of reported household, occupational, and parenting activities to the measures of MET-min (the product of the minutes for each activity times the MET intensity level) of both moderate and moderate/vigorous PA. (MET intensity is defined as the associated metabolic rate for a specific activity divided by a standard resting metabolic rate.) In a previous article, the authors reported such contributions to moderate activity for only African-American and Native American women (2). Unlike the current study, those minority women reported for three, rather than for two, 4-day periods. The authors also did not show that each individual type of activity is significantly associated with fasting insulin after adjusting for other activities.

The authors' current study may lack sufficient statistical power to show such associations. After statistical adjustment, only the aggregate measure of moderate/vigorous PA was significantly associated with decreased fasting insulin for the following strata: ethnicity (except for African-Americans), low cardiorespiratory fitness, and central obesity (Table 5). For moderate PA alone, only low fitness and central obesity were significantly associated with decreased fasting insulin. Stratifying the data further would probably not support the implied activity-specific associations.

Aside from problems of statistical power, the authors' task would be difficult because efforts to find significant associations between household, occupational, and child care activities and cardiovascular risk factors have failed (3,4). Without knowing the individual contribution of such activities to health outcomes, monitoring their occurrence in national surveillance systems is unjustifiable (5).

The MET-min measure the authors use implies that women who do more PA should have better weight control. Paradoxically, this measure does not correspond well to the BMI values reported in their study. Native American women reported 15% more moderate activity (median 528 MET-min/day) than Caucasian women (median 461 MET-min/day), but had a 13% greater mean BMI (28.6 vs. 25.2 kg/m$^2$); Native American women also reported 84% more moderate activity than African-American women (median 287 MET-min/day), but were only 8% lighter than African-American women (BMI 31.1 kg/m$^2$).

Furthermore, the overlapping interquartile ranges of group MET-min/day (Table 2) indicate that group differences in activity were negligible; yet, the authors state that "comparison of the PA levels by race/ethnicity showed lower energy expenditures among African-Americans than among the other races/ethnicities" (1). More likely, the authors' admittedly unrepresentative samples (1) belie the cross-cultural scope of the study mentioned in the article's title.

Even if household, occupational, and parenting activities were shown to have potent biologic health benefits and were worth monitoring, intervening on such activities may be problematic. Minority women report as stressful the very activities that distinguish the authors' assessment method from those questionnaires emphasizing more enjoyable "traditional sports and recreational activities" (6). If instead the authors prefer to focus on the benefits of brisk walking in preventing diabetes (1), as they note others have done in prospective studies (7,8), then they should accordingly conduct specific analyses.

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## Moderate-Intensity Physical Activity and Fasting Insulin Levels in Women

Response to Caspersen et al.

We appreciate Caspersen et al.'s (1) interest in our article (2), and we value their perspective. We feel, however, that they took what was meant as commentary for potential applications and/or future directions and discussed it in a manner, relative to our analyses, that we would not have anticipated. By doing so, we feel that they overlooked the main finding of our work: namely, that evidence was provided for an association between moderate-intensity physical activity (PA) and fasting insulin levels.

Specifically, we found that an increase of 30 min of moderate-intensity PA per day was associated with a 5.2% lower fasting insulin level after adjusting for ethnicity, age, educational attainment, central obesity, BMI, fitness, fasting glucose levels, and site ($P < 0.05$). We then concluded that moderate-intensity PA is beneficial and that future research should focus on trying to elucidate ways to increase participation in moderate-intensity activities. Our suggestion was "to intervene on activities in which women report participating" (1). This was meant as a commonsensical approach of intervening on activities in which women already participate, which might be more effective than introducing unfamiliar activities in hopes of long-term adoption of these new activities (3).

Furthermore, although we did not look at the singular contributions of specific activities, the majority of moderate-intensity activities reported by the participants in our study were household, gardening, child care, walking, and occupational activities. Of the activities recorded by participants in their Physical Activity Records, <1% were sports and conditioning activities. Other studies have confirmed our finding that household activities, gardening, and walking are reported as common activities among women and are significantly associated with reduced chronic disease morbidity (4,5).

It is true that "the sample size was small and may not be representative of the participants' respective ethnic groups (1)." The small sample size did not allow us to have enough power to observe significant associations between PA and insulin by subgroups (ethnicity, fitness, and central obesity). However, the differences in fasting insulin levels observed by subgroup was of sufficient interest to reviewers to warrant a table in the letter.

Lastly, our PA MET-min measure (the product of the minutes for each activity times the MET intensity level, with MET intensity defined as the associated metabolic rate for a specific activity divided by a standard resting metabolic rate) was used to examine differences in insulin levels for the sample as a whole and by subgroups of ethnicity, fitness, and obesity. We were not examining the association between PA and BMI by certain subgroups. However, we recognize the merit of their comment that the inclusion of individuals who may not have represented the activity habits of the underlying population most likely resulted in the inconsistent findings of higher BMIs among ethnicities with higher PA and lower BMIs among ethnicities with lower PA. It is extremely important to note that, although the lack of external generalizability with regard to activity patterns likely exists, this would not inherently lead to compromises in the internal validity of the study. The biologic effect of activity on insulin levels would not be expected to differ between individuals included in and those excluded from the study population.

In conclusion, our study found a significant association between moderate-intensity PA, at levels recommended by the Centers for Disease Control and American College of Sports Medicine, and fasting insulin levels. Future studies with larger sample sizes from diverse populations need to examine the association between types of specific moderate-intensity activities (such as household activities, gardening, and walking) and chronic disease morbidity and mortality outcomes. Such analyses may also need to consider whether energy expended was in aerobic or isometric activities, because the reason for the expenditure of energy (work or play) would not itself make a difference in biologic effects. However, the type of activity could be critical in terms of identifying activities in which participants could be successfully encouraged to increase overall PA.

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## Are Tumor Necrosis Factor-α Receptor 2 Levels Associated With Age?

We read with great interest the article by Fernandez-Real et al. (1). They concluded in their study that tumor necrosis factor-α receptor 2 (TNFR2) levels positively correlate with age (1). However, a potential bias may have been introduced by the unequal distribution of type 2 diabetes prevalence and BMI ranges in the different age-groups. As shown in Tables 2 and 3 in the article, patients with diabetes were significantly older than healthy control subjects, and the older subjects had a

higher mean BMI. Numerous data support the relationship between both tumor necrosis factor-α (TNF-α) (2–4) and TNFR2 (5,6) and obesity-related insulin resistance. Therefore, one would expect to find elevated TNF-α and TNFR2 levels in type 2 diabetic patients, especially if such patients are of an older age-group. Thus, a multivariate analysis that would take into account BMI, age, insulin resistance status, and the presence of the TNFR2 A2 allele should be conducted. The results of such an analysis would be of special interest to us, because we could not detect an association between age and TNF-α levels in nondiabetic obese children (2).

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# Plasma Tumor Necrosis Factor-α Receptor 2 Levels Are Associated With Age

## Response to Taha, Paz-Priel, and Anhalt

Taha, Paz-Priel, and Anhalt wonder whether the relationship between plasma levels of the soluble fraction of tumor necrosis factor-α receptor 2 (sTNFR2) and age was merely due to an unequal distribution of the subjects among groups. In our previous article (1), we reported that 50% of the subjects were control subjects and 50% were type 2 diabetic subjects. The relationship between sTNFR2 and age was similar in both groups and remained so after excluding the diabetic patients. To clarify such a relationship, we have further evaluated 261 control subjects with BMIs <40 kg/m$^2$, normal glucose levels, no medication, and no acute illness in the previous month. In these subjects, sTNFR2 significantly correlated with age ($r = 0.27$, $P < 0.0001$) (Fig. 1), and this relationship was even stronger in women (107 subjects, $r = 0.34$, $P < 0.0001$). A similar correlation coefficient between sTNFR2 levels and age has been described in a recent article (2).

The results reported in the abstract by Taha, Paz-Priel, and Anhalt (3) are in sharp contrast with the findings of Paolisso et al. (4), who found a correlation between plasma TNF-α and age ($r = 0.64$, $P < 0.001$) that was independent of sex and body fat. These differences may be attributed to the pediatric age of the patients evaluated and to the inclusion of morbidly obese children in Taha, Paz-Priel, and Anhalt's study. In fact, adipose tissue expression of TNF-α is paradoxically decreased in adult subjects with morbid obesity (5).

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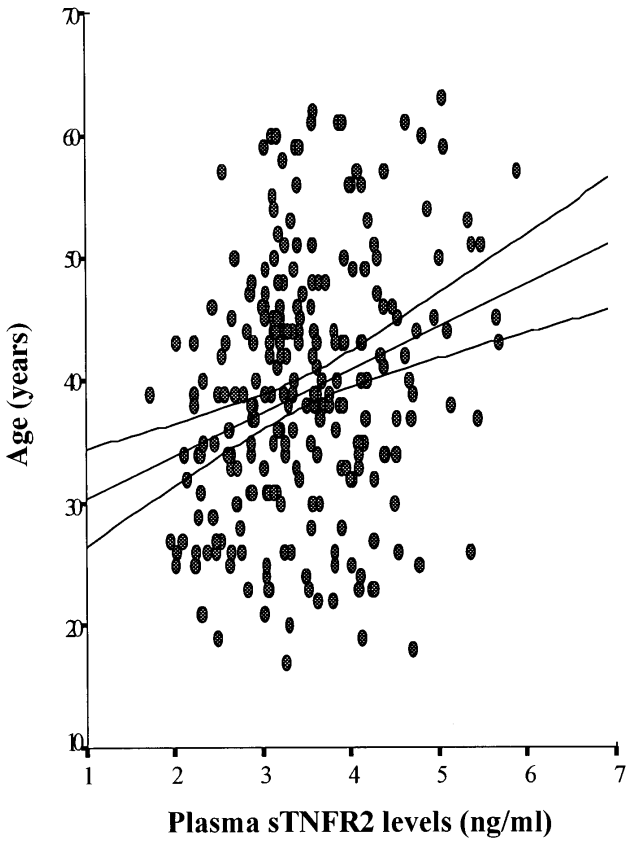


**Figure 1—***Correlation between plasma sTNFR2 levels and age.* r = *0.27;* P < *0.0001.*

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## Hypoglycemia, Seizures, and Pulmonary Edema

Ortega et al. (1) are to be congratulated for resuscitating the well-described but easily forgotten association between severe hypoglycemia and noncardiac pulmonary edema.

I suggest that the common denominator in most of these cases is a grand mal seizure, which is a well-known complication of hypoglycemia. In 1975, we (2) described two patients with recurrent postictal noncardiac pulmonary edema and found 24 additional reported cases. We noted that these episodes could be unilateral, recurrent, associated with fever and leucocytosis, and, especially when seen in isolation, typically mistaken for pneumonia and aspiration. Prompted by Ortega et al.'s (1) observations, I quickly perused several of their references. In the study by Nielsen et al. (3), one patient had initial unilateral pulmonary edema that later became bilateral, and another had what was described as "violent torsion spasms" before the development of acute respiratory distress syndrome (ARDS). Arem and Zoghebi (4) reported on two patients who developed pulmonary edema, both of whom were described as having seizures before developing ARDS. Baruh and Sherman's (5) patient also had left-sided seizures before developing pulmonary edema.

In reviewing deaths caused by therapy in psychiatric patients, Maclay (6) does not comment on seizures in patients treated for insulin coma, although this complication has been described. In his listing of causes of death, Maclay (6) includes seven patients with pulmonary edema and one with bronchopneumonia. Under the category of causes of death related to electroconvulsive therapy, he included three with pulmonary edema and four with pneumonia. Finally, Ortega et al.'s patient had a grand mal seizure before developing pulmonary edema.

I therefore suggest that, at least in the majority of patients with hypoglycemia-associated ARDS, the common pathway to pulmonary edema is having one or more seizures. This hypothesis strongly supports the possibility that a neurogenic mechanism is the major culprit in the development of hypoglycemia-associated ARDS.

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## Can All Newly Diagnosed Subjects Without Type 1 Diabetes–Associated Autoimmune Markers Be Classified as Type 1b Diabetic Patients?

Comparison among recent studies shows variability in clinical and biologic features at the onset of type 1 diabetes among different ethnic populations of origin (1–3).

We are reporting data from a cohort of newly diagnosed type 1 diabetic subjects with a follow-up period of up to 1 year at our institution. We investigated the presence of cytoplasmic islet cell antibodies (ICAs) and GAD65 antibodies (GADAs) and their relation to other clinical and biologic parameters in 68 type 1 diabetic subjects consecutively seen at diagnosis. The study included 44 men and 24 women (mean age 22.5 ± 9.3 years). Antibodies were determined as previously described (4). ICAs and GADAs were positive in 87 and 66% of subjects at diagnosis, respectively. Only four patients (6%) were negative for both antibodies. Antibody-negative subjects did not differ from those positive for one or two antibodies in terms of clinical characteristics (i.e., age, BMI, hyperglycemic symptoms' duration, insulin requirements, $HbA_{1c}$, glycemia, proportion of ketoacidosis, and C-peptide levels) at diagnosis and during the follow-up. Only $GADA^-$ patients, as compared with $GADA^+$ patients showed lower insulin requirements (units per kilogram per day) during follow-up: 3 months (0.24 ± 0.19 vs. 0.45 ± 0.23), 6 months (0.27 ± 0.2 vs. 0.46 ± 0.23), and 12 months (0.37 ± 0.22 vs. 0.55 ± 0.2) after diagnosis ($P < 0.01$ for all comparisons).

We could not find any other differences after stratification of ICA or combined ICA/GADA status. Further analysis revealed that the subgroup of patients with $HbA_{1c}$ value above the mean for the whole group (i.e., 10.7%) and with longer duration of symptoms (>2 weeks) showed higher insulin requirements and lower C-peptide levels at follow-up with no influence of antibody status. The latter data are clearly discordant with recent findings in a Japanese study (3). Thus, no major differences are found between antibody-positive and antibody-negative subjects at onset in our cohort.

Our results are clearly concordant with recent studies in which the proportion of antibody-negative subjects at onset of type 1 diabetes in Caucasian populations is very low (3.5–7%) (1,2). This is at variance with recent data in Japanese type 1 diabetic patients for whom a novel subtype of fulminant nonautoimmune diabetes is claimed to exist (3). This novel subtype of diabetes does not seem to exist in the Caucasian population. Further, patients with type 1b diabetes, as described in the American Diabetes Association classification (5), are hardly identified in European populations of Caucasian origin. There seems to be no major differences in type 1 diabetic subjects at onset when autoimmune markers are taken into account (1–3,6). Moreover, as recently demonstrated, markers of autoimmunity may not be present at onset but may appear later at follow-up or even may have been present in the prediabetic period (2). On these grounds, the absence of humoral autoimmune markers at onset of type 1 diabetes in Caucasian populations does not necessarily preclude the existence of an ongoing autoimmune process directed against β-cells. This group of patients may not be classified as type 1b diabetic subjects, as suggested by other investigators (2).

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