

## OBSERVATIONS

## GAD Antibodies in Elderly Men in Different Categories of Glucose Tolerance

Antibodies to glutamic acid decarboxylase (anti-GAD) may identify individuals at risk of developing type 1 diabetes in the future (1,2). In addition, 4–25% of patients initially presenting with type 2 diabetes express anti-GAD at the time of diagnosis and are likely to progress slowly to insulin deficiency (3).

It is not known whether anti-GAD positivity in nondiabetic people is suggestive of an extremely slowly progressing  $\beta$ -cell destruction reaching insulin deficiency at a long-delayed stage, or whether the increased frequency of anti-GAD in adults is attributable to aging itself. Thus, aging in itself may be associated with minor degrees of pancreatic cell damage that expose cytoplasmic elements such as GAD to the immune system, which in turn leads to the formation of antibodies against GAD. Since the mere existence of anti-GAD per se has no known pathological role, simultaneous defects in glucose tolerance might not appear. A recent population-based report indicates low prevalence rates of anti-GAD in 50- to 74-year-old Dutch subjects with normal and abnormal glucose tolerance, suggesting that there is no increase in anti-GAD prevalence with increasing age (4).

We studied the relationship between anti-GAD and the glucose tolerance status and the 5-year changes in glucose tolerance in a population-based cohort of 404

Finnish men aged 70–89 years (5–7). Glucose tolerance of the men was tested both in 1984 (6) and in 1989 (7), classifying the men into normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes. Anti-GAD were measured in 1993 by radioimmunoprecipitation (8). All sera that tested positive with the porcine brain GAD assay were retested and confirmed as positive by an identical assay format using radiolabelled recombinant yeast GAD.

Only 8 of 404 men (2.0%) were positive for anti-GAD in 1989, 4 with NGT (Table 1). The majority (6 of 8) of anti-GAD positive men had abnormal glucose tolerance either in 1984 or in 1989, mostly IGT, but only three in both surveys. The prevalence of abnormal glucose tolerance was not increased in anti-GAD-positive men. In 1989, only 3 men were treated with insulin, and 21 men with oral agents alone. All were anti-GAD negative. Sera collected in 1984 were available from seven anti-GAD positive men in 1989; four of these men were anti-GAD positive in 1984. Neither sustained seropositivity nor seroconversion was related to worsening of the glucose tolerance status, and HbA<sub>1c</sub>, serum insulin, and BMI did not differ between anti-GAD-positive and -negative men. None of the diabetic men in 1989 had absolute insulin deficiency. The only diabetic anti-GAD-positive man had a C-peptide level of 0.7 nmol/l. If anti-GAD positivity were to be used to classify subjects as likely to have type 1 diabetes, as proposed, for instance, by the American Diabetes Association (9) and the World Health Organization Consultation recently, it is necessary to know the prevalence of these antibodies in the population at large, including the elderly.

After 1989, the two men with the highest anti-GAD values repeatedly had ele-

vated blood glucose values, but none of the men with lower anti-GAD values was diagnosed as diabetic by 1998. Anti-GAD positivity was not associated with increased mortality. In Finnish symptomatic middle-aged type 2 diabetic patients, anti-GAD positivity at diagnosis was 9%—in control subjects it was 2.4%—and it predicted subsequent insulin-dependency (10). In a recent British study, the proportion of anti-GAD-positive patients clinically diagnosed with type 2 diabetes at the age of 55–65 years was 7% (11). In a Dutch study, the anti-GAD positivities found in different glucose tolerance categories were comparable with our findings (4). The appearance of anti-GAD in an unselected population, therefore, can be interpreted neither as a part of progressive increase in autoantibodies in normal populations with aging nor as a marker for general degenerative processes.

HILKKA YLIHÄRSILÄ, MD  
 JAAKKO TUOMILEHTO, MD  
 IAN R. MACKAY, MD  
 PAUL ZIMMET, MD  
 EVA TUOMILEHTO-WOLF, MD  
 MERRILL J. ROWLEY, PHD  
 AULIKKI NISSINEN, MD

From the National Public Health Institute (H.Y., J.T., E.T.-W.), Helsinki; the University of Kuopio (A.N.), Kuopio, Finland; the Department of Biochemistry and Molecular Biology (I.R.M., M.J.R.), Monash University, Clayton; and the International Diabetes Institute (P.Z.), Caulfield South, Victoria, Australia.

Address correspondence to Jaakko Tuomilehto, Diabetes and Genetic Epidemiology Unit, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland. E-mail: hilkka.ylihaarsila@ktl.fi.

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Table 1—Characteristics of anti-GAD-positive men in 1989

Anti-GAD (units)		Age (years)	Glucose tolerance status		Plasma glucose (mmol/l)		Insulin (pmol/l)		HbA <sub>1c</sub> (%)	BMI	Change in weight from 1984 to 1989 (kg)
1984	1989		1984	1989	Fasting	Postload	Fasting	Postload			
ND	131	76	IGT	Normal	6.1	6.7	30	705	6.0	26.4	-1.0
67	78	70	IGT	Diabetes	6.2	13.3	68	383	5.5	20.5	-1.3
83	75	71	IGT	Normal	5.6	6.5	98	390	5.1	40.6	+1.8
58	48	73	IGT	IGT	4.9	9.5	38	345	2.5	27.0	-0.1
63	46	71	Diabetes	IGT	5.3	9.3	60	345	5.6	22.0	-12.0
5	45	78	IGT	Normal	4.1	5.9	30	180	6.3	21.9	-14.7
4	39	84	Normal	ND	4.9	ND	ND	ND	4.7	ND	ND
18	19	70	Normal	Normal	4.8	5.1	15	300	4.8	21.2	-4.5

ND, not determined. The cut-off for positivity for anti-GAD units is >18.

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## Depression in Subjects With Type 2 Diabetes

Predictive factors and relation to quality of life

**W**e researched depression in subjects with type 2 diabetes aged <65 years: prevalence, predictive factors, and association with health-related quality of life (HRQOL).

The prevalence of depression has been reported to be higher in type 2 diabetic subjects than in the general population, and the lifetime depression rates have been estimated to be >30% (1-4), but all studies do not confirm this finding (5). Depression in subjects with type 2 diabetes has been associated with several factors, such as previous depressive disorder (3,4), being retired, comorbidity, type of treatment (2), and symptomatic neuropathy (5). The role of hyperglycemia has been controversial (2-4,6). Depression has also had a marked affect on HRQOL (7-8).

We studied type 2 diabetic subjects and nondiabetic control subjects living in the Mikkeli District, in eastern Finland (a total population of 53,000). The formation of the study population, loss analysis, and methods have been discussed previously (9,10). Subjects with type 2 diabetes were examined for metabolic control and diabetic complications, and they completed

the Zung Self-Rating Depression Scale (ZSDS) and Medical Outcomes Study short-form 20 (SF-20) questionnaires in the waiting room or at home. Age- and sex-matched nondiabetic control subjects completed these questionnaires at home.

ZSDS has 20 items, and it yields scores from 20 to 80. The ZSDS index is calculated by multiplying the score value by 1.25. In the age-group of 20- to 64-year-olds, the ZSDS index is >50 in depressed subjects (11). In the Finnish population, depression has been considered to be present if scores in ZSDS are ≥45 (i.e., ZSDS index ≥56), and that cut-off score was used in this study (2). Diagnosis of depression can be set only with a structured interview, but in epidemiological studies, self-administered rating scales are generally used (2,5,7,8).

The SF-20 questionnaire also has 20 items, which provide six numerical values (0-100) for functioning and well-being. The dimensions for functioning are physical, role, and social, and for well-being they include mental health, health perception, and physical pain. A higher numerical value indicates better functioning or well-being, except for the assessment of pain (12).

In univariate analyses,  $\chi^2$  and Wilcoxon tests were used. Multivariate logistic regression analysis was used to calculate odds ratios (ORs) of factors that were considered significant in univariate analyses.

Of 381 identified type 2 diabetic subjects, 260 (68%) participated in the study. Of these 260 subjects and their 260 control subjects, 222 (85%) and 166 (64%), respectively, completed the ZSDS questionnaire. The corresponding numbers of subjects completing the SF-20 were 239 (92%) and 163 (63%). Diabetic subjects had distinctly higher median scores in the ZSDS than did control subjects (38 vs. 34), and the prevalence of depression was 28.8%, twice the prevalence (14.5%) in the control population. The difference was marked in those diabetic subjects who were married (24 vs. 9%,  $P = 0.003$ ) or had

Table 1—Quality of life scores among diabetic patients with and without depression

HRQOL dimension	Physical	Role	Social	Mental health	Health perception	Pain
Depressive	50 (0-100)	0 (0-100)	60 (0-100)	52 (0-88)	50 (5-82)	50 (0-100)
Nondepressive	66.7 (0-100)*	100 (0-100)*	100 (0-100)*	72 (16-100)*	66.7 (0-100)*	25 (0-100)*
OR (95% CI)	12.0 (5.5-26.0)	4.1 (2.3-7.1)	8.6 (4.6-16.0)	30.0 (10.0-88.0)	50.0 (11.0-220.0)	3.8 (1.9-7.5)
Goodness of fit ( $\chi^2$ )	0.406	0.095	0.029	0.547	0.338	0.456

Data are median (range). In the total study population, ORs show the risk of the depressed subjects to be in the lowest tertile in each dimension, adjusted for age, sex, marital status, existence of diabetes, coronary heart disease, and other macrovascular diseases. \* $P < 0.001$ , Wilcoxon.

no cardiovascular diseases (22 vs. 10%,  $P = 0.018$ ), compared with control subjects.

Of diabetes-related factors, depression was associated with  $HbA_{1c} > 9\%$  and combination treatment (oral hypoglycemic agents and insulin). In logistic regression analysis,  $HbA_{1c} > 9\%$  (OR 2.92 [95% CI 1.41–6.05]), being divorced or widowed (OR 2.53 [1.18–5.46]) and combination treatment (OR 2.43 [1.10–5.56]) were associated with depression in diabetic subjects, adjusted for duration of diabetes and existence of cardiovascular diseases.

The median scores of SF-20 in the diabetic subjects with depression were 26–55% lower than those in subjects without depression (Table 1). In logistic regression analysis, those subjects with depression had relatively high ORs for being in the lowest tertile of HRQOL dimensions.

It is concluded that depression was more common in subjects with type 2 diabetes than in the general population and that it was a major factor that impaired the HRQOL. Depression was associated with poor glycemic control and being divorced or widowed, not with duration of diabetes or diabetic complications. Detecting and treating depression may be essential to improve the HRQOL in the type 2 diabetic population.

JOUKO A. HÄNNINEN, MD

JORMA K. TAKALA, MD, PHD

SIRKKA M. KEINÄNEN-KIUKAANNIEMI, MD, PHD

From Health Center of Mikkeli, Mikkeli (J.A.H.); Department of Community Health and General Practice (J.K.T.); University of Kuopio, Kuopio; Department of Public Health Science and General Practice and Oulu University Hospital (S.M.K.-K.), University of Oulu, Oulu, Finland.

Address correspondence to Jouko A. Hänninen, Health Center of Mikkeli, Kiiskinmäenkat. 5-7, FIN-50130 Mikkeli, Finland. E-mail: jouko.hanninen@finnet.fi.

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## Central Pontine Myelinolysis

An unusual complication of diabetes

**C**entral pontine myelinolysis complicating severe hyponatremia has been widely reported, but there are few reports of myelinolysis occurring in diabetes. Here, we describe two cases in which myelinolysis followed recurrent vomiting due to diabetic gastroparesis in the absence of documented electrolyte changes.

Both patients were women with long duration diabetes characterized by chronic

poor control and multiple complications. The first patient, a 49-year-old woman diagnosed as diabetic at the age of 36, was repeatedly hospitalized from the age of 40 because of persistent vomiting. During these admissions, she frequently complained of left-sided pain of variable character. At times, this was mainly truncal, affecting the left chest wall and left upper quadrant of the abdomen, but on other occasions it appeared to be more generalized. She was referred to our unit for further assessment in 1997, and examination confirmed the presence of peripheral sensory neuropathy, with bilateral loss of ankle jerks and diminution of all sensory modalities in the feet. More striking was an asymmetric loss affecting all sensory modalities affecting the entire left side of the body, sparing the face, that was accompanied by dysaesthesia over the left side of the trunk and left limbs that did not cross the midline. On the right side of the body, sensation was normal above the knee.

Initial investigations confirmed autonomic neuropathy and gastroparesis, and in view of the asymmetry of her neurological signs, magnetic resonance brain imaging was performed. This revealed the classical appearances of central pontine myelinolysis, with symmetrical high signal areas on T2 weighted images extending through the full length of the pons and rostrally to the level of the cerebral peduncles (Fig. 1).

The second patient, a 29-year-old woman, was first diagnosed as diabetic at age 8. From the age of 23 onwards, she suffered recurrent episodes of ketoacidosis precipitated by persistent vomiting. Investigation confirmed the presence of profound autonomic neuropathy and gastroparesis, and surgical intervention to improve gastric emptying was considered but deferred after a spontaneous improvement in her vomiting. At the age of 28 years, she commenced on peritoneal dialysis, and 6 months later presented acutely with a short history of progressive incoordination and recurrent falls. Examination revealed marked ataxia, with a broad-based unsteady gait and poor limb coordination bilaterally. The remainder of her neurological examination was normal except for longstanding distal sensory loss consistent with peripheral neuropathy. Magnetic resonance brain imaging revealed the classical changes of myelinolysis, with extensive areas of high signal in the upper medulla and pons.

Central pontine myelinolysis was first described in 1959 in a clinicopathological study of four fatal cases occurring in alcoholic or malnourished patients (1). Since this first description, there have been numerous further reports in the literature, and it is now apparent that the clinical presentation of myelinolysis is very varied (2). Only very few of the previous reports have included patients with diabetes (3,4).

The mechanisms underlying myelinolysis are now being elucidated. During hyponatremia, adaptive changes occur in the central nervous system to prevent the development of cerebral edema. These include a gradual loss of intracellular organic osmolytes, including phosphocreatine, myoinositol, and glutamate, which fall significantly in the first 24 h of hyponatremia, lowering the osmotic gradient between blood and brain (5,6). Once depleted, these osmolytes only reaccumulate slowly, requiring >5 days to reach normal levels during correction of hyponatremia and placing the brain at risk of osmotic dehydration if serum osmolarity is corrected rapidly (7). How this leads to selective loss of myelin is uncertain, but several possible mechanisms have been postulated, including physical shearing of myelin from axons due to cell shrinkage, effects of localized perivascular edema after disruption of the blood-brain barrier, and increased oxidation of myelin components (2,8).

Our cases are unusual in that severe hyponatremia was not recorded at any

time in either patient. However, it is possible that both patients experienced marked shifts in serum osmolarity while out of hospital due to electrolyte losses during recurrent vomiting and subsequent decompensation of diabetes. In addition to changes in osmolarity, other factors may contribute to the development of myelinolysis. Nutritional deficiency has been a common feature of many reported cases and may have been a factor in our patients. Potassium depletion due to vomiting or as part of ketoacidosis may also be relevant and appears to be an important cofactor in the development of myelinolysis present in the majority of reported cases (9). Given the marked shifts in osmolarity that occur in diabetes, it is perhaps surprising that myelinolysis has not been observed more often, and this raises the question of whether any adaptive changes occur in brain metabolism that may intrinsically protect diabetic patients from the effects of osmotic stress. Alternatively, it is possible that this syndrome is underrecognized in diabetes and that with increased use of magnetic resonance imaging, more unsuspected cases of myelinolysis will come to attention.

EDEL CASEY, MRCP  
ALISON EVANS, MRCP  
ANDREW KRENTZ, MD  
PETER WATKINS, MD  
DAVID HOPKINS, MRCP

From the Diabetes Department, King's College Hospital (E.C., P.W., D.H.), London; and the Diabetes Department, Southampton General Hospital (A.E., A.K.), Southampton, U.K.

Address correspondence to Dr. David Hopkins, Department of Medicine, King's College School of Medicine & Dentistry, Bessemer Rd., London, SE5 9PJ, U.K. E-mail: david.hopkins@kcl.ac.uk.

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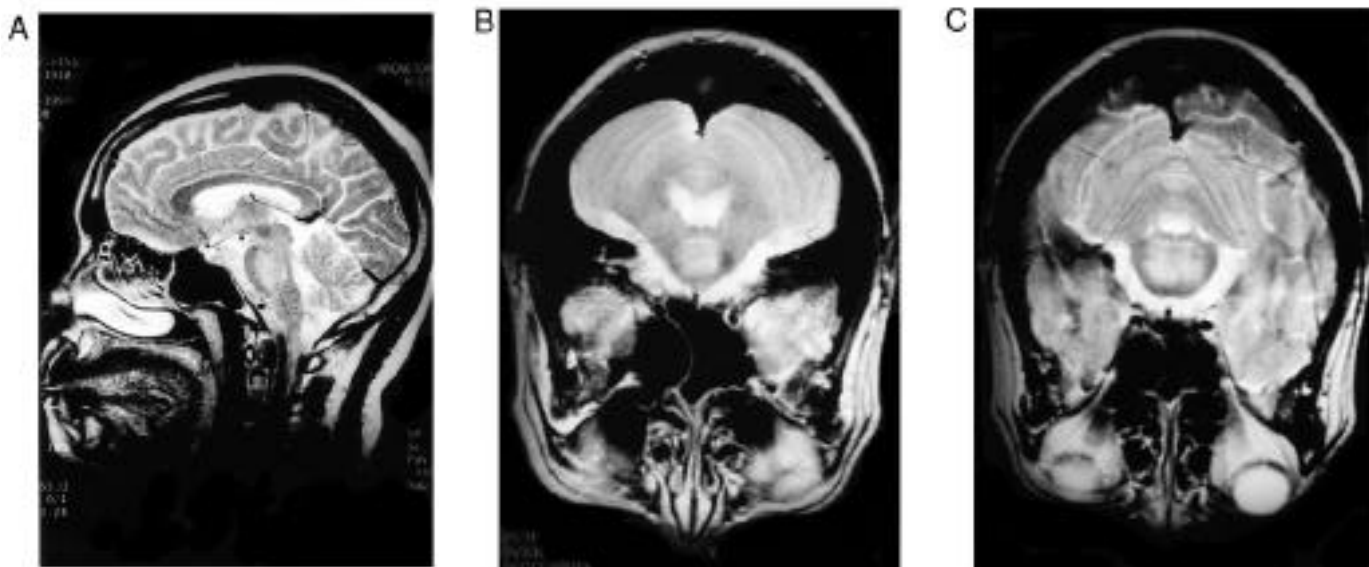


Figure 1—Patient 1: T2 weighted magnetic resonance saggital (A) and axial images (B and C) showing extensive areas of high signal intensity in the pons consistent with myelinolysis.

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## Gastroparesis Cured By Gastrectomy

One of the most frustrating manifestations of diabetic autonomic neuropathy to treat is diabetic gastroparesis. The frustration is caused by the lack of efficacy of existing therapies for all but the milder forms of the disease. Therapy is limited to small frequent liquid or semi-liquid low-fat and low-fiber meals, antiemetic medications, prokinetic agents such as metoclopramide, cisapride, domperidone, and erythromycin, H<sub>2</sub> blockers, Na-H<sup>+</sup> pump blockers, a feeding jejunostomy, and the tincture of time, since the manifestations of gastroparesis in the early stages are cyclical. The use of a feeding tube jejunostomy is seldom successful in the more advanced stages of the disease. Furthermore, mortality in patients with advanced diabetic gastroparesis is as high as 30% per year (1). Therefore, any therapy that might improve symptoms, limit hospitalization, and improve prognosis would be a welcome addition to our armamentarium for treating this disease.

We describe a patient with diabetic gastroparesis who, because of carcinoid polyps that caused gastrointestinal hemorrhage, had a total gastrectomy with a Roux en Y esophagojejunostomy, which effectively cured her gastroparesis: a 56-year-old white female with vitiligo and hypothyroidism became symptomatic because of type 1 diabetes at age 41 and was started on insulin, on which she has remained. At age 48, she developed early satiety, anorexia, nausea, and occasional vomiting of food that she recognized as having been consumed several hours earlier. In addition, her glycemic control became erratic and she had frequent episodes of hypoglycemia, hyperglycemia, ketosis, and ketoacidosis. There was also a very significant weight loss and multiple hospitalizations.

She responded poorly to metoclopramide and other prokinetic agents. Intermittently, she had diarrhea that responded within 1-2 weeks to antibi-

otics, and she intermittently had symptoms from orthostatic hypotension. Her medications included insulin, L-thyroxine, metoclopramide, and fludrocortisone. Physical examination at the time of her gastrectomy revealed a thin white female (BMI 21) without retinopathy, but who had ample evidence of diabetic peripheral and autonomic neuropathy on exam.

At age 51, she was admitted to hospital with an upper gastrointestinal bleed. Esophagoduodenoscopy revealed multiple small polyps in the fundus and cardia of the stomach. A total gastrectomy with a Roux en Y esophagojejunostomy was performed. On pathological examination, there was diffuse infiltration of the gastric mucosa with carcinoid without evidence of local or distant spread. Imaging studies of the abdomen revealed no evidence of metastases. Postoperatively, she had a wound infection, diabetic ketoacidosis, and a cardiac arrest, but recovered rather rapidly.

After her surgery, the only nausea that occurred was occasional early morning bouts without vomiting thought to be due to nocturnal hypoglycemia. She reported no early satiety, she tolerated large and solid meals, and her weight stabilized with better glycemic control. She has continued to have problems with intermittent diarrhea, which responds to metronidazole and cholestyramine.

The literature has a plethora of information on postsurgical nondiabetic gastroparesis that does not respond to medical therapy. Karlstrom and Kelly (2) reported a 66% improvement in quality of life with a completion gastrectomy, and Eckhauser et al. (3) reported a 86% satisfactory clinical outcome with the same procedure. In addition, Vogel and Woodward (4) reported a 73% satisfactory postoperative response and McCallum et al. (5) a 100% satisfactory quality of life. However, the postsurgical patient does not have denervation of the small and large bowel as the diabetic neuropathic patient does, and because of this, there has been a reluctance to use gastrectomy in the recalcitrant diabetic neuropathic patient. It has even been recommended that evidence of diabetic enteropathy in these patients should be assessed by monitoring the rate of the passage of barium through the small and large bowel, and if motility is markedly impaired, gastrectomy should not be undertaken. However, delay in transit of barium through the small and large bowel will invariably be slowed in the diabetic

patient with autonomic neuropathy with or without gastroparesis.

In contrast to the extensive literature available on postoperative gastroparesis, there is little supportive information available on gastrectomy in the patient with diabetic gastroparesis. Karlstrom and Kelly (2), using a Roux-Y gastrectomy for chronic gastric atony, reported surprising improvement in two patients with diabetic gastroparesis in spite of the fact that gastroparesis is only one manifestation of a widespread diabetic enteropathy. Several other surgical options, including gastric resection and pyloroplasty, have been tried with limited success (6), and it has been suggested that in an advanced situation, total gastrectomy might be the best option (7). Recently, Watkins and Thomas (8) reported that in four patients with gastroparesis in whom vomiting was persistent and intolerable, a two-thirds gastrectomy with a low Roux en Y loop 60 cm beyond the anastomosis had been successful.

In this case, there was resolution of gastroparesis with a gastrectomy. As expected, postoperatively enteropathy occurred intermittently in the form of diabetic diarrhea that was easily cured with courses of metronidazole and cholestyramine. Because controlling diabetic enteropathy is much less difficult than controlling gastroparesis, we would therefore suggest, based on this case and the available literature, that in recalcitrant cases of diabetic gastroparesis, Roux en Y gastrectomy could be a legitimate therapeutic intervention.

DAVID S.H. BELL, FACP, FACE  
FERNANDO OVALLE, MD

From the Division of Endocrinology and Metabolism, Department of Medicine, School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama.

Address correspondence to David S.H. Bell, MB, 2000 6th Ave. S., Birmingham, AL 35233.

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## Implanted Insulin Pump May Represent A Chance for Young Women With Unstable Type 1 Diabetes to Give Birth

Continuous intraperitoneal insulin infusion (CIPII) using programmable implanted pumps has proven to achieve safety and efficacy in patients with type 1 diabetes (1,2). However, this new therapeutic approach to the management of diabetes is still under clinical investigation because the insulin used in implanted systems (Genapol-stabilized U400 HOE 21 PH insulin; Hoechst, Frankfurt, Germany) has not yet completed marketing approval. Thus, this therapy is still submitted to the regulations of clinical trials in Europe, and pregnancy in patients using this therapy cannot be currently allowed. However, in several French centers, some patients became unexpectedly pregnant during treatment by implanted pump. Present EVADIAC (Evaluation dans le Diabète du Traitement par Implants Actifs) experience consists of eight cases of successful pregnancies in five women with type 1 diabetes being treated with CIPII by means of an implanted pump. Two of these cases have been previously reported elsewhere (3,4). Among these eight reported pregnancies, three occurred in the same patient, and two in another patient, whereas the remaining cases were isolated.

At the time of pregnancy, mean maternal age was 30.5 years (range 26-33) and mean diabetes duration was 21 years (9-27). All five patients suffered from

severe retinopathy stabilized by laser. Two women presented with nephropathy and were treated by ACE inhibitors either for microalbuminuria (in one case) or macroalbuminuria with hypertension (in the other). Mean duration of treatment by CIPII was 3.5 years (6 months to 8 years). This mode of treatment had been indicated in all patients because of poorly controlled diabetes under intensive subcutaneous treatment, including repeated hypoglycemic events with transient neurological complications while under continuous subcutaneous insulin infusion (CSII) in one case. Pregnancies occurred during clinical trials with different models of implanted pumps: one with an Infusaid M1000 pump (Shiley Infusaid, Norwood, MA), one with a Siemens Promedos ID3 pump (Siemens-Elema, Solna, Sweden), and six with a Minimed MIP 2001 pump (Minimed Technologies, Sylmar, CA).

Throughout pregnancy, HbA<sub>1c</sub> (measured by high-performance liquid chromatography with normal value  $5 \pm 0.5\%$ ) decreased from 6.9 (5.1-8.6) to 6% (5.3-7.9). No severe hypoglycemia was reported. Two events of moderate ketosis without acidosis occurred in two patients: in the first one, ketosis was associated with a tonsillitis at the beginning of pregnancy, and in the second one, ketosis occurred just before delivery. Arterial blood pressure remained in the normal range in four patients. ACE inhibitors were stopped during all pregnancies. Treatment with atenolol and dihydralazine was started in the patient with pregestational high blood pressure. Finally, mean weight gain was 12.6 kg at the end of pregnancy, with a range of 9-20 kg.

As detailed elsewhere (1,2), pumps were implanted subcutaneously in the abdominal wall, and a major potential issue during pregnancy was the increased risk of pump-pocket complication while subcutaneous tissue at the implantation site was stretched by the increment of abdominal content during pregnancy progression. Among the eight pregnancies, local tolerance of the implanted pump was excellent in seven cases, even though one patient reported some discomfort in standing position during the 3 days before delivery. One patient developed an aseptic seroma in the pump pocket and, subsequently, a local cutaneous inflammatory reaction. To obtain a good local tolerance, wearing of an abdominal belt had been recommended

as a preventive measure in two women. Two patients had reimplantation during pregnancy. In one case, the battery of the implanted pump was depleted, and the surgical procedure for replacement of the pump was performed in the first trimester while pregnancy was still unknown. In the other case, the implanted pump presented a slowdown. The patient went back to CSII, but diabetes was poorly controlled, so medical staff decided to replace the pump during the second trimester of pregnancy.

In uncomplicated pregnancies, planned delivery, by Caesarian section in two cases or vaginal route in three cases, was induced at 38 weeks of gestation. In complicated pregnancies, early Caesarian section was performed at 33.5 weeks in one case because of macrosomia, hydramnios, and poor glycemic control and respectively at 32 and 33 weeks in both pregnancies of the patient with pregestational hypertension because of decrease of fetal movements. The situation of the implanted pump in the abdominal wall did not cause any complications for delivery. During labor or Caesarian section, the implanted pump was switched to its lowest basal rate, and all patients received intravenous insulin and intravenous 10% glucose. After delivery, CIPII was started again without any complication. Four female and four male children were delivered. Mean birth weight of the children born at 38 weeks was 3,560 g (3,200-4,280); premature children weighed 3,260, 1,720, and 1,600 g. Some transient neonatal complications were observed as infection and decreased renal function in one premature child and polyglobulia and icterus in another one. One child had hypospadias, which was surgically cured a few months later. Evolution was secondarily good in all children. After pregnancy, the retinal and renal status of all mothers remained at pregestational grades.

In summary, five pregnancies progressed without any complication until delivery, and three pregnancies were complicated with various degrees of severity. Maternal complications included one local problem at the implantation site of the pump because of an aseptic seroma and two episodes of moderate ketosis. The patient who experienced local cutaneous incident during pregnancy was temporarily explanted. Thus, in 7 of 8 pregnancies, no specific problem related to the implanted pump was reported,



Olanzapine was discontinued, and 15 days later, the insulin requirement decreased and then stopped because of the low blood glucose level. Basal C-peptide was 1.69 nmol/l and rose to 2.6 nmol/l after glucagon. The patient was discharged with diet information and with his usual antipsychotic treatment without any olanzapine. He remained metabolically stable, and 8 months later he is still free of diabetic symptoms, his blood glucose tolerance is quite normal, and his HbA<sub>1c</sub> is normal.

Severe hyperglycemia and diabetic ketoacidosis have already been reported with clozapine, but no such adverse effects have been noted with olanzapine. Our patient has no family or personal history of diabetes. Obesity was the only predisposing factor to diabetes, but his initial presentation with ketoacidosis and weight loss is not a common means of initial type 2 diabetes diagnosis. Moreover Colli's recent report (1) suggests an increase in insulin resistance phenomena as the underlying mechanism of glucose metabolism perturbation with clozapine. The C-peptide level and its evolution after olanzapine removal in our observation is not in accord with Colli's observations, and studies are needed to investigate the mechanism by which olanzapine and clozapine interfere with glucose metabolism. Clinicians should now be on alert when blood glucose deteriorates in psychotic patients, and glucose level should perhaps be monitored when these drugs are used.

BLANDINE GATTA, MD  
VINCENT RIGALLEAU, MD  
HENRI GIN, MD

From the Service de Nutrition-Diabetologie et Maladies Métaboliques, Centre Hospitalier Universitaire Groupe Sud, Pessac, France.

Address correspondence to H. Gin, Service de Nutrition-Diabetologie et Maladies Métaboliques, Centre Hospitalier Universitaire Groupe Sud, Avenue de Magellan, 33604, Pessac Cedex, France.

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## Revised Concept for the Estimation of Insulin Sensitivity From a Single Sample

Insulin resistance is common in the general population and is related to glucose intolerance, dyslipidemia, and high blood pressure. Accurate and reproducible methods for measuring insulin sensitivity in vivo, such as the euglycemic clamp or the minimal model procedure, require trained personnel and are rather expensive (1). There is undoubtedly a need for simpler tests, especially in the field of large epidemiological studies. The circulating level of insulin has been widely used as a surrogate for insulin sensitivity, since a high plasma insulin concentration is supposed to reflect a state of insulin resistance, when the insulin-glucose feedback is considered. Different indexes have been proposed from baseline values of plasma insulin and glucose. Actually, there is a paradox concerning this approach, since both the product of fasting insulin and fasting glucose and their ratio are found to be correlated with insulin sensitivity. Recently, Kahn et al. (2) supported the concept that a hyperbolic relationship existed between fasting insulin and insulin sensitivity. Such a relationship could be described by a formula on the model of insulin sensitivity ( $S_I$ ) =  $a/\text{insulin}$  (I), where the coefficient  $a$  would be a constant. Therefore, the general ratio  $a/I$  could be proposed as a new index of insulin sensitivity.

First, we tried to determine a value for coefficient  $a$ . A sample of 70 subjects (22 normal subjects who had participated as control subjects in previous metabolic studies, and 48 overweight patients; age 11-73 years, BMI 17-43 kg/m<sup>2</sup>, female/male ratio 1:1) was randomly selected from a file of patients who performed an intravenous glucose tolerance test for calculation of  $S_I$  by the minimal model, as previously described (3,4). They represented the whole range of  $S_I$  values (0.01-25 10<sup>-4</sup> min<sup>-1</sup> · [μU/ml]<sup>-1</sup>). All subjects were nondiabetic, control subjects had normal glucose tolerance, and 21 overweight patients were glucose intolerant, according to World Health Organization criteria. Plasma insulin was assayed by the Bi-Insulin immunoradiometric assay kit (ERIA-Diagnostics Pasteur, Marnes la Coquette, France), which shows excellent

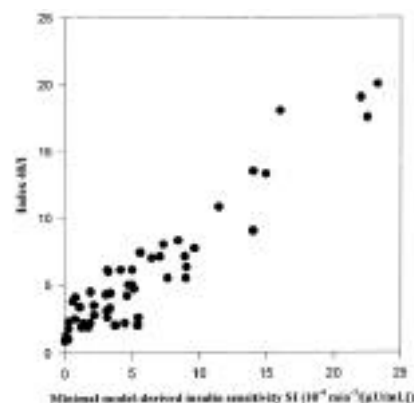


Figure 1—Correlation between  $S_I$  and the index  $40/I$ .  $n = 49$ ,  $r = 0.882$ ,  $P < 0.0001$ .

performance characteristics in terms of sensitivity (0.2 μU/ml) and reproducibility and does not cross-react with proinsulin. Plasma glucose was measured by the glucose oxidase method (Beckman, Palo Alto, CA).

The best-fit relationship was described by  $S_I$  (10<sup>-4</sup> min<sup>-1</sup> · (μU/ml)<sup>-1</sup>) × I (μU/ml) = 39.65 ( $r = 0.880$ ,  $P < 0.0001$ ), i.e.,  $S_I \times I = \sim 40$ .

Second, a separate sample of 49 subjects (14 normal subjects and 35 overweight patients; age 19-62 years, BMI 19-41.5 kg/m<sup>2</sup>) was built on the same criteria to compare the accuracy of four indexes in the assessment of insulin sensitivity: the well-known HOMA-R (homeostasis model assessment, defined as the product of fasting insulin and fasting glucose divided by 22.5) (5), fasting insulin, the ratio of fasting insulin to fasting glucose (I/G), and the above-defined ratio  $40/I$ . The statistical analysis was performed using the SigmaStat package (Jandel Scientific, Erkrath, Germany). The index  $40/I$  gave a better prediction of minimal model-derived  $S_I$  ( $r = 0.882$ ,  $P < 0.0001$ , Fig. 1) than did HOMA-R ( $r = 0.546$ ,  $P < 0.01$ ), fasting insulin ( $r = 0.589$ ,  $P < 0.01$ ), and I/G ( $r = 0.597$ ,  $P < 0.01$ ). Fasting glucose was not correlated to  $S_I$  ( $r = 0.09$ , NS).

In conclusion, the ratio  $40/I$ , with methods and units used in this study, proved to be a more precise marker of insulin sensitivity than the fasting value of insulin recommended by epidemiologists. Nevertheless, further studies are needed to validate this measure in other populations.

ERIC RAYNAUD, PHD  
ANTONIA PEREZ-MARTIN, MD  
JEAN-FREDERIC BRUN, MD, PHD  
AOMAR AISSA BENHADDAD, MD  
JACQUES MERCIER, MD, PHD

From the CERAMM (Centre d'Exploration et de Réadaptation des Anomalies Métaboliques et Musculaires) (E.R.), University Hospital Lapeyronie; and the Department of Clinical Biochemistry, Faculty of Pharmacy, Montpellier, France.

Address correspondence to Dr. Eric Raynaud, PhD, CERAMM, University Hospital Lapeyronie, F-34295 Montpellier cedex 5, France.

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## Acute Hyperinsulinemia Reduces Plasma Concentrations of Homocysteine in Healthy Men

Recent studies suggested that hyperhomocysteinemia is an important risk factor for the development of premature cardiovascular disease in type 2 diabetes (1,2). Insulin resistance and/or hyperinsulinemia is also a risk factor for cardiovascular disease (3). However, there is only one report on the relationship between plasma homocysteine levels and acute hyperinsulinemia. Fonseca et al. (4) reported that acute hyperinsulinemia using a hyperinsulinemic-euglycemic clamp decreases plasma homocysteine levels in nondiabetic, but not type 2 diabetic, subjects. Unfortunately, however, they did not describe the serum insulin levels during the hyperinsulinemic-euglycemic clamp,

and they did not observe any dose-dependent effect of insulin on plasma homocysteine levels. Therefore, we investigated whether plasma homocysteine levels are decreased by insulin in a dose-dependent manner.

We measured serum insulin and plasma homocysteine levels during fasting and during a hyperinsulinemic-euglycemic clamp (at 90 and 180 min) in nine healthy men (age  $26.7 \pm 3.1$  [mean  $\pm$  SD] years, BMI  $22.4 \pm 2.2$  kg/m<sup>2</sup>) without hypertension, glucose intolerance, or hyperlipidemia. The glucose clamp study was performed as follows: each subject was connected to the artificial pancreas (Nikkiso STG-22; Nikkiso, Tokyo) and received a constant infusion of insulin (Novolin R; Novo Nordisk, Copenhagen, Denmark) for two successive 90-min periods at rates of 0.5 and 3.0 mU  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>, respectively, using a modified version of the method of Rizza et al. (5). Serum insulin levels were measured by immunoradiometric assay, and plasma homocysteine by high-performance liquid chromatography.

During the glucose clamp study, serum insulin levels increased from  $38.4 \pm 24.0$  pmol/l at baseline to  $234.6 \pm 75.6$  and  $1,464.0 \pm 214.2$  pmol/l at 90 and 180 min, respectively. Plasma homocysteine levels decreased from  $11.9 \pm 1.5$  nmol/ml to  $10.3 \pm 1.4$  ( $P < 0.05$ ) and  $9.5 \pm 1.4$  nmol/ml ( $P < 0.01$ ), respectively. These results confirm the reduction of plasma homocysteine levels by acute hyperinsulinemia in healthy subjects and concord well with the results of Fonseca et al. (4). However, our results on the dose-dependency of the suppressive effect of insulin are in conflict with the data of Fonseca et al. (4), which showed no dose-dependent effect of insulin on plasma homocysteine levels. The reason for this discrepancy remains unclear, but it may be partly due to the difference in BMI between the two studies ( $22.4 \pm 2.2$  vs.  $30.7 \pm 5.3$  kg/m<sup>2</sup>). The mechanism of the suppressive effect of insulin on plasma homocysteine levels also remains unclear. Although we did not evaluate type 2 diabetic subjects, Fonseca et al. (4) reported that acute hyperinsulinemia did not influence plasma homocysteine levels, suggesting that a resistance to insulin's effect on homocysteine may contribute to the increased cardiovascular disease associated with insulin resistance syndrome and type 2 diabetes. We can be sure, at least, that acute hyperinsulinemia

cannot induce the elevation of plasma homocysteine levels. Further investigation of the effect of chronic hyperinsulinemia on plasma homocysteine levels using long-term glucose clamp study will be needed.

YUKIHIRO NAGAI, MD  
TOSHINARI TAKAMURA, MD  
ERIKA NOHARA, MD  
HARUHISA YAMASHITA, MD  
KEN-ICHI KOBAYASHI, MD

From the First Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, Ishikawa, Japan.

Address correspondence to Yukihiko Nagai, MD, First Department of Internal Medicine, School of Medicine, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa, Japan 920-8641. E-mail: ynagai@med.kanazawa-u.ac.jp.

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## Switching Insulin-Sensitizing Agents in Patients With Type 2 Diabetes Who Require Insulin

Because insulin resistance is a major metabolic defect in people with type 2 diabetes, the development of drugs that increase the sensitivity of hepatic and peripheral tissues to the action of insulin

has revolutionized the treatment of patients with this disease. Eventually, however, many patients with type 2 diabetes experience  $\beta$ -cell failure, and the administration of exogenous insulin becomes necessary.

The severity of the underlying insulin resistance in patients with type 2 diabetes frequently requires the administration of insulin doses in excess of 100 U/day, yet a sizable number of insulin-treated patients still do not achieve adequate glycemic control. Furthermore, the glycemic improvement that is achieved is frequently accompanied by weight gain and an increased risk of hypoglycemia, both of which may discourage the use of maximally effective insulin regimens.

The administration of an insulin-sensitizing agent to insulin-treated patients with type 2 diabetes who have inadequate glucose control reduces fasting plasma glucose (FPG) and HbA<sub>1c</sub> concentrations, and, in some cases, allows a reduction in daily insulin dose (1–4). Until recently, the thiazolidinedione troglitazone (Rezulin) was the only insulin-sensitizing agent cleared by the Food and Drug Administration for use in combination with insulin for type 2 diabetes. Recently, metformin (Glucophage), a biguanide that promotes the action of insulin in the liver and in peripheral tissues, has been cleared in the U.S. for use in combination with insulin.

In addition to its antihyperglycemic efficacy, metformin also has beneficial effects on cardiovascular risk factors. In contrast to treatment with sulfonylureas or insulin, metformin therapy is not associated with weight gain, as recently confirmed by the findings of the U.K. Prospective Diabetes Study (5), and some studies have documented weight loss (3,6). Metformin also improves plasma lipid profiles, lowering concentrations of triglycerides and LDL cholesterol (2,3,6). Troglitazone, in contrast, has neutral-to-negative effects on body weight and lipids, causing weight gain in combination with sulfonylureas or insulin. Troglitazone lowers triglyceride and raises HDL cholesterol concentrations, but it is also associated with increased LDL cholesterol concentrations in some patients (1,7).

Metformin is associated with mild gastrointestinal upset that is usually transient. In very rare cases (0.03 cases/1,000 patient-years), metformin use has been associated with lactic acidosis (8). However, avoiding the use of metformin when it is contraindicated, especially in those with diminished renal function, markedly decreases this risk.

Troglitazone is generally safe, but may cause hepatic dysfunction (7). Of the 2,510 patients who received troglitazone in the North American clinical trials, 1.9% experienced hepatic dysfunction (defined as serum aminotransferase concentrations  $>3$  times the upper limit of normal), compared with 0.6% who received placebo (9). Very rarely, troglitazone can be associated with severe idiosyncratic hepatocellular toxicity that can lead to hepatic failure necessitating liver transplantation or causing death (10). As a result, patients receiving troglitazone should have monthly liver enzyme testing for the first 8 months of therapy, then every other month for the next 4 months and periodically thereafter.

Because one cannot identify who may be at risk of hepatotoxicity while taking troglitazone, the use of troglitazone in a noncompliant patient may be problematic. Some patients may also find such monitoring inconvenient and prefer an alternative to troglitazone therapy. The relatively high cost of troglitazone and the expense of the required liver function testing may also limit its availability.

Adding an insulin-sensitizing agent to insulin therapy for poor glycemic control is clearly effective. The choice between metformin and troglitazone should depend on individual patient factors, including the presence of renal dysfunction or other risk factors for lactic acidosis, obesity, dyslipidemia, and hepatic dysfunction.

For some patients currently receiving combination therapy with troglitazone and insulin (for example, those with dyslipidemia or hepatic dysfunction, those who are noncompliant with liver function testing, or those experiencing significant increases in body weight), switching to a combination of metformin and insulin may be appropriate. This transition should be approached judiciously, with careful monitoring for both hypo- and hyperglycemia. For those with hepatic dysfunction, metformin should be initiated only after liver enzyme tests have returned to normal.

We recommend completely discontinuing the troglitazone and on the same day initiating metformin therapy at a daily dose of 500 mg with the evening meal. The dose should be escalated at 1–2 week intervals, first to 500 mg b.i.d., and gradually up to the usual optimally effective dose of 1,000 mg b.i.d. (11). During the transition period, frequent glucose monitoring is essential, and insulin doses may need to be adjusted to avoid hypoglycemia or hyperglycemia. We

generally follow the recommendations in the metformin package insert, reducing the insulin dose by 10–25% if FPG concentrations are  $<120$  mg/dl. In patients taking troglitazone and insulin with FPG concentrations consistently in this range, it may be wise to similarly reduce the insulin dose before initiating metformin therapy. Once the maximally effective or best-tolerated metformin dose is achieved, insulin doses should be adjusted as usual to optimize glycemic control.

Conversely, in patients who develop renal dysfunction or other risk factors for lactic acidosis while taking metformin or who have other significant adverse effects, switching from combination therapy with insulin and metformin to insulin and troglitazone may be appropriate. Physicians should apply the same cautions regarding hypo- and hyperglycemia during the transition. The metformin can be stopped immediately and troglitazone initiated in a dose of 200–400 mg/day. The insulin-sensitizing effect of the discontinued metformin is likely to have ceased before that of troglitazone has reached maximum efficacy. During this period, increased insulin dosage may be required to maintain adequate glycemic control.

Patients with type 2 diabetes who require insulin to treat their insulin secretory deficit almost always remain insulin resistant. Treatment with insulin corrects only one of their two defects. Adding an insulin-sensitizing agent to a regimen of insulin therapy has the potential to improve glycemic control by addressing both of the pathophysiologic abnormalities. The choice between metformin and troglitazone should be based on individual patient factors as described above. When circumstances suggest switching from one insulin sensitizer to another, attention to prescribing guidelines and careful monitoring should allow the transition to be safely accomplished.

LAWRENCE BLONDE, MD  
MARC I. SANDBERG, MD  
RICHARD D. GUTHRIE JR, MD

From the Section on Endocrinology, Diabetes and Metabolic Diseases, Department of Internal Medicine, Ochsner Clinic and the Alton Ochsner Medical Foundation, New Orleans, Louisiana.

Address correspondence to Dr. Lawrence Blonde, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121. E-mail: lblonde@ochsner.org.

L.B. has served as a consultant to and/or has received honoraria for presentations from Amilyn, Bayer, Becton Dickinson, Bristol-Myers Squibb, Eli Lilly, Hoechst Marion Rousell, Merck, Novo Nordisk, Parke-Davis, Pfizer, and SmithKline

Beecham and has been an investigator or subinvestigator in clinical trials sponsored by the aforementioned companies and by Proctor & Gamble. M.I.S. has served as a consultant to and has received honoraria for speaking engagements from Bristol-Myers Squibb, Eli Lilly, Hoechst Marion Rousell, and Parke-Davis and has been an investigator or subinvestigator in clinical trials sponsored by the aforementioned companies and by Bayer, Becton Dickinson, Merck, Pfizer, SmithKline Beecham, and Wyeth-Ayerst. R.D.G. has served as a consultant to and has received honoraria for speaking engagements from Bayer, Bristol-Myers Squibb, Eli Lilly, Hoechst Marion Rousell, Parke-Davis, and Pfizer; has served as an unpaid consultant to Novo Nordisk; and has been an investigator or subinvestigator in clinical trials sponsored by the aforementioned companies and by Becton Dickinson, Merck, Proctor & Gamble, and Smith-Kline Beecham.

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## COMMENTS AND RESPONSES

### Antiproteinuric Effect of Pentoxifylline in Patients With Diabetic Nephropathy

In a recent letter in *Diabetes Care* (1), Dr. Gorson reported the reduction of macroalbuminuria in three patients with diabetic nephropathy after treatment with pentoxifylline. The potential influence of other factors in the reduction of proteinuria cannot be completely ruled out, however, because the patients presented by Dr. Gorson were under tight glycemic control and were concomitantly receiving ACE inhibitors or angiotensin-receptor antagonists (ARAs).

The results of the Diabetes Control and Complications Trial (2) demonstrated that intensified glycemic control retards the rate of development of both microalbuminuria and overt proteinuria in patients with type 1 diabetes. Similarly, a reduction in the rate of development of diabetic nephropathy has also been observed by other authors after intensive glycemic control in patients with type 2 diabetes (3). In diabetic patients, it is known that hyperglycemia is a major determinant of progression of diabetic nephropathy. Although blood glucose control by itself does not slow the rate of progressive renal injury once overt proteinuria has developed, tight glycemic control may play a role in the setting of concomitant pharmacological therapy.

The renin-angiotensin system has been implicated in the pathogenesis of diabetic nephropathy and the progression of renal dysfunction (4,5). In animal models of diabetes, ACE inhibitors produce a reduction in intraglomerular pressure, but the major effects of these substances on the long-term development of albuminuria and glomerular injury are related to their capacity to inhibit the formation of angiotensin II (6). Studies in animals have reported that ARAs produce changes in the intraglomerular hemodynamic parameters similar to those produced by ACE inhibitors (6). Most importantly, in patients with overt proteinuria from diabetic nephropathy, both ACE inhibitors and ARAs have been shown to reduce significantly urinary protein excretion (7-10).

In spite of these criticisms, I agree with Dr. Gorson that pentoxifylline may have significant antiproteinuric properties. In 1993, a noncontrolled study in diabetic patients with overt proteinuria by Tripathi et al. (11) showed a significant reduction in urinary protein excretion after pentoxifylline administration. Guerrero-Romero et al. (12) reported 2 years later that pentoxifylline was able to clearly decrease both microalbuminuria and overt proteinuria in patients with type 1 or 2 diabetes and normal renal function. Recently, we have completed a controlled study that demonstrates that pentoxifylline also reduces proteinuria in diabetic patients with advanced renal failure (13). In this study, 14 patients received pentoxifylline (400 mg/day) for 6 months. At the end of this period, urinary protein excretion decreased from 2.7 (1.2-5.8) to 1.1 (0.3-4) g/day ( $P < 0.001$ ). Interestingly, we observed a concomitant reduction in the serum levels of tumor necrosis factor (TNF)- $\alpha$  from  $569 \pm 285$  to  $329 \pm 232$  pg/ml ( $P < 0.001$ ). On the other hand, proteinuria and serum TNF- $\alpha$  did not experience any modification in the control group.

The antiproteinuric mechanisms of pentoxifylline are unknown. However, some possibilities have been suggested. Pentoxifylline is an adenosine receptor antagonist, which may reduce hyperfiltration and proteinuria (14,15). On the other hand, based on its important hemorheological properties, pentoxifylline produces a decrease of blood viscosity (16). These effects may result in a reduction of intraglomerular pressure and proteinuria. Finally, our investigations suggest another possible mechanism to explain the antiproteinuric effect of this substance. After 6 months of follow-up, serum concentrations of TNF- $\alpha$  and urinary protein excretion experienced a significant and parallel reduction in patients treated with pentoxifylline, but not in control subjects. Moreover, the decrease in proteinuria was strongly correlated with the reduction in serum TNF- $\alpha$  ( $r = 0.72$ ,  $P < 0.01$ ). Thus, our study suggests that the antiproteinuric effect of pentoxifylline may be related to its capacity to reduce circulating levels of TNF- $\alpha$  (13), a cytokine that has been implicated in the development and progression of diabetic nephropathy (17,18).

JUAN F. NAVARRO, MD  
CARMEN MORA, MD



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## Potential Impact of HbA<sub>1c</sub> Determination on Clinical Decision Making in Patients With Cystic Fibrosis-Related Diabetes

Allen et al. (1) report on the results of a survey among cystic fibrosis (CF) centers throughout the U.S. in which physicians had been asked whether and how they screen asymptomatic patients with CF for abnormalities in glucose homeostasis. Their conclusion was that screening for impaired glucose tolerance (IGT) was not routinely done in CF patients and, if performed, that screening tests vary.

The frequency of diabetes in CF patients has increased dramatically in the last decades because of the longer survival of CF patients. Usually, diabetes occurs after the first decade of life, with mean age at diagnosis reported to be around 20 years. The reported prevalence ranges from 4 to 15% (1,10), and diagnosis of impaired glucose tolerance (IGT) has been documented to be much higher, namely between 20 and 75% (5,7,12).

The diabetes type seen in CF is thought to occur in part secondary to pancreatic fibrosis, which destroys the islets of Langerhans and leads to insulin deficiency. In fact, the combination of insulin resistance and decreased insulin secretion discriminates this type of diabetes from classical type 1 or type 2 diabetes. The term cystic fibrosis-related diabetes (CFRD) has therefore been coined (1,6).

An early diagnosis of CFRD is mandatory to ensure adequate metabolic control. The main aim for patients with CFRD is to

prevent loss of weight and the catabolic state that follow hypoinsulinemia, glucosuria, and loss of energy and protein stores. The question of how to screen for CFRD in CF patients is of clinical importance. In 1990, a consensus conference of the Cystic Fibrosis Foundation (CFF) published guidelines for the identification of CFRD (3). As screening methods, urinalysis two to three times per year and fasting blood glucose and 2-h postprandial blood glucose measured every 2-4 years during late childhood and adolescence are recommended. Routine glycosylated hemoglobin (HbA<sub>1c</sub>) measurements have not been established as a useful screening tool in CF patients. Ko et al. (9) report that in a large group of Hong Kong Chinese, ~80% of oral glucose tolerance tests could have been avoided by using the paired values of fasting plasma glucose (FPG) and HbA<sub>1c</sub> or FPG and fructosamine for identifying potentially diabetic subjects.

Glycosylated hemoglobin levels reflect the integrated blood glucose levels during the preceding 2-3 months. They are, therefore, thought to be an objective measurement of long-term metabolic control in patients with diabetes of any type. Our hypothesis was that HbA<sub>1c</sub> measurement is a useful screening tool in identifying subjects with CFRD as well.

Between February 1997 and May 1998, we have prospectively measured HbA<sub>1c</sub> levels using a monoclonal antibody based test (Tina-Quant aHbA<sub>1c</sub>; Boehringer Mannheim/Hitachi, Mannheim, Germany) in 62 patients with CF (30 male, 32 female) treated at the Children's Hospital of the University of Leipzig. The mean age was 13.6 ± 4.7 years. Seven of the patients were older than 18 years. In four patients, CFRD is currently being treated with insulin. HbA<sub>1c</sub> levels were determined yearly. HbA<sub>1c</sub> data from 107 metabolically healthy children and adolescents (61 male/46 female) served as a reference group.

Both subject groups were divided into age-classes (0-5, 6-10, 11-15, and 16-21 years). In the control group, means of HbA<sub>1c</sub> levels were in accordance with normative data provided from the assay manufacturer (Boehringer Mannheim) (standard area HbA<sub>1c</sub> 4.3-5.8%). There were no differences in the means of HbA<sub>1c</sub> levels between the age-groups.

In the group of CF patients, the overall mean of HbA<sub>1c</sub> was significantly higher than that in the control group ( $P < 0.001$ , Mann-Whitney) and higher than expected

for the manufacturer's normative data. In the age-group 16-21 years, this difference was significant when analyzed separately. From 148 determinations of HbA<sub>1c</sub> levels in the CF group, 28 determinations were above the standard range given by the manufacturer and above the range measured in metabolically healthy control subjects. These pathologic laboratory results were obtained in 10 patients. Six patients with elevated HbA<sub>1c</sub> levels were in the age group 16-21 years.

All four patients with CFRD were treated with insulin in consensus with the recommendations of the CFF. The number of insulin injections per day in these four patients varied: one patient needed only one insulin injection per day, two were on two injections, and one practiced an insulin regimen with multiple insulin injections. Despite their insulin therapy, all four patients have repeatedly had elevated HbA<sub>1c</sub> levels (5.86 ± 0.32%).

In conclusion, only two-thirds of physicians screen asymptomatic patients with CF for abnormalities in glucose homeostasis. Most importantly, it is still unclear how and when screening for CFRD should be initiated in patients with CF. We propose to include routine (every 6 months) measurements of HbA<sub>1c</sub> levels as a screening and follow-up test for diabetes in CF patients of >12 years of age. Specificity and sensitivity of the screening procedure should be tested in a large multicenter prospective trial.

FRED HUNKERT, MD  
TONI LIETZ, MD  
BARBARA STACH, MD  
WIELAND KIESS, MD

From Children's Hospital, University of Leipzig, Leipzig, Germany.

Address correspondence to F. Hunkert, MD, Children's Hospital, University of Leipzig, Oststr. 21-25, D-04317 Leipzig, Germany. E-mail: hunf@server3.medizin.uni-leipzig.de.

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## Reply to Hunkert et al.

The HbA<sub>1c</sub> is a simple test to do and does not require fasting or timed sampling. Intuitively, because it reflects integrated blood sugars over several months, the HbA<sub>1c</sub> would seem to be a reasonable way to assess overall blood glucose control in individuals with early undiagnosed diabetes or, perhaps, intermittent abnormal glucose homeostasis (which might be missed by a point measurement). Last year, we reported (1) that half of physicians caring for patients with cystic fibrosis (CF) perform HbA<sub>1c</sub> tests yearly or more often to screen for cystic fibrosis–related diabetes (CFRD). Hunkert et al. (2) hypothesize that HbA<sub>1c</sub> is a useful screening tool in this population, and present data showing elevated HbA<sub>1c</sub> levels in their CF patients.

The mean HbA<sub>1c</sub> reported by Hunkert et al. for CF patients was 5.28%, versus 5.06% for the control group. Both are within the manufacturer's normal range of 4.3–5.8%. The four patients with CF who have diabetes and are treated with insulin might better not have been included in the analyses, since they are not from the target population and raise the mean for the CF group. Multiple measurements from some patients (148 measurements were made on 62 CF patients) might also be expected to artificially raise the reported mean for CF patients. Yet, despite these methodological issues, the findings described by Hunkert et al. are, for the most part, in accordance with those previously reported by others.

Several studies of glucose homeostasis in CF patients have described median or mean HbA<sub>1c</sub> levels at the upper end of the normal range in groups of patients with CF who have normal or impaired glucose tolerance (3–6). Unfortunately, the correlation between HbA<sub>1c</sub> values and glucose responses to oral glucose tolerance testing has been poor (5,7–9). HbA<sub>1c</sub> levels have not consistently been shown to be age dependent or to trend upward with age when patients were followed prospectively. Correlation between HbA<sub>1c</sub> and CF clinical score or pulmonary function parameters has been demonstrated by some (6), but not by others (5,7).

In the absence of evidence that an elevated HbA<sub>1c</sub> without symptoms of diabetes is a risk factor for either development of diabetic complications or CF-related problems (pulmonary deterioration, weight loss, etc.), the critical point in evaluating the use of HbA<sub>1c</sub> in screening for CFRD is how well it predicts the onset of frank diabetes. The prospective study by Lanng et al. (8) showed that an HbA<sub>1c</sub> on the day of diagnosis of diabetes had a positive predictive value of 40–56%, depending on age, and a negative predictive value of 89–96%. These data were cross-sectional, and one might predict that longitudinal data (which was not reported for HbA<sub>1c</sub> levels) would demonstrate even poorer predictive values.

The conclusion of a meta-analysis by Peters et al. (10) suggested that HbA<sub>1c</sub> might be a reasonable alternative to oral glucose tolerance testing for diagnosing type 2 diabetes. This finding should not be generalized to CFRD. While studies to date suggest a possible weak correlation between increasing HbA<sub>1c</sub> measurement and decreasing glucose tolerance, HbA<sub>1c</sub>

measurements have not been shown to be sensitive markers of glucose tolerance and are poor predictors of development of diabetes in patients with CF. The poor sensitivity of HbA<sub>1c</sub> in these patients may be a result of the variability of average blood glucose over days to weeks because of intercurrent illness, and the fact that even major, but intermittent, postprandial excursions may not result in much elevation in the HbA<sub>1c</sub> measurement.

I agree with Hunkert and associates that before suggesting the use of HbA<sub>1c</sub> as a screening tool, we need prospective data from a large population of CF patients. A multicenter prospective trial would be needed to answer this type of question and might be most efficiently and economically executed by inclusion of HbA<sub>1c</sub> data and appropriate glucose tolerance end point measurements in a CF registry.

HOLLEY F. ALLEN, MD, MSPH

From Baystate Medical Center Children's Hospital, Tufts University School of Medicine, Springfield, Massachusetts.

Address correspondence to Holley F. Allen, Baystate Medical Center Children's Hospital, 759 Chestnut St., Springfield, MA 01199. E-mail: holley.allen@bhs.org.

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## Metformin and Lactic Acidosis

In a recent edition of *Diabetes Care*, Brown et al. (1) attempt to evaluate the risk of lactic acidosis in type 2 diabetic subjects not receiving metformin, and compare their findings with reported rates of metformin-induced lactic acidosis. They conclude that the observed association between metformin and lactic acidosis may be coincidental rather than causal, and that patients who might benefit from this drug are therefore being denied access to it.

We have major concerns about the design of this study and its conclusions. Brown et al. reviewed data from three diabetes registries, comprising >41,000 patient-years of information. They identified potential lactic acidosis events on the basis of a discharge diagnosis of acidosis, a serum lactate of 2.2 mmol/l, or an anion gap of 16 mEq/l, reviewed the records of the relevant patients, and obtained a lactic acidosis rate overall of 9.7 per 100,000 patient-years (95% CI 0.2–19.1). That figure would rise to 16.9 per 100,000 patient-years if some less well-characterized patients were included. They note that the lactic acidosis rate in the first year of Food and Drug Administration data in U.S. patients receiving metformin was 5 per 100,000 patient-years and 1–15 per 100,000 patient-years in studies from European countries based on >2 decades of metformin use. They suggest, therefore, that the relationship between metformin and lactic aci-

dosis may be coincidental, or, to use the phrase employed by Stacpoole in the same issue (2), a matter of “guilt by association” with the well-established induction of lactic acidosis by the now discontinued biguanide phenformin.

The cases identified in the survey of Brown et al. of non-metformin takers all had critical illnesses involving hypotension and/or cardiac failure. They were, therefore, instances of type A lactic acidosis (3), which is the variety associated with clinical evidence of circulatory failure or hypoxia. This variety of lactic acidosis is very common and is grossly underdiagnosed because serum lactate is not a routine measurement. A large proportion of us will eventually suffer terminal lactic acidosis. But a salient feature of biguanide-associated lactic acidosis is that in a substantial proportion of cases it occurs (3) without clinical evidence of circulatory failure or hypoxia (type B lactic acidosis). After many hours of increasing acidosis, such patients may develop circulatory insufficiency, presumably because of the well-described cardiac and other hemodynamic effects of severe acidosis—but in the early stages, the circulation is clinically normal. Brown et al. therefore asked the wrong question in their survey. The appropriate question would have been “what is the incidence of lactic acidosis in patients with type 2 diabetes not treated with metformin who, at presentation with lactic acidosis, had no clinical evidence of circulatory failure or hypoxia?” We wonder if the answer might be zero!

The results of the U.K. Prospective Diabetes Study (UKPDS) (4) have provided good evidence for the beneficial effect of metformin on the long term incidence of diabetic complications in overweight patients. Premature easing of the prescribing guidelines for metformin, on the basis of inadequate evidence of its freedom from lactic acidosis-inducing propensities, may perversely have the opposite effect of that intended by Brown et al. if it results in a substantial rise in the incidence of type B lactic acidosis. The evidence from the UKPDS study (5) showed that it was control of blood glucose that was the final common pathway in the beneficial effects of hypoglycemic agents. There are alternative methods of lowering blood glucose for those patients who have any degree of renal insuffi-

ciency while this matter is being sorted out. Finally, it may be noted that in Sweden, the only country cited by Brown et al. where reporting of fatal and serious drug reactions is compulsory for physicians, the “metformin-induced” lactic acidosis rates have progressively fallen over the period 1977–1991 (1); the most obvious reason for this is that physicians have been observing more closely instructions to avoid prescribing in patients with renal failure or whose condition puts them at risk of renal failure (6).

What is needed is a prospective and independent survey of the incidence of type B lactic acidosis in type 2 diabetic patients receiving various modalities of hypoglycemic therapy. When we reviewed the literature on phenformin-induced lactic acidosis (3), a notable feature was that about half of the cases presented soon after the start of phenformin therapy or an increase in dose. Such temporal associations add weight to the arguments for a causal association and should be sought in future surveys. In addition, the temporal relationship between the onset of lactic acidosis and the occurrence of circulatory insufficiency needs to be carefully analyzed, for reasons outlined above.

In the meantime, we would strongly advise drug regulatory agencies, manufacturers, and physicians to continue to observe the current precautions when prescribing metformin.

ROBERT D. COHEN, MD, FRCP  
H. FRANK WOODS, DPHIL, FRCP

From the Medical Unit (R.D.C.), The Royal London Hospital, St Bartholomew's; the Royal London School of Medicine and Dentistry (R.D.C.), Queen Mary and Westfield College, University of London, London; and the Division of Molecular and Genetic Medicine (H.F.W.), University of Sheffield School of Medicine, Sheffield, U.K.

Address correspondence to R.D. Cohen, MD, Medical Unit, The Royal London Hospital, Whitechapel Road, London, E11BB, U.K. E-mail: r.d.cohen@mds.qmw.ac.uk.

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## Response to Cohen and Woods

We would like to thank Drs. Cohen and Woods for their comments and clarifications (1). We agree with them that a prospective study of metformin use in non-ill individuals with diabetes would be the ideal way to resolve the issue of incident lactic acidosis events. Pending such a study, inferential evidence such as ours (2) is most probably the best method for studying this issue.

We should point out that in a recent issue of *Diabetes Care*, Lalau et al. (3) reported that in a group of 13 patients who had intentionally overdosed on metformin, and for whom blood levels of lactate and metformin were available, clinical acidosis developed only in those either with underlying disease that caused excessive lactate production or with defective lactate elimination. There was not a direct correlation between the development of clinical lactic acidosis and metformin levels. Such evidence supports our conclusion that lactic acidosis among metformin users occurs in those predisposed to lactic acidosis, irrespective of metformin use.

JONATHAN B. BROWN, PHD, MPP  
 KATHRYN PEDULA, MS  
 JOSHUA BARZILAY, MD  
 MICHAEL K. HERSON, MD  
 PEGGY LATARE, MD

From the Kaiser Permanente Center for Health Research (J.B.B., K.P.); the Permanente Medical Group of Georgia (J.B.), Atlanta, Georgia; the Per-

manente Medical Group of the Northwest (M.K.H.), Portland, Oregon; and the Permanente Medical Group of Hawaii (P.L.), Honolulu, Hawaii.

Address correspondence to Jonathan B. Brown, PhD, MPP, Center for Health Research, 3800 N. Kaiser Center Dr., Portland, OR 97227-1098. E-mail: brownjon@chr.mts.kpnw.org.

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## GAD Antibodies in Classification of Asian Type 2 Diabetes

We read with great interest the recent letter from Ramachandran et al. (1) reporting GAD65 antibodies in the classification of Asian Indian diabetic subjects with onset between 20 and 40 years. They concluded that GAD65 antibody (Ab) estimation may be of limited use in Asian subjects because of the low positivity and the lower sensitivity in detecting insulin-requiring diabetes and that serum C-peptide seemed to be a more sensitive index of  $\beta$ -cell reserve, and probably a better indicator for the classification and choice of treatment in adult diabetic subjects.

Certainly, the positive rate for GAD Ab in insulin-deficient Asian diabetic subjects initially diagnosed with type 2 diabetes is low (28.6% in their study [1] and 21.7% in our study [2]) compared with those in Australian subjects (76 and 73.7% in the study of Tuomi [3] and Zimmet [4], respectively), which is compatible with previous data showing different positivities for autoimmune diabetes (type 1 diabetes) among countries. Serum C-peptide measurement quantifies  $\beta$ -cell reserves, and it can be an important factor in selecting treatment. However, it cannot be used as a predictor for later development of insulin deficiency because its level varies with some factors, such as treatment (5) and level of blood glucose (glucose toxicity) (6). Furthermore, GAD Ab+ patients with

type 2 diabetes would develop insulin-deficiency (7), especially those with specific genetic backgrounds (8). We reported that HLA-DRB1 alleles contribute to determining the prognosis of Japanese diabetes in patients positive for GAD Ab (8). GAD Ab has been shown to be more predictive for diabetes than either insulin or islet cell cytoplasmic antibodies, and can be a useful marker for the prevention or delay of type 1 diabetes by the administration of nicotinamide and prophylactic insulin.

In conclusion, we are convinced that GAD Ab can be an informative and useful marker for classification and early intervention of diabetes in type 2 as well as in type 1 diabetes, even in ethnic groups presenting lower positivity for GAD Ab than do Western countries.

MICHIAKI FUKUI, MD  
 NAOTO NAKAMURA, MD  
 MOTOHARU KONDO, MD

From the Department of Medicine and Endocrine Unit (M.F.), Ayabe Municipal Hospital; and the First Department of Internal Medicine (M.F., N.N., M.K.), Kyoto Prefectural University of Medicine, Kyoto, Japan.

Address correspondence to Michiaki Fukui, The Department of Medicine and Endocrine Unit, Ayabe Municipal Hospital, 20-1 Otsuka Aono-cho, Ayabe City, Kyoto, 623-0011, Japan.

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## Poor Metabolic Control Decreases the Growth Velocity of Diabetic Children

We read with interest the article by Bognetti et al. (1), published in the August 1998 issue of *Diabetes Care*, in

which they analyzed the changes in growth of children and adolescents with type 1 diabetes during their first 3 years with this disease. They did not, however, refer to our recent study, published in 1996 (2), in which we evaluated the effect of glycemic control on the growth velocity of children and adolescents with type 1 diabetes during the 5 years after their diagnosis.

Bognetti and associates found height-SDS (HSDS) to be greater than zero (the normal population mean) in their patients at diagnosis, as did we in our study ( $0.59 \pm 1.04$  and  $0.30 \pm 0.97$ , respectively). Furthermore, HSDS decreased significantly between the onset of type 1 diabetes and the 3-year cut-off in their study. Similar findings were reported by us after 5 years of type 1 diabetes in poorly controlled patients, who decreased from an HSDS of  $0.32 \pm 1.27$  during the 1st year to  $-0.57 \pm 1.32$  after the 5th year of diabetes. However, better controlled patients maintained their HSDS over time ( $0.27 \pm 0.67$  at diagnosis vs.  $0.24 \pm 0.64$  after 5 years).

Bognetti et al. found no relationship between HbA<sub>1c</sub> levels and HSDS, while

we clearly found diabetic children and adolescents with poor metabolic control to grow less well than patients under better control. Weight-SDS changed significantly between onset of type 1 diabetes and the 1st year of follow-up, but not subsequently, in their study, while weight-SDS remained similar during the 5-year follow-up in our patients.

PETER GUNCZLER, MD  
ROBERTO LANES, MD

From the Pediatric Endocrine Unit, Hospital de Clínicas Caracas, Caracas, Venezuela.

Address correspondence to Peter Gunczler, MD, M-209, P.O. Box 020010, Miami, FL 33102.



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