OBSERVATIONS

Comparison of Glycemic and Lipid Response to Pioglitazone Treatment in Mexican-Americans and Non-Hispanic Caucasians With Type 2 Diabetes

The risk of type 2 diabetes in Mexican-Americans is almost twice that of non-Hispanic Caucasians (1). Mexican-Americans are also, in general, more likely to have insulin resistance, impaired fasting glucose, and impaired glucose tolerance than non-Hispanic Caucasians (1,2). Given these increased risks of type 2 diabetes in the Mexican-American population and the fact that poor glycemic control is more common in diabetic Mexican-Americans than in non-Hispanic Caucasians (3), it is important to consider the efficacy of diabetes therapy in this specific population.

In a retrospective chart review, our clinic identified patients with type 2 diabetes who had been treated with pioglitazone 45 mg/day for 6 or more months without interruption. Patient charts were then selected if HbA_{1c} and lipids were available within 4 weeks of starting treatment and ~4 months into treatment. Patients whose lipid-lowering medication was changed during this same time period were excluded. In total, data from 98 non-Hispanic Caucasians and 81 Mexican-Americans were reviewed.

The majority of patients (>75%) were taking pioglitazone in combination with metformin, sulfonylurea, or insulin, with the remainder of the patients receiving pioglitazone as monotherapy. The percentage of patients on monotherapy was the same in both groups. Fifty-three percent of non-Hispanic and 31% of Mexican-American patients were taking statin medication ($P = 0.002$). One patient in the Mexican-American group and three in the non-Hispanic group were taking a fibrate. Baseline characteristics (duration of diabetes, BMI, C-peptide, and male-to-female ratio) for the two groups were similar with the exception of age. The mean and standard deviation for age was 61.2 ± 12.8 years in the non-Hispanic Caucasian population and 52.7 ± 15.2 in the Mexican-American population ($P < 0.001$). The younger age in the Mexican-American population is consistent with the younger age of onset of diabetes that has been reported elsewhere for this population (4). The mean duration of treatment, at which time the laboratory data were obtained, was 3.9 months in the Mexican-American patients and 4.4 months in the non-Hispanic Caucasians ($P = 0.312$).

Our analysis showed that mean reduction in HbA_{1c} was similar between the two populations. Mean baseline HbA_{1c} was 8.0 ± 1.9% for non-Hispanics and 8.2 ± 1.9% for Mexican-Americans. At 3 months, the mean reductions from baseline were 1.2 ± 1.8% and 1.1 ± 1.4%, respectively (the difference between two populations was not statistically significant, $P = 0.616$).

Similarly, there was no difference between the two populations in terms of lipid effects. Baseline triglyceride levels were 216 and 207 mg/dl, respectively; baseline HDL cholesterol levels were 41.6 and 43.1 mg/dl, respectively; and baseline LDL cholesterol levels were 106 and 113 mg/dl, respectively. Mean reductions in triglycerides from baseline were 10.1 ± 47.1% in non-Hispanic Caucasians and 8.4 ± 47.3% in Mexican-Americans ($P = 0.802$ for two populations). Mean increases in HDL cholesterol were 17.0 ± 21.0 and 16.0 ± 18.8%, respectively ($P = 0.748$), and mean increases in LDL cholesterol were 5.1 ± 25.2 and 6.5 ± 48.1%, respectively ($P = 0.826$). In a subanalysis, there was no significant ($P > 0.05$) difference within each ethnic group in the lipid response to pioglitazone regardless of whether the patient was concurrently taking a statin.

Also of interest was the fact that weight gain was similar in both groups. Baseline BMI was practically identical between the two population groups (33.9 and 33.1 kg/m^2, respectively, for non-Hispanics Caucasians vs. Mexican-Americans), although overall, the Caucasians weighed more at baseline than the Mexican-Americans (mean weight 99.6 and 89.2 kg, respectively). Mean weight gain at 3 months was 1.64 and 1.41 kg, respectively ($P = 0.540$).

Although Mexican-Americans have a higher incidence of type 2 diabetes and an earlier age of onset, our analysis suggests that their response to treatment with pioglitazone is similar to that seen in non-Hispanic Caucasians in terms of HbA_{1c} and lipid changes. Such a comparison of pioglitazone treatment between these two ethnic groups has not previously been conducted, and thus these data provide some interesting and encouraging insights. Certainly, good glycemic control can greatly reduce the risk for diabetic complications in all ethnic groups; however, because of the increased risk in Mexican-Americans, treatments that improve glycemic control potentially offer a greater benefit in this population (5). Further prospective comparative studies in Mexican-American populations should be conducted to confirm and expand upon our results.

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Diabetic Vasculopathy and Alcohol Tolerance Trait in Type 2 Diabetes

In 1978, Pyke and Leslie (1,2) first proposed the hypothesis that clinical pictures of patients with type 2 diabetes can be characterized by two clinical presentations in response to chlorpropamide use and tolerance to alcohol. Chlorpropamide alcohol flushing (CPAF) is often observed in diabetic patients with a family history of diabetes, but among those patients without CPAF, there is a high probability of developing severe diabetic retinopathy. Subsequently, Barnett et al. (3) has reported that persistent proteinuria is also more commonly observed in patients without CPAF. However, the role and significance of CPAF and diabetic vasculopathy still remains controversial.

Aldehyde dehydrogenase-2 (ALDH2) and alcohol dehydrogenase-2 (ADH2) are the key enzymes for alcohol metabolism. Many Asians lack enzyme activity of ALDH2 and have superactive enzyme activity of ADH2, attributed to point mutations within both structural genes (4). Hence, the expression of these two enzyme mutations could determine the alcohol tolerance among the Japanese population.

We have found an increase in the prevalence of nephropathy and advanced diabetic retinopathy among Japanese patients with diabetes and a specific ADH2 and ALDH2 genotype. A total of 158 patients with type 2 diabetes (114 men and 44 women aged 17–81 years) were examined. The subjects were consecutively selected from our outpatient clinic and were all unrelated. After informed consent, a blood sample was obtained from each subject. Genotyping of ALDH2 and ADH2 was performed by the PCR-restriction fragment–length polymorphism (RFLP) method, details described elsewhere (4). The phenotype of ALDH2 inactivity is compatible with possession of the genotype ALDH2*1/ALDH2*2 or ALDH2*2/ALDH2*2, and the phenotype of ADH2 superactivity is compatible with possession of the genotype ADH2*2/ADH2*2 (4). Diabetic retinopathy was assessed and categorized by ophthalmologist examination. Nephropathy was diagnosed if proteinuria was found on testing with CLINITEK-200+ (Bayer Medical) on at least three consecutive clinic visits in the absence of other causes of proteinuria.

The results of this study showed that 41 subjects have active ALDH2 and superactive ADH2 genotypes, which was regarded as the alcohol tolerance (ATO) group. The other 117 subjects were regarded as the alcohol intolerance (AIT) group, because these patients had usual ADH2 and/or inactive ALDH2 genotypes, which accounts for delayed alcohol metabolism. There was no difference between the two groups in sex, age, age of diabetes onset, duration of diabetes, height, BMI, fasting plasma glucose, and HbA_{1c} level (for ATO vs. AIT, respectively, male/female 28/13 vs. 86/31, age 59.1 ± 9.6 vs. 57.7 ± 11.2 years, onset of diabetes 47.6 ± 10.4 vs. 46.5 ± 12.4 years, duration 11.7 ± 7.3 vs. 11.0 ± 7.7 years, height 161.3 ± 9.7 vs. 162.9 ± 7.9 cm, BMI 23.2 ± 3.9 vs. 22.8 ± 3.4 kg/m^2, fasting plasma glucose 149.5 ± 38.9 vs. 146.5 ± 42.4 mg/dl, and HbA_{1c} 7.8 ± 1.4 vs. 7.8 ± 1.3%). However, the ATO group had a higher frequency of having persistent proteinuria than the AIT group (ATO 15 of 41, 36.6%; AIT 24 of 117, 20.5%; $P < 0.05$ by χ^2 analysis). Among all, retinopathy was found in 31.7% (13 of 41) of the ATO group and in 32.5% (38/117) of the AIT group, showing no difference. However, among the patients with retinopathy, the frequency of proliferative retinopathy was three times higher in the ATO group (5 of 13, 38.5%) than in the AIT group (5 of 38, 13.2%) ($P < 0.05$). Thus, the ATO group had higher frequency of having nephropathy and of developing diabetic proliferative retinopathy than the AIT group.

It has been noted that activation of protein kinase C (PKC)-β under hyperglycemia can lead to a number of downstream sequelae, which are potentially damaging to the vascularity of glomerulus and retina in diabetes (5). ADH and ALDH are the enzymes not only for alcohol metabolism, but also for degradation of 4-hydroxy-2-nonenal (4-HNE) and other aldehydes (6–8). 4-HNE is a by-product of lipid peroxidation and has a role in pathophysiological conditions by acting as a signal molecule able to modulate relevant biological events, such as cell signaling, gene expression, cell proliferation, and cell differentiation. Interestingly, Chiarpotto et al. (9) has reported on differential regulation of protein PKC isoforms by a concentration of 4-HNE that is actually detectable in specific biological fluids or tissues. PKC-β1 and PKC-βII activities are markedly increased by 0.1 μmol/l 4-HNE, whereas they are unaffected or even inhibited by 1–10 μmol/l 4-HNE. Decreased tissue levels of 4-HNE could result from active ALDH2 and superactive ADH2 expression, as represented by subjects of the ATO group (6–8). Therefore, we speculate, in the ATO group, that the 4-HNE in the low micromolar range is able to have an influence on cell function through upregulation of PKC-β isoforms, which aggravates the damaging effects of PKC-β isoforms induced by hyperglycemia. Then, in the chronic situation, the lower concentration trait of 4-HNE in the ATO group may account for the long-term development of diabetic nephropathy and severe retinopathy.

In conclusion, we suggest that in Japanese individuals, the alcohol tolerance genetic trait is associated with the occurrence of diabetic vasculopathy. Our finding seemingly has a similar importance to that of the CPAF hypothesis, in terms of a suggestion for a relationship between alcohol tolerance and diabetic vasculopathy (2,3).

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Screening Using Compressed Digital Retinal Images Successfully Identifies Retinopathy

Digital retinal photographs can be integrated into a computerized network that more easily enables communication and quality assurance (1). Image compression overcomes the difficulty of transmitting and storing large file sizes. Concern has been raised that major compression of ≥70% results in clinically significant loss of retinal detail with inadequate screening sensitivities (2). It is unclear whether low levels of compression result in loss of screening sensitivity compared with the original bit-map image.

We used a Topcon TRC-NW6S non-mydriatic fundus camera with a Sony DXC950P to photograph 171 patients with diabetes (one eye each for the study), without the use of mydriasis. Original bit-map images (768 × 576 pixels, 1.27 MB) were stored and compressed to make a JPEG image (104 KB) of the highest quality using Paintshop Pro (Jasc Software, Eden Prairie, MN) with standard encoding. All images were anonymized and presented to the grader in random order. Images were graded on a 17-inch Cathode ray tube monitor with 1,024 × 768 pixel resolution in a darkened room by a single grader. Severe and very severe nonproliferative retinopathy, proliferative retinopathy, and maculopathy were defined as vision-threatening retinopathy.

On the original bit-map images, 80 patients had normal retina (46.7%), 35 had background retinopathy (20.5%), 38 had vision-threatening retinopathy (22.2%, 5 proliferative and 33 maculopathy), 8 had non–diabetes-related changes (4.7%), and 10 were unreadable (5.8%). Compared with bit-map images, grading using the JPEG images achieved a sensitivity of 95.8% (±5.1%, 95% CI) and a specificity of 95.0% (±4.2%) in the detection of any identifiable disease. This yields a positive predictive value of 94.6% and a negative predictive value of 96.2%. In terms of identifying vision-threatening retinopathy, the sensitivity of using highest-quality compressed JPEG images was 97.4% (±2.4%) with a specificity of 100%. The positive predictive value was 100%, and the negative predictive value was 99.3%. The difference between JPEG images and bit-map images in the detection of vision-threatening referable disease amounted to a disagreement about the presence of one microaneurysm in one image, which did not require subsequent laser photocoagulation.

Using highest-quality compressed JPEG images (Paintshop Pro) does not appear to result in any loss of sensitivity when compared with uncompressed bit-map images for detecting potentially vision-threatening disease. This finding helps confirm earlier pilot studies (3,4). JPEG files compressed to highest-quality images result in file sizes that are 8% of the original bit-map image file size, which allows them to be more readily stored, more easily transferred across a web-interface, and transmitted at a faster rate.

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Indications That Phototherapy Is a Risk Factor for Insulin-Dependent Diabetes

In a previous study (1), we found that the diagnosis of maternal-child blood group incompatibility appeared as a risk factor for type 1 diabetes, but we were not able to disentangle possible treatment effects from that of diagnosis. A European population-based multicenter study confirmed the association of type 1 diabetes

with jaundice and blood group immunization (2). Since our previous study, the number of infants recorded in the Swedish Childhood Diabetes Registry has almost doubled. We therefore repeated our study with special stress on the possible risk associated with phototherapy.

The Childhood Diabetes Registry, containing information on 7,343 children with diabetes and born during the period 1973–1997, was linked with the Medical Birth Registry to get individual and diabetes-independent information on neonatal events. No linkage occurred for 327 (4.5%) diabetic children. We excluded twins, infants born of diabetic mothers, and infants whose county of birth was unknown, leaving 6,487 cases for analysis and 2.8 million births for comparison. We used Mantel-Haenszel's weighted estimates of odds ratios (ORs), stratifying for year of birth. A logistic multiple regression analysis was also made with further adjustments for putative confounders.

A diagnosis of jaundice gave an OR of 1.13 (95% CI 1.01–1.26). The OR for therapy, irrespective of diagnosis, was 3.79 (3.13–4.59). Therapeutic traditions and coding habits may vary by county and over time; the OR was relatively constant over time but varied between counties. We selected three counties with more than five treated infants who developed type 1 diabetes and added the other 21 counties into one group (0–5 treated cases per county, 54 total). The OR for therapy and type 1 diabetes was 2.41 (1.36–4.17) in the first county, 6.03 (3.29–10.8) in the second county, 4.80 (2.64–8.53) in the third county, and 2.62 in the remaining counties. The heterogeneity was significant between the groups ($P = 0.015$). The ORs for a jaundice diagnosis for the two high-risk counties was 1.30 (0.79–2.16) and thus not different from the rest (1.01 [0.57–1.53]). We analyzed the type 1 diabetes risk in the two high-risk counties with enough recorded events and in the remaining counties in logistic multiple regression analyses, entering year of birth, preterm birth, respiratory symptoms in the newborn, blood group immunization, and phototherapy as explanatory variables. The phototherapy OR was 1.95 (1.19–3.20) in the two selected counties and 1.06 (0.78–1.43) in the other counties.

Our findings indicate that previous observations that neonatal jaundice and/or blood group incompatibility syndromes are associated with type 1 diabetes risk may be due to phototherapy treatment independent of diagnosis. The difference in OR between the counties indicates that actual treatment regimes could be of importance, and a medical record study could pinpoint such differences. The mechanism behind the association is unknown; however, effects on the neonatal gut and gut immune response are possible, and the frequent use of this treatment combined with the increasing incidence of childhood type 1 diabetes requires further study.

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Celiac Disease and Type 1 Diabetes

Type 1 diabetes is a chronic autoimmune disorder with varying degrees of insulin deficiency resulting from an immune-mediated destruction of pancreatic β-cells, usually starting in young individuals with an acute onset (1).

Type 1 diabetes can be associated with other clinical, subclinical, or potential organ-specific autoimmune diseases, mainly of thyroid, stomach, adrenals, and intestine, contributing to depict the constellation of autoimmune polyglandular syndromes (2,3).

Celiac disease is an autoimmune enteropathy characterized by small intestinal lesions of variable severity (4). In genetically predisposed individuals, the disease is triggered by ingestion of gluten. Celiac disease is diagnosed by small-bowel biopsy and is associated with antigliadin antibodies (AGAs), endomysial (EmA), and tissue transglutaminase autoantibodies (tTGAs) of IgA class (4). It is well known that clinical celiac disease represents only the tip of the iceberg. The subclinical disease is not infrequent in the general population, and AGAs associated to EmA can be used as markers for the identification of these asymptomatic individuals (5).

Coexistence of type 1 diabetes and celiac disease was first suspected in 1954 (6). The recognition of celiac disease in asymptomatic patients with type 1 diabetes is important. From 1984 to 2001, a population of 15,712 patients with type 1 diabetes has been examined in 38 published articles. Using different screening procedures for autoantibodies, the reported prevalence of celiac disease ranged from 0.6 to 16.4%.

Recently, tTGAs were measured in 305 patients from Germany with newly diagnosed type 1 diabetes: 11 (3.6%) and 12 (3.9%) subjects were positive for tTGA-IgA and IgG, respectively. Of 12 patients, 5 gave informed consent for small-bowel biopsy and all showed either partial or total villous atrophy (7).

A total of 200 patients with type 1 diabetes at onset (107 men, 93 women; mean age 21.5 years, range 9 months to 72 years) were screened for celiac disease, testing tTGAs of IgA class by commercial kit Quanta Lite tTG ELISA (INOVA Diagnostic, San Diego, CA) with purified antigen from guinea pig liver. The sera with values <20 units were considered negative. One of them had a known history of celiac disease.

Of the 200 patients who underwent tTGA-IgA testing, 8 (6 women and 2 men) (4%) were positive; levels ranged from 20.7 to >200 units. One of them was the

patient with known celiac disease, who did not maintain the diet. Of the seven patients who remained tTGA-IgA positive, four (with titers of 34.9 units, 36.8 units, 159.6 units, and >200 units, respectively) gave informed consent for small-bowel biopsy. All showed either partial or total villous atrophy, thus confirming the diagnosis of celiac disease.

This study shows that the appearance of tTGA-IgA represents a specific marker to identify subjects with silent celiac disease. This is important because the treatment of asymptomatic patients with type 1 diabetes with a gluten-free diet has a positive effect on glycemic control (8) and on the growth. Furthermore, it can prevent osteoporosis and the development of other autoimmune diseases.

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Influence of Alcohol Intake and Aldehyde Dehydrogenase 2 Phenotype on Peripheral Neuropathy of Diabetes

In Asians, the differences of alcohol tolerance are mainly determined by a polymorphism of aldehyde dehydrogenase 2 (ALDH2), which metabolizes acetaldehyde produced from ethanol into acetate (1). To examine whether the inactive ALDH2 influences the peripheral neuropathy in diabetes, 194 Japanese patients with type 2 diabetes (135 men and 58 women, aged 59.1 ± 11.7 years) were divided by ALDH2 phenotype and alcohol consumption and then the correlation of NCV (nerve conduction velocity in tibial motor nerve) with clinical parameters was compared. It was found that 99 and 95 patients had the active and inactive ALDH2 phenotype, respectively. In the first set of patients, 22 were nondrinkers (group 1) and 77 were drinkers (group 2). In the second set, 42 were nondrinkers (group 3) and 53 were drinkers (group 4). As determined by regression analysis, NCV was inversely correlated with diabetes duration and HbA_{1c} in the nondrinkers (group 1: $r = 0.433$, $P < 0.05$ for HbA_{1c}; group 3: $r = 0.509$, $P < 0.01$ for duration). In the drinkers, alcohol consumption was calculated as amounts of alcohol weight (in grams) per week. NCV was inversely correlated with the past maximum alcohol consumption per week in group 4 only ($r = 0.502$, $P < 0.001$), not in group 2. These results suggest that peripheral neuropathy in diabetes is related to alcohol consumption, especially in drinkers who are genetically alcohol intolerant.

Because the ALDH2 gene is transcribed in the nervous system, the ALDH2 deficiency may directly contribute to excess acetaldehyde accumulation after alcohol ingestion. Alternatively, nerve lipid peroxidation increases in experimental diabetic neuropathy (2). Among lipid-peroxidative-derived toxic aldehydes, 4-hydroxynonenal (4-HNE) is one of the most reactive aldehydes under physiological conditions. 4-HNE inhibits Na/K ATPase and has multiple deleterious effects on nerve (3). Aldehydes, including 4-HNE and acetaldehyde, are cometabolized by ALDH isozymes (4). Therefore, in group 4, due to the increased needs of acetaldehyde oxidation after alcohol ingestion, the patients with inactive ALDH2 may have a high nerve tissue concentration of toxic aldehydes such as 4-HNE, thereby developing neuropathy and slowing NCV.

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High Prevalence of Insulin Resistance and Metabolic Syndrome in Overweight/Obese Preadolescent Hong Kong Chinese Children Aged 9–12 Years

During the past decade, the rising prevalence of childhood obesity has been accompanied by a rapid increase in young-onset type 2 diabetes (1). The associations among obesity, insulin resistance, hypertension, and dyslipidemia are not well defined in preadolescent children. Furthermore, the impact of family history of diabetes, low birth weight, and non–breast-feeding on the clustering of features of insulin resistance syndrome in children remained to be determined. In a cross-sectional study of 271 primary school children between 9 and 12 years of age, we compared the effects of family history of diabetes, breast-feeding, and extremes of birth weight on obesity, insulin resistance, and cardiovascular risk factors between an obese/overweight ($n = 129$) and a nonobese group ($n = 142$). Anthropometric indexes, blood pressure, fasting plasma lipids, glucose, and insulin were measured. Family history of diabetes, birth weight, and feeding mode in the first 3 months of life were obtained from parents.

Overweight/obese children were taller and had higher systolic blood pressure, fasting triglycerides, fasting serum insulin, and insulin resistance index (homeostasis model assessment) but lower HDL cholesterol level than nonobese children (Table 1). The odds ratios for a family history of diabetes and formula feeding in overweight/obese children were 4.37-(95% CI 2.25–8.52, $P < 0.001$) and 2.20-fold (1.29–3.76, $P = 0.004$). Overweight/obese children had increased risk of high blood pressure (3.21 [1.60–6.45], $P = 0.001$), dyslipidemia (2.72 [1.58–4.66], $P < 0.001$), and hyperinsulinemia (defined as insulin level above the age- and sex-specific 85th percentile; 14.1 [7.75–25.48], $P < 0.001$). Nearly 50% of overweight/obese children had at least two of the three cardiovascular risk factors of dyslipidemia, high blood pressure, and hyperinsulinemia, and 8% had all three risk factors. Seventy-seven percent of overweight/obese children had insulin resistance, which was best predicted by waist circumference ($\beta = 0.52$, $P < 0.001$) and HDL cholesterol level ($\beta = -0.19$, $P = 0.001$) on multivariate analysis.

Clustering of cardiovascular risk factors is common in overweight/obese preadolescent children in Hong Kong. Overweight/obese children are more likely to have a positive family history of diabetes and formula milk-feeding in infancy. Our findings support the notion that breast-feeding may be associated with a reduction in childhood obesity risk (2). In agreement with the recent report by Sinha et al. (3), >77% of overweight/obese children in the present study had hyperinsulinemia. Given the predictive value of insulin resistance on future development of type 2 diabetes and coronary heart disease (4,5), the high prevalence of insulin resistance in these preadolescent children is an important public health issue.

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Table 1—*Clinical characteristics and cardiovascular risk profiles in overweight/obese and nonobese Chinese preadolescent children*

	Boys			Girls		
	Nonobese	Obese	*P*	Nonobese	Obese	*P*
n	67	84		75	45	
Age (years)	10.5 ± 1.1	10.4 ± 0.9	NS	10.4 ± 1.0	10.5 ± 1.1	NS
BMI (kg/m^2)	16.7 ± 1.7	24.7 ± 3.1	<0.001	16.5 ± 1.7	23.4 ± 2.4	<0.001
Birth weight (kg)	3.26 ± 0.50	3.39 ± 0.52	NS	3.18 ± 0.46	3.26 ± 0.46	NS
Waist circumference (cm)	61.1 ± 5.6	80.6 ± 8.0	<0.001	60.5 ± 4.8	75.2 ± 7.9	<0.001
Systolic blood pressure (mmHg)	98 ± 10	107 ± 9	<0.001	99 ± 10	107 ± 11	<0.001
Diastolic blood pressure (mmHg)	63.5 ± 11	67 ± 13.0	NS	64 ± 11	67 ± 11	NS
Fasting triglycerides (mmol/l)*	0.72×/÷1.38	0.96×/÷1.51	<0.001	0.77×/÷1.46	0.99×/÷1.53	<0.01
Fasting HDL cholesterol (mmol/l)	1.80 ± 0.37	1.41 ± 0.37	<0.001	1.65 ± 0.42	1.40 ± 0.33	<0.01
Fasting plasma glucose (mmol/l)	4.8 ± 0.3	4.8 ± 0.4	NS	4.7 ± 0.3	4.7 ± 0.4	NS
Fasting serum insulin (pmol/l)*	41.7×/÷1.9	110×/÷2.1	<0.001	57×/÷2.1	102.1×/÷1.8	<0.001
Insulin resistance index (HOMA)*	1.22×/÷1.9	3.22×/÷2.2	<0.001	1.66×/÷2.2	2.94×/÷1.8	<0.001

Data are means ± SD or *geometric means ×/÷ antilog SD. HOMA, homeostasis model assessment; NS, not significant.

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Effect of Structured Group Education on Glycemic Control and Hypoglycemia in Insulin-Treated Patients

We investigated the effect of a structured group diabetes education program (1) on insulin-treated patients who had received individual counseling (at the time of diagnosis and insulin initiation). A total of 1,369 type 1 and insulin-treated type 2 diabetic patients with mean disease duration of 11.7 and 13.7 years, respectively, were allocated to receive or not receive structured group education, which was delivered in 10 45-min sessions over 3–5 days.

Baseline GHb levels of type 1 diabetic patients were 9.3% for the education group and 9.13% for the control group and decreased at 6 months by −0.82 and −0.22%, respectively ($P = 0.0005$). The number of injections per day and self-monitoring increased, while the total insulin dose remained unchanged. The incidence of severe hypoglycemia was reduced by 0.18 events/6 months in the education group, whereas it increased by 0.03 events/6 months in the control group ($P = 0.003$).

In type 2 diabetic patients, baseline GHb was 9.1% in the education and 8.7% in the control group, with a significant difference in the changes after 6 months in favor of the education group: −0.48 vs. 0.17%, respectively ($P = 0.0005$). A trend of reduced incidence of hypoglycemic episodes was observed.

Education for people with diabetes is a prerequisite for an understanding and acceptance of their condition and its successful self-management (2). A recent study found that group education was as effective as individual tuition in achieving improvements in glycemic control (3). In our study, structured group education after initial individual counseling at diagnosis and insulin initiation resulted in improved glycemic control and reduction of hypoglycemia. This observation is in line with results from previous publications (4,5). These improvements could be attributed to better self-care (increased frequency of self-monitoring in both type 1 and insulin-treated type 2 diabetic patients) and the increase in the number of insulin injections (in type 1 diabetic patients). It should be noted that there was not a significant difference in the mean insulin doses at the 6-month follow-up visit compared with baseline in both type 1 and type 2 diabetic patients; therefore, it was not the amount of injected insulin but the educational intervention that contributed to the improved glycemic control.

It can be suggested that a group education program following individual counseling could be an effective tool in diabetes management.

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Relationship of β2-Adrenergic Receptor Polymorphism With Obesity in Type 2 Diabetes

Adrenergic receptor genes are candidate genes for obesity and type 2 diabetes because they regulate lipid mobilization. An association has been reported between the frequently occurring Gly27Gln polymorphism of the β2-adrenergic receptor (B2ADR) gene with obesity (1,2) and triglycerides (3) in nondiabetic subjects.

We studied 542 unrelated type 2 diabetic subjects to assess the possible relationship of the Glu27Gln polymorphism of the B2ADR gene with obesity, as well as with plasma lipids. The Medical Ethics Committee of the University Medical Center Utrecht approved the study, and all participants signed an informed consent. The Glu27Gln polymorphism was examined by a modification of a PCR/restriction fragment–length polymorphism–based method (3) in duplicate and included sequence-verified controls.

After exclusion of PCR failures, genotypes were obtained for 502 type 2 diabetic patients. Subjects were subdivided according to three genotype groups: 109 subjects were Gln27Gln, 225 were Glu27Gln, and 168 were Glu27Glu. ANOVA of age at diagnosis of type 2 diabetes (61 ± 10, 60 ± 9, and 61 ± 9 years for the Gln27Gln, Glu27Gln, and Glu27Glu genotype groups, respectively), BMI (27.2 ± 3.8, 27.9 ± 4.4, and 28.2 ± 4.0 kg/m^2), HbA_{1c} (7.2 ± 1.4,

7.4 ± 1.3, and 7.2 ± 1.2%; normal values <6.1%), plasma cholesterol (5.3 ± 1.2, 5.3 ± 1.0, and 5.3 ± 1.0 mmol/l), plasma HDL cholesterol (1.2 ± 0.3, 1.1 ± 0.3, and 1.2 ± 0.3 mmol/l), and plasma triglycerides (1.8 ± 1.1, 1.9 ± 0.9, and 1.9 ± 0.1 mmol/l) showed no statistically significant differences (all $P > 0.26$). After exclusion of the insulin-treated subjects, the differences were also not statistically significant. We also found no significant differences for men or women separately.

We conclude that, at least in our cohort of subjects with type 2 diabetes, the Glu27Gln polymorphism of the β2-adrenergic receptor has no important effect on BMI, age at diagnosis of diabetes, metabolic control, or plasma lipids.

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Decreased Glucagon-Like Peptide 1 Fasting Levels in Type 2 Diabetes

The significance of over- or underproduction of glucagon-like peptide 1 (GLP-1) (7–36) amide in diabetes remains controversial (1,2). Although it has been proposed that at least one factor contributing to the pathogenesis of type 2 diabetes is desensitization of the GLP-1 receptor on β-cells (2), exogenous administration of GLP-1 in patients with type 2 diabetes fully normalizes fasting hyperglycemia and reduces postprandial glycemic increments (3). Also, the GLP-1 response to oral glucose is not altered in postmenopausal women with impaired glucose tolerance (2). The purpose of the present study was to establish any difference in the fasting state concentration of GLP-1 in type 2 diabetes as compared with the normal state.

We examined 26 subjects (12 men and 14 women) with type 2 diabetes who were aged 67.6 ± 10.09 years (means ± SD) and had a BMI of 29.2 ± 3.5 kg/m^2 and a diabetes duration of 137.0 ± 23.7 months. As a control group, we included 15 normal subjects (9 women and 6 men) who were aged 65.8 ± 8.01 years and had a BMI of 28.1 ± 3.7 kg/m^2. Patients with type 2 diabetes were treated by diet and were on metformin and/or sulfonylurea therapy with HbA_{1c} 6.81 ± 1.37% and fasting glucose 87.30 ± 5.20 mg/dl. Written consent was obtained from all participants. Blood samples were obtained at rest between 8:00 and 9:00 A.M. after an overnight fast and 24 h alcohol abstention. Insulin and GLP-1 were measured using an enzyme-linked immunosorbent assay (AxSYM; Abbott Lab, North Abbott, IL) and competitive radioimmunoassay (Peninsula Lab, Belmont, CA), respectively.

Interestingly, GLP-1, displaying a normal distribution, exhibited a statistically significant decrease ($P < 0.001$) in type 2 diabetic patients (23.8 ± 3.17 pg/ml) compared with control subjects (76.4 ± 4.47), whereas the plasma insulin concentration was higher in type 2 diabetic subjects (20.9 ± 13.4 ÌU/ml) than in control subjects (9.8 ± 1.3), with the difference being statistically significant ($P < 0.03$).

Using linear regression analysis, we found that GLP-1 was more negatively correlated with insulin in the type 2 diabetic patients than in the normal subjects ($r = -0.64$, $P < 0.001$ vs. $r = -0.43$, $P = 0.040$). In addition, GLP-1 was also negatively correlated with HbA_{1c} in type 2 diabetic subjects at a statistical level ($r = -0.43$, $P = 0.037$). Interestingly, the results were independent of diabetes duration.

The physiological importance of the decreased fasting level of GLP-1 in type 2 diabetic patients requires further clarification. If it is a reflection of increased sensitivity of β-cell responsitivity to secretagogues, then this study further confirms previous findings on the existence of a negative feedback loop between GLP-1 and insulin secretion and provides further evidence for the importance of the entero-insular axis in the regulation of insulin secretion. Moreover, the dissociation of GLP-1 levels with the duration of the disease suggests an early impairment of the entero-insular axis.

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Docosahexaenoic Acid But Not Eicosapentaenoic Acid Increases LDL Particle Size in Treated Hypertensive Type 2 Diabetic Patients

The dyslipidemia of type 2 diabetes includes the accumulation of small dense LDL particles in plasma that have an increased propensity to glycation and oxidation and may contribute to the endothelial dysfunction in type 2 diabetic patients. We recently reported that both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major dietary long-chain n-3 fatty acids, significantly reduced triglycerides and increased HDL_2 cholesterol without changing total, LDL, or HDL cholesterol in a group of type 2 diabetic subjects (1). We now report additional data on the differential effects of EPA and DHA on LDL particle size in the same subjects.

Nonsmoking treated hypertensive diabetic men and postmenopausal women, aged 40–75 years, were stratified by sex, age, and BMI and randomized to receive 4 g/day purified EPA, DHA, or olive oil (placebo) for 6 weeks in a double-blinded trial. LDL particle diameter was determined by gradient gel electrophoresis (2).

At baseline there were no significant differences among the olive oil, EPA, and DHA groups in plasma LDL cholesterol level and LDL particle size (25.69 ± 0.13 nm, 26.0 ± 0.16 nm, and 25.74 ± 0.16 nm, respectively). Relative to placebo, LDL particle size was decreased by 0.12 ± 0.10 nm ($P = 0.49$) with EPA and increased by 0.26 ± 0.10 nm ($P = 0.02$) with DHA after adjusting for multiple comparisons (Bonferroni).

These data support our previous study in overweight hypercholesterolemic subjects, in whom LDL particle size increased after supplementation with DHA but not EPA (2). While the increase in LDL particle size with DHA supplementation seen in our present study appears relatively small, a significant difference in size of 1.02 nm distinguished between middle-aged healthy men with no risk factors and men with the metabolic syndrome (3). The differential effects on LDL particle size after EPA and DHA cannot be explained by the reduction in triglycerides alone, since both EPA and DHA significantly decreased serum triglycerides by a similar extent relative to placebo (19 and 15%, respectively) (1). Additionally, the association between the change in LDL size and triglycerides was only weak ($r = -0.30$, $P = 0.04$).

Supplementation with purified DHA increases LDL particle size, reduces serum triglycerides, and increases HDL_2 cholesterol (1), as well as improves vascular function (4) and blood pressure (5). Therefore, for subjects with type 2 diabetes, DHA may have more therapeutic value than EPA as a food additive, but longer-term prospective studies are needed to address this issue.

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The Human Insulin Analogue Aspart Is Not the Almighty Solution for Insulin Allergy

Although human insulin is beneficial for most diabetic patients, some patients suffer from an allergy to exogenous insulin. Human insulin analogues, lispro or aspart, have been well tolerated in cases of insulin allergy. However, we report herein the first case of allergy to both lispro and aspart.

A 53-year-old woman with a history of type 2 diabetes for the past 3 years consulted our hospital for management of uncontrolled diabetes. Her postprandial blood glucose level was 12.9 mmol/l, and her HbA_{1c} level was 10.2%. She was initially treated with oral hypoglycemic agents (voglibose, glimepiride, metformin, and pioglitazone), which led to a decrease in her HbA_{1c} to 6.8%. However, her hyperglycemia became difficult to control over the next year (HbA_{1c} 7.6%), and treatment with intermediate-acting human insulin (Novolet N; Novo Nordisk, Bagsværd, Denmark) was begun. Two months after starting insulin injections, the patient noticed a skin rash and itching at the injection sites, so her insulin was changed to the analogues aspart and lispro, in succession. The local reactions continued, however, and the insulin analogue injections were suspended.

The patient had no previous history of any allergy. The percentage of eosinophils in her peripheral white blood cell count was 8.0%. She showed a high level of total IgE (748 IU/ml; normal, <400 IU/ml) and human insulin-specific IgE (19.80 IU/ml; normal, <0.34) measured by radioallergosorbent test. She had a positive test for anti-insulin antibodies (52%; normal, <7%). Prick tests were

positive for lispro, aspart, human insulin, and porcine insulin, as well as for an additive of insulin preparations, protamine, using the Novo insulin allergy kit (Novo Nordisk), for which in vitro drug-induced lymphocyte stimulation tests were all positive. A biopsied specimen of the skin with prick tests revealed subcutaneous edema with infiltrated cells, including eosinophils. Her illness was diagnosed as insulin allergy.

Because the anti-allergenic drug ebastine did not reduce the allergic reaction, insulin and insulin analogues had to be discontinued. Since the patient's hospitalization, administration of oral hypoglycemic agents with intensification of nutrition therapy and exercise has conveniently led to an HbA_{1c} of 5.5%.

The human insulin analogues aspart (B28Asp human insulin) and lispro (B28Lys-B29Pro human insulin) have been reported to be beneficial for the reduction of allergic reactions to insulin because of less antigenicity due to increased clearance of insulin analogue monomers from injection sites. Aspart has been confirmed to be less immunogenic for development of antibodies against human insulin (1). Lispro and aspart have been available internationally since 1996 and 1999, respectively; and both analogues, especially aspart, certainly seem to be beneficial for patients with insulin allergy (2,3). To our knowledge, there has been no report that aspart is intolerable in cases of insulin allergy. However, our patient showed an allergic reaction to both insulin analogues. Therefore, these analogues are not necessarily tolerated as alternatives when insulin allergy has already developed. We need follow-up of patients treated with insulin analogues that focuses on the evocation of insulin allergy.

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Intensive Diabetes Management May Improve Pregnancy

Outcomes in Chinese gravidas with impaired glucose tolerance

In a study of diabetes in pregnancy in Tianjin, China (1,2), gravidas with impaired glucose tolerance (IGT) were found to have poor pregnancy outcomes (3). We studied the effect of an intensive diabetes management plan (IDMP) on pregnancy outcomes in 150 gravidas who developed IGT during pregnancy.

Women were randomized to receive either intensive care (IC; $n = 95$) or usual obstetric care (UC; $n = 55$). Of the 95 women randomized to the IC group, 48 (50%) completed the IDMP. All 55 women of the UC group completed the study. Comparisons of pregnancy outcomes were performed by intention to treat. The IDMP consisted of diet and exercise advice, self–home blood glucose monitoring, and/or insulin treatment if indicated, as well as a fortnightly clinical review of glycemic status and other intervention goals. Low intake of calories was prescribed according to pregravid BMI (4), with subjects consuming six evenly spaced meals per day. The goal of the IDMP was fasting capillary whole blood glucose <5.5 mmol/l and a 1.5-h postprandial glucose <7.0 mmol/l. Glucose tests were carried out 1.5 h postprandial. Fasting glucose tests were also performed when the fasting glucose level at the diagnostic OGTT was elevated.

The IC and UC groups were comparable in age, pregravid BMI, weight gain during pregnancy, gestational age at delivery, and fasting and 2-h OGTT glucose levels. The rate of premature rupture of membranes (P-ROM) was significantly lower in the IC group than in the UC group (4.21% [4/95] vs. 20% [11/55], $P = 0.0034$). The reduced risk for P-ROM in the IC group persisted after controlling for age, stature, pregravid body weight, fasting and 2-h OGTT glucose levels, gestational weeks at the OGTT, caesarean delivery status, and hospital levels (secondary versus tertiary) (odds ratio [OR] 0.135 [95% CI 0.032–0.559]). The frequency of caesarean delivery was also significantly lower in the IC group than in the UC group (64.2% [61/95] vs. 80.0% [44/55], $P = 0.0445$); the reduced risk was marginally significant after controlling for covariates (0.479 [0.211–1.084]).

Differences in preterm birth, birth weight, perinatal morbidity and mortality, and deformations between the two groups were not statistically significant. No birth trauma or shoulder dystocia occurred in either group. Before the current study, gravidas in Tianjin were not screened for diabetes in pregnancy and IGT was not treated.

This study investigated the effect of an established IDMP on pregnancy outcomes in order to provide evidence for (or indicate the lack of) public health planning toward improved population obstetric care in Tianjin, China. Notwithstanding the inherent limitations in introducing the intensive diabetes management and a small sample size, the current study shows that intensive diabetes management can result in statistically detectable and clinically important improvements in pregnancy outcomes. The challenge for developing countries, such as China, who faces the rising prevalence of type 2 diabetes (5), is to develop evidence-based health services that integrate a traditional beliefs system and century-old practice and that consider economic rationale and, most importantly, the health of women and their children.

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COMMENTS AND RESPONSES

Thyroid Stimulating Hormone Screening Is More Sensitive for Detecting Thyroid Abnormalities in Children and Adolescents With Type 1 Diabetes

Kordonouri et al. (1) provide interesting information regarding the frequency of thyroid autoimmunity in pediatric-aged patients with type 1 diabetes. Their recommendations of "yearly examinations of thyroid antibodies" and "in cases of thyroid antibody positivity, thyroid function tests and ultrasound assessment" "to minimize the risk of undiagnosed hypothyroidism in young patients with type 1 diabetes" are not supported by the data. If the goal is to detect subjects with hypothyroidism, then as shown in Table 1 of their study, 15.8% (241) of 1,530 patients who were thyroid antibody positive had an elevated thyroid stimulating hormone (TSH) and would be considered true positives; 7.8% (434) of 5,567 thyroid antibody–negative patients had an elevated TSH and would be considered false negatives. Thus, the sensitivity [true positives/(true positives + false negatives)] for thyroid antibody testing equals 35%. There were 5,133 antibody-negative patients with normal TSH values (true negatives) and 1,289 thyroid antibody–positive TSH-normal patients. Thus, the specificity [true negatives/(true negatives + false positives)] for thyroid antibody testing in their study was 80%. In regard to patients requiring thyroxine treatment, 10.6% (162) of the antibody-positive patients were true positives (antibody positive and thyroxine treated) and 0.6% (33) of the antibody-negative patients were false negatives (antibody negative and thyroxine treated). In addition, there were 5,534 true negatives (antibody negative, no treatment) and 1,388 false positives (antibody positive, no treatment). Thus, antibody testing was 83% sensitive and 80% specific.

Since there is no proven benefit in treating antibody-positive patients with normal TSH levels (2), and since screening tests should be highly sensitive, the data actually support yearly primary TSH screening with possible secondary antibody testing.

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Thyroid Antibody Screening in Children and Adolescents With Type 1 Diabetes

Response to Hoffman

We thank Dr. Hoffman for his critical comments (1). According to his calculations, based on our cross-sectional study data, he found a specificity of 80% and only a low sensitivity of 35% for the thyroid antibody–screening test. Thus, he does not support our recommendation for yearly examinations of thyroid antibodies (2).

We agree with him that screening tests should be highly sensitive, but the data of our multicenter study do not allow a true estimation of the sensitivity, since patients have not been followed longitudinally and since we missed those patients who will develop hypothyroidism later on during their course of diabetes. Indeed, we examined patients with type 1 diabetes at the Pediatric Diabetes Outpatient Clinic of the Otto-Heubner-Center, Charité, Berlin, and found that 8 of 16 patients with positive antibodies developed thyroid stimulating hormone (TSH) elevation after an observation time of 2–6 years (median 3.5) (3). Therefore, patients with positive antibodies should be monitored for TSH elevation at yearly intervals.

In addition, the German Association of Pediatric and Adolescent Medicine recommends that patients with positive thyroid antibodies and concomitant thyroid gland enlargement with a typical hypoechogenic pattern in ultrasound studies should receive treatment with L-thyroxine.

For these reasons, we have been performing thyroid antibody–screening tests at our institution in all patients with diabetes since 1998.

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Reproducibility of the Continuous Glucose Monitoring System Matches Previous Reports and the Intended Use of the Product

A recent article by Metzger et al. (1) questioned the reproducibility of the continuous glucose monitoring system (CGMS; Medtronic MiniMed). We were surprised by the authors' conclusions, as their results were consistent with previously published reports. We believe the authors' expectations for the CGMS did not coincide with its intended use. We were also puzzled by their use of a subjective assessment of clinical decision making when a validated tool, i.e., the Clarke error grid, is available (2). Finally, Metzger et al. dismissed the impact of an update to the CGMS software (Solutions 3.0) that does in fact improve the reproducibility evident in their data.

Although Metzger et al. reported results based on a limited number of subjects ($n = 11$), the results are quite similar to those reported in a large postmarketing study ($n = 235$) (3). Correlation was 0.93 mg/dl (vs. 0.91), and bias was 0.0 mg/dl (vs. −3.91). Metzger et al. also reported that 69% of sensor-sensor pairs had >10% difference, which compares closely with the previously reported median difference of 12.6% between sensor-meter pairs. Even the meters used to calibrate the CGMS provide only 56 to 69% of self-monitored blood glucose values within 10% of corresponding laboratory results (4).

As stated in the instructions for use, information provided by the CGMS "is intended to supplement, not replace, blood glucose information using standard home glucose monitoring devices" by providing glucose pattern and trend information for 24–72 h. Metzger et al. stated, "Clinical decisions should not be made on the sole basis of glucose sensor data" (1). When used with self-monitored blood glucose and HbA_{1c} values, clinical decisions based on CGMS profiles are designed to help the diabetes team optimize management.

Metzger et al. included several figures depicting discrepancies between sensor-sensor profiles, the most obvious being patient K. The authors failed to note that the sensor software labeled the depressed tracing as not meeting optimal accuracy criteria and that it therefore should have been further investigated by the clinician before use. The authors further report a 35% discrepancy in the clinical interpretation of sensor-sensor profiles. This method of assessment is subjective and has not been validated. Moreover, based on a Clarke error grid analysis, >93% of the CGMS readings are clinically accurate or acceptable.

Metzger et al. report technical problems in 18% of the profiles generated by Solutions 2.0 software. The upgraded Solutions 3.0 software resolves many of the technical reasons for which data were discarded in their analysis, corrects the abrupt shift in value at midnight, improves the accuracy and reproducibility of the data downloads, and improves the agreement between sensor and meter values as measured by mean absolute percent difference (18.4 vs. 16.1%) and correlation (0.91 vs. 0.92) (5).

An established body of literature, including a supplement to the journal *Diabetes Technology & Therapeutics* (6), supports the performance and utility of the CGMS to guide therapy adjustments based on glycemic excursions and to improve and predict HbA_{1c}. The results reported by Metzger et al. should be weighed against the encouraging results and conclusions of both evolving and previously reported research.

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Response to Mastrototaro and Gross

We thank Mastrototaro et al. (1) for their comments. For more than 30 years, development of a reliable ambulatory continuous glucose monitor has appeared to be an insur-

mountable technological challenge. The Medtronic MiniMed continuous glucose monitoring system (CGMS), the first commercially available system, provides retrospective analysis of glucose levels, making confirmation of unexpected findings difficult. As stated by Mastrototaro et al., when our sensor data were evaluated using correlation tests, a high degree of correlation with capillary blood measurements was found, confirming several previous reports. However, simple correlation tests do not identify potentially important clinical discrepancies. The tools to evaluate the clinical efficacy of new monitoring systems are limited. We did not use the Clarke error grid because the boundaries used in the published version (2) are not consistent with the requirements of tight glycemic control. For example, reference/sensor glucose value pairs such as 200 vs. 90 or 80 vs. 160 would fall into the acceptable "B" zone, although today such differences are unacceptable. Indeed, in the data reported by Gross et al. (3), many points falling in the B zone may not be considered clinically acceptable today. Therefore, pending the publication of a validated modern version of the Clarke error grid or another validated tool, we used an admittedly more subjective tool, the clinical judgment of a diabetologist blinded to the subject's identity.

Our profiles were generated using Solutions version 2 software, which was the version available at the time of the study and the one used in most previously published reports. Recalculation of our data with the newer software showed significant improvement, particularly in correcting the "midnight shift." However, other discrepancies apparent in our study, and our ultimate conclusions, were unchanged.

Recently, McGowan et al. (4) used a different technique to validate CGMS readings in seven patients and found that in four, falsely low sensor readings "might have resulted in inappropriate reduction of overnight insulin dose," a finding that supports our results. They conclude that many hypoglycemic episodes identified by the sensor may be spurious, thus questioning recent reports that showed an unexpectedly high incidence of asymptomatic nocturnal hypoglycemia.

We recognize the importance of this new technology and its inherent technical difficulties. We applaud Medtronic MiniMed for producing the first commercial system and for their continuing efforts to improve its reliability. The need for continued development is obvious, and clearly this technology will greatly improve our ability to treat diabetes. However, the current model has limitations that must be recognized, and new tools are needed to critically evaluate the clinical reliability of future devices.

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