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Diagnosis of Diabetes in Cystic Fibrosis and Thalassemia Major

The American Diabetes Association has recently published new guidelines for the diagnosis of diabetes, derived from studies on adults with type 2 diabetes (1). In contrast, little information is available on the performance of the new criteria in patients with "other specific types" of diabetes. Secondary diabetes is frequent, but usually asymptomatic, in patients with cystic fibrosis (CF) or thalassemia and requires a sensitive diagnostic test (2–4).

Oral glucose tolerance tests (OGTTs) were performed according to standard recommendations (5,6). CF patients on glucocorticoid therapy were excluded. Venous plasma glucose was measured enzymatically. Fasting glucose was classified as normal, impaired (IFG), or diabetic according to the new criteria (1), while 2-h plasma glucose values were interpreted as normal, impaired (IGT), or diabetic according to World Health Organization criteria (5).

Data from OGTTs performed in 92 patients with CF (age 14.3 ± 5.4 years, 53 boys and 39 girls), 25 patients with thalassemia major (age 17.2 ± 6.8 years, 17 boys and 8 girls), and 133 control subjects (age 15.7 ± 6.8 years, 76 boys and 57 girls) were available. According to OGTT results, the frequency of diabetes among CF patients was 14.1% (IGT 17.4%). Among thalassemia patients, 24% were diabetic and 20% displayed IGT.

Comparing the new classification based on fasting glucose with the OGTT revealed considerable diagnostic discrepancies (Table 1): of 13 CF patients diagnosed as diabetic by the OGTT, 11 displayed normal fasting glucose. All 16 CF patients with IGT (based on OGTT) had a fasting glucose <110 mg/dl. In contrast, 5 of 6 diabetic thalassemia patients were diagnosed correctly by fasting glucose alone. Among 133 control subjects, 3 were diabetic (two patients with type 1 diabetes and one massively overweight), with concordant results for fasting glucose (133, 137, and 137 mg/dl). In the OGTT, 10 normal subjects had IGT, from which 9 had normal fasting glucose and 1 had IFG.

Comparing the classifications "diabetic" or "nondiabetic" between the two diagnostic systems, and using the OGTT as the reference method, yields a sensitivity of 7.7% and a specificity of 100% for CF patients. In thalassemia, sensitivity of fasting glucose to diagnose diabetes is 83.3%, and specificity is 94.7%. In the control group, both sensitivity and specificity amount to 100%; however, the number of diabetic control subjects studied was low. When detection of impaired glucose metabolism was considered, the sensitivity was 0% in CF patients, 20% in thalassemia patients, and 10% in control subjects.

We and other groups have reported that the glucose rise in response to oral glucose is increased in CF patients and that diabetic CF patients preserve normal fasting glucose values for a long period (7–9). The assumption that roughly equal prevalences of diabetes will be detected by both classification schemes is definitely not true for patients with a high risk of secondary diabetes, and especially those with CF. Given these dramatic differences between the traditional and the new criteria and the limited experience with the new criteria in both pediatric subjects and patients with a high risk of secondary diabetes, we strongly recommend that diagnosis or exclusion of diabetes in these patients be based on the OGTT.

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Table 1—*Comparison of the traditional diagnostic classification based on the OGTT versus the new classification based on fasting blood glucose*

	Fasting blood glucose							
	Patients with CF				Patients with thalassemia major			
OGTT	Diabetes	IFG	Normal fasting glucose	Total	Diabetes	IFG	Normal fasting glucose	Total
Diabetes	1	1	11	13	5	0	1	6
IGT	0	0	16	16	0	1	4	5
Normal glucose tolerance	0	0	63	63	1	1	12	14
Total	1	1	90	92	6	2	17	25

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Changes in Erythrocyte Sorbitol Concentrations Measured Using an Improved Assay System in Patients With Diabetic Complications and Treated With Aldose Reductase Inhibitor

An accelerated polyol pathway may induce the development of diabetic complications (1–10). In previous reports, the erythrocyte sorbitol concentration was measured both enzymatically and by gas-liquid chromatography. These assay systems were complicated, however, and provided contradictory results on the role of sorbitol metabolism, probably because of the poor reproducibility of the assay methods (11–16). We devised an improved assay system for the measurement of sorbitol concentration (17). Our method enabled us to measure the erythrocyte sorbitol concentration with good reproducibility and to analyze the correlation between the sorbitol concentration and diabetic complications and the influence of an aldose reductase inhibitor on its concentration.

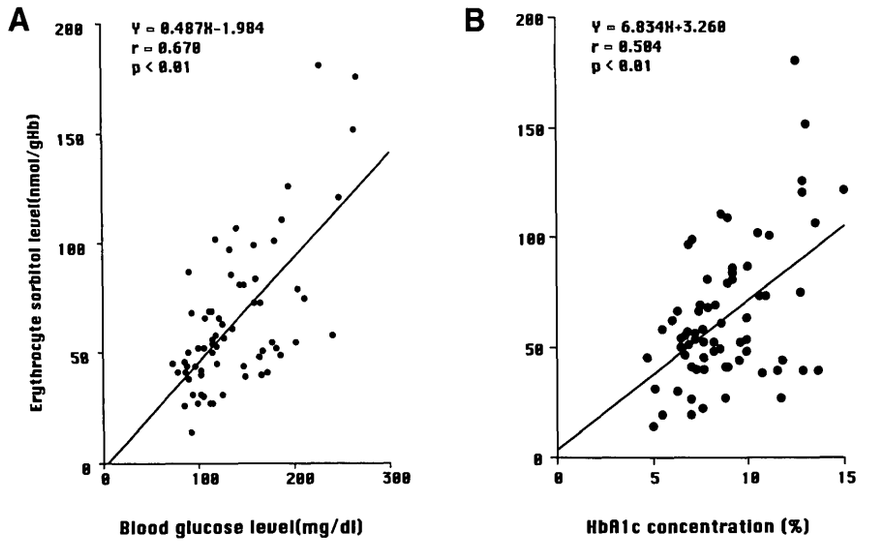

Figure 1—*A significant correlation was observed between erythrocyte sorbitol concentration and both blood glucose level* (A) *and HbA_{1c} concentration* (B).

Of 68 diabetic patients (12 from the outpatient clinic and 56 from admitted patients), 5 had IDDM and the others had NIDDM. The mean age of IDDM patients (2 men and 3 women) was 29.2 ± 11.8 (12–44) years, while that of NIDDM patients (32 men and 31 women) was 56.0 ± 12.4 (22–77) years. There were 39 healthy volunteers (29 men and 10 women, mean age 35 ± 8 [22–56] years) studied.

The erythrocyte sorbitol concentrations were compared between the patients with and without the diabetic complications of ophthalmopathy (more severe than proliferative retinopathy), nephropathy (positive microalbuminuria or proteinuria and/or lowered creatinine clearance), and peripheral neuropathy (numbness and low tibial motor nerve conductivity [MCV]).

Before and after the treatment with aldose reductase inhibitor (ARI) (epalrestat, 5-[(1Z, 2E)-2-methyl-3-phenylpropenylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid (Ono Pharmaceutical, Chuō-ku, Osaka, Japan), the sorbitol concentrations in the erythrocytes of the patients were determined.

Enzymatic measurement of sorbitol concentration

To remove the protein components of the erythrocyte suspension, 1.0 ml of 0.475 mol/l NaOH and 1.0 ml of 0.5 mol/l $ZnSO_4$ were added and mixed to a uniform consistency. The mixture was then centrifuged at 1,000*g* for 10 min at 4°C. Then 2 ml of this supernatant was mixed with 1.0 ml of 0.165 mol/l Tris-HCl buffer (pH 8.6) containing 0.02 mol/l EDTA, 1.0 ml (250 mg/dl) NAD, and 0.05 ml (40 U/ml) sorbitol dehydrogenase. After a 30-min incubation of the reaction mixture at 37°C, the NADH concentration produced was determined by spectrophotometry (excitation at 366 nm and emission at 452 nm), and then the concentration of sorbitol was calculated. The reproducibility and linearity in this assay system were more reliable than those of the previously reported method (17). The intra- and interassay coefficients of variance were 3.9 and 3.6%.

We investigated the relationship between erythrocyte sorbitol levels and complications in diabetic patients. The erythrocyte sorbitol concentrations in diabetic patients (68.43 ± 34.29 nmol/gHb in NIDDM; 50.20 ± 18.21 nmol/gHb in IDDM) were significantly increased compared with those in healthy control subjects (38.50 ± 8.10 nmol/gHb). A significant correlation was observed between the erythrocyte sorbitol concentrations and blood glucose levels or HbA_{1c} concentrations (Fig. 1). Treatment with ARI effectively reduced the increased erythrocyte sorbitol concentrations in the NIDDM patients (14 patients, decreased from 98 ± 12 to 58 ± 8 nmol/gHb, $P <$