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References

1. Castillo MJ, Scheen AJ, Lefebvre PJ: Amylin/islet amyloid polypeptide: biochemistry, physiology and pathophysiology. *Diabetes Metab* 21:3–25, 1995
2. Alevizaki M, Grigorakis SI, Rapti E, Anastasiou E, Alevizaki CC, Souvatzoglou A: Decreased islet amyloid polypeptide (IAPP) to insulin ratio in gestational diabetes (GDM) (Abstract). *Diabetologia* 36 (Suppl. 1):A167, 1993
3. Zweers EJK, Bravenboer B, van Hulst KL, Lips CJM, Christiaens GCML, Hackeng WHL, Erkelens DW: Glucose stimulated islet amyloid polypeptide and gestational diabetes mellitus (Abstract). *Diabetologia* 35 (Suppl. 1):A179, 1992
4. Kautsky-Willer A, Thomaseth K, Ludvik B, Nowotny P, Rabensteiner D, Waldhäusl W, Pacini G, Prager R: Elevated islet amyloid pancreatic polypeptide and proinsulin in lean gestational diabetes. *Diabetes* 46: 607–614, 1997
5. Swinn RA, Wareham NJ, Gregory R, Curling V, Clark PM, Dalton KJ, Edwards OM, O'Rahilly S: Excessive secretion of insulin precursors characterizes and predicts gestational diabetes. *Diabetes* 44:911–915, 1995
6. Percy AJ, Trainor DA, Rittenhouse J, Phelps J, Koda JE: Development of sensitive immunoassays to detect amylin and amylin-like peptides in unextracted plasma. *Clin Chem* 42:576–585, 1996
7. Rittenhouse J, Chait BT, Bierle JR, Janes SM, Park DR, Phelps JL, Fineman MS, Qin J, Koda JE: Heterogeneity of naturally-occurring human amylin due to glycosylation (Abstract). *Diabetes* 45 (Suppl. 2):234A, 1996
8. Kahn SE, D'Alessio DA, Schwartz MW, Fujimoto WY, Ensinck JW, Taborsky GJ Jr, Porte D Jr: Evidence of cosecretion of islet amyloid polypeptide and insulin by β-cells. *Diabetes* 39:634–638, 1990

A Critical Issue

Intensive insulin treatment and macrovascular disease

It is not yet known whether insulin treatment is beneficial, adverse, or neutral for cardiovascular disease in type 2 diabetes (1). The applicability of the Diabetes Control and Complications Trial (DCCT) findings to the prevention of microvascular complications of type 2 diabetes and to its cardiovascular consequences is a matter of controversy (2). Even the authorities who recommend normal glycemic levels as a treatment goal in people with type 2 diabetes (3,4), including the substantial proportion of patients who ultimately need insulin (5), indicate that such goals might have to be moderated in the presence of obesity, severe cardiovascular disease, or advanced age (3,4). The majority of patients with type 2 diabetes in western industrialized countries are obese, have a high prevalence of cardiovascular disease, and are in the later decades of life (6,7). Thus, the optimal degree of intensity of insulin treatment in such patients remains undetermined. Other authorities directly posit that the DCCT findings for type 1 diabetes should not be applied to type 2 diabetes until appropriate trials are conducted (8–10). These uncertainties were anticipated by the Department of Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes (VA CSDM) planning committee when it designed a clinical trial to evaluate the risk-to-benefit ratio of intensive glycemic control on macrovascular disease and other complications in type 2 diabetic patients no longer optimally controlled with diet and oral agents (6,11). The feasibility trial, completed in five medical centers in July 1993, demonstrated that a glycemic separation slightly exceeding that of the DCCT could be maintained for >2 years between study groups receiving standard treatment and intensive treatment without increased risk of severe hypoglycemia (7). Toward the end of the feasibility study, a final protocol for a 7-year trial of 1,400 patients from 18 hospitals was scientifically approved with an outstanding rating by the Department of Veterans Affairs (DVA) Cooperative Studies Program. The approved budget, although modest by National Institutes of Health standards, amply exceeded the usual budget of individual DVA cooperative studies, which often required extramural funding. Preliminary negotiations did not result in firm budgetary commitments, which prompted the DVA Cooperative Studies Program to put the long-term trial on a "waiting for funding" status. Because external funding was not forthcoming, the VA CSDM was removed from the "awaiting for funding" list in 1996. Given the distinguished record of the DVA in cooperative trials and the prevalence of type 2 diabetes in the DVA, it may still address, in the future, a long-term intensive treatment trial on type 2 diabetes.

There has been strong support for such a study. The American Diabetes Association made two presentations to Congress, in 1994 and 1995, and a grassroots campaign was launched among the readers of their journal, *Diabetes Forecast*, on behalf of funding for the VA CSDM (12). The Fifth Regenstrief Conference concluded that this is the single most critical study in type 2 diabetes (13).

On completion of the VA CSDM feasibility trial, an analysis of the high incidence of new cardiovascular endpoints (12%/year) and their correlates indicated a nonsignificant excess of new nonfatal cardiovascular events in the intensive-treatment group and a borderline correlation of new cardiovascular events with lower attained HbA_{1c} (14). Before the publication of the results, one review erroneously reported that there was excess mortality in the intensive-treatment group (9). It could also be erroneously implied that an adverse effect of intensive treatment caused the discontinuation of the long-term trial, otherwise scientifically approved with high priority. In fact, the relative imbalance of new cardiovascular events between groups in the feasibility trial has been considered inconclusive by the VA CSDM group (14), by the external Data Monitoring Board of the VA CSDM in their final report, and also by the 1996 American Diabetes Association consensus statement on the pharmacological treatment of hyperglycemia in NIDDM (5).

The issue of intensive insulin treatment of type 2 diabetes has not gone away. It is often quoted that the large U.K. Diabetes Prospective Study (UKDPS), already in its second decade, might answer whether intensive glycemic control in type 2 diabetes could prevent cardiovascular complications (1,8,15). This large trial compares diet alone with several treatment modalities and will be invaluable in comparing their relative safety and effectiveness. The UKDPS was to be interrupted if a significant difference in cardiovascular mortality occurred in any of the treatment groups (15). This has not happened. A possible reason is that difference in HbA_{1c} has been only 0.7% between the pharmacologically-treated and the control groups (diet alone) (16). This is little more than one-third of that obtained in the DCCT and the VA CSDM. Only individuals

with newly diagnosed diabetes were enrolled, and there were predetermined crossovers from one treatment to another. A substantial number of patients have remained responsive to either diet or oral agents alone (16). The question of how aggressive insulin therapy must be after oral agent failure may not be answered.

It also is hoped that non-sulfonylurea oral agents will offer alternative treatments and delay or prevent the need for insulin in people with type 2 diabetes. On the other hand, existing data suggest that the majority of such patients will ultimately require insulin (alone or in combination with non-sulfonylurea oral agents) for glycemic normalization. This was indicated in a recent review of metformin (17). Preliminary results of the newest agent, troglitazone, as submitted to the Food and Drug Administration, suggest that combined insulin and oral-agent therapy will continue to be needed for optimal glycemic control.

Recently, a beneficial effect of intensive insulin management on microvascular disease was reported in the Kumamoto trial of 110 Japanese type 2 diabetic subjects after 6 years of treatment (18). Similar benefits of intensive insulin management on microalbuminuria were also found in the VA CSDM (19). However, the cardiovascular risk profile of the Kumamoto population is of marginal applicability to Occidental patients. The patients of the Kumamoto trial had a BMI of only 20 kg/m^2 (in the VA CSDM it was 31 kg/m^2) and were insulin-sensitive and free of hypertension, dyslipidemia, or electrocardiographic abnormalities. No more than 5–10% of patients in Western countries would meet the same definition, as indicated by the cohorts participating in the University Group Diabetes Program (UGDP) (20), the VA CSDM (7,14), and the UKDPS (15,16). As could be expected, the cardiovascular event rate in the Kumamoto trial was extremely low and would not allow a statistical analysis of the effect of glycemic control on macrovascular disease. The only other similar long-term trial was the older UGDP. The data suggested a higher cardiovascular mortality in the oral agent groups. An effect on cardiovascular complications between standard and intensive insulin-treatment groups was not present (20). Glycemic separation, however, was small and comparable to that of the UKDPS (1,16).

For the present, the question of the optimal intensity of insulin treatment in people with type 2 diabetes remains uncertain. Given the demographic prevalence of type 2 diabetes and its disproportionately large share of health care costs in the U.S. (21), the issue of insulin therapy and macrovascular disease remains the most urgent treatment problem in diabetes management and can only be resolved in a prospective clinical trial.

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References

1. Genuth S: Exogenous insulin administration and cardiovascular risk in non-insulin-dependent and insulin-dependent diabetes mellitus. *Ann Intern Med* 124:104–109, 1996
2. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
3. Eastman RC, Gorden P: The DCCT: implications for diabetes treatment. *Diabetes Rev* 2:263–271, 1994
4. American Diabetes Association: Implications of the Diabetes Control and Complications Trial (Position Statement). *Diabetes* 42:1555–1558, 1993
5. American Diabetes Association: The pharmacological treatment of hyperglycemia in NIDDM (Consensus Statement). *Diabetes Care* 19 (Suppl. 1):S54–S61, 1996
6. Abraira C, Emanuele N, Colwell J, Henderson W, Comstock J, Levin S, Nuttall F, Sawin C, VA CS Group (CSDM): Glycemic control and complications in type II diabetes: design of a feasibility trial. *Diabetes Care* 15:1560–1571, 1992
7. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, Emanuele W, Levin SR, Henderson W, Lee HS, VA CSDM Group: Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM): results of the feasibility trial. *Diabetes Care* 18:1113–1123, 1995
8. Lebovitz ME: The DCCT and its implications for NIDDM. *Clin Diabetes* 12:3–4, 1994
9. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995
10. Nathan DM: Inferences and implications: do results from the Diabetes Control and Complications Trial apply in NIDDM? *Diabetes Care* 18:251–257, 1995
11. Whitehouse F: Toward risk factor control for all patients with diabetes. *Diabetes Care* 15:1818–1820, 1992
12. McCarren M: How tight for type II? *Diabetes Forecast* 48:29–32, 1995
13. Fifth Regenstrief Conference: Risks and benefits of intensive management in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 124:178–179, 1996
14. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS, VA CSDM Group: Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. *Arch Intern Med* 157:181–188, 1997
15. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study. VIII. Study design, progress and performance. *Diabetologia* 34:877–890, 1991
16. Turner R, Cull C, Holman R: United Kingdom Prospective Diabetes Study 17: the effect of improved metabolic control on complications in NIDDM. *Ann Intern Med* 124:136–145, 1996
17. Bailey CJ, Turner RC: Metformin. *N Engl J Med* 334:574–579, 1995
18. Ohkkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin*

Pract 28:103–117, 1995
19. Levin SR, Coburn J, Abraira C, Colwell J, Comstock J, Nuttall F, Henderson W, Emanuele N, Sawin C, and the VA Cooperative Study Diabetes (VACSDM) Group: Glycemic control retards progression of albuminuria in NIDDM (Abstract). *Diabetes* 45 (Suppl. 2):3A, 1996
20. University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VIII. Evaluation of insulin therapy: final report. *Diabetes* 31 (Suppl. 5):1–78, 1982
21. Rubin RJ, Altman WM, Mendelson DN: Health care expenditures for people with diabetes mellitus, 1992. *J Clin Endocrinol Metab* 78:809A–809F, 1994

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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References
1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
2. Lanng S: Glucose intolerance in cystic fibrosis. *Dan Med Bull* 44:23–39, 1997
3. Wonke B, Hanslip JI: Glucose intolerance and diabetes in thalassaemia major. In *Endocrine Disorders in Thalassemia*. Ando S, Bancati C, Eds. Ulm, Germany, Springer, 1995, p. 65–67
4. Zuppinger K, Molinari B, Hirt A, Imbach P,

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