studying the induction of fetal hemoglobin in the adult. *Blood* 77:1326–1333, 1991
9. Fibach E, Burke L, Schechter A, Noguchi C, Rodgers G: Hydroxyurea increases fetal hemoglobin in cultured erythroid cells derived from normal individuals and patients with sickle cell anemia or β-thalassemia. *Blood* 81:1630–1635, 1993
10. Burns L, Glauber J, Ginder G: Butyrate induces selective transcriptional activation of a hypomethylated embryonic globin gene in adult erythroid cells. *Blood* 72: 1536–1542
11. Constantoulakis P, Papayannopoulou T, Stamatoyannopoulos G: Alpha-amino-N-butyric acid stimulates fetal hemoglobin in the adult. *Blood* 72:1961–1967, 1988
12. Perrine S, Miller B, Faller D, Cohen R, Vichinsky E, Hurst D, Lubin B, Papayannopoulou T: Sodium butyrate enhances fetal globin gene expression in erythroid progenitors of patients with Hb SS and β thalassemia. *Blood* 74:454–459, 1989
13. Constantoulakis P, Knitter G, Stamatoyannopoulos G: On the induction of fetal hemoglobin by butyrates: in vivo and in vitro studies with sodium butyrate and comparison of combination treatment with 5-azaC and araC. *Blood* 74:1963–1971, 1989

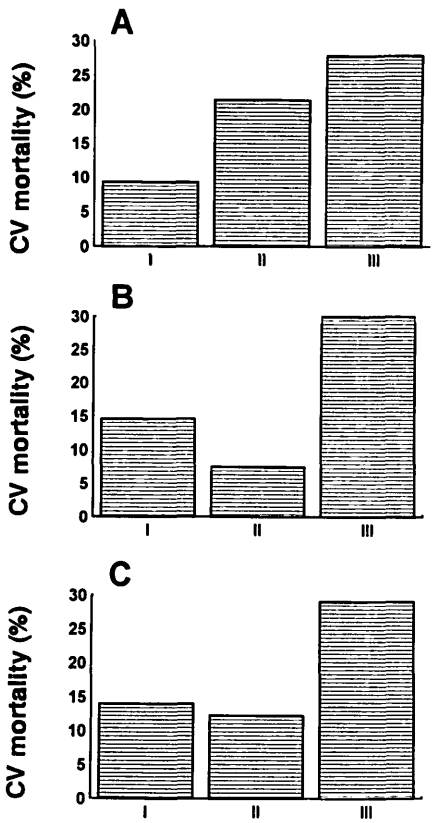

Figure 1—*Cardiovascular mortality in NIDDM patients in a 10-year follow-up from diagnosis according to the tertiles of fasting blood glucose at baseline (A) and plasma glucose (B) or HbA_{1c} (C) measured 5 years from diagnosis. Data based on Uusitupa et al. (5).*

Hyperglycemia and Cardiovascular Risk In NIDDM

In their technical review on standards of care for diabetes, Weir et al. (1) dealt with the significance of glycemic control in the prevention of macrovascular complications. There are no controlled intervention studies showing that improved glycemic control, achieved by diet, oral drugs, or insulin, would lead to a reduced risk of cardiovascular complications in NIDDM. Previous studies have failed to show a benefit from oral drugs or even insulin (2,3), and the U.K. Prospective Study, which eventually will clarify this issue, is not finished yet (4). There is, however, indirect evidence based on long-term observational studies of NIDDM patients showing that glycemic control could also be of importance in the prevention of macrovascular complications in NIDDM (5,6).

In our 10-year follow-up study of newly diagnosed middle-aged patients with NIDDM, baseline fasting blood glucose as well as plasma glucose and HbA_{1c} measured at the 5-year examination predicted the 10-year cardiovascular mortality in both diabetic men and women (Fig. 1). As for baseline fasting blood glucose level, those patients in the lowest tertile (cutoff point 155 mg/dl [8.6 mmol/l]) had significantly lower cardiovascular mortality (9.3%) than those in the highest tertile (27.9%) (cutoff point 214 mg/dl [11.9 mmol/l]). The impact of metabolic control was independent of numerous known cardiovascular risk factors including urinary albumin excretion rate. Furthermore, cardiovascular mortality had no association with the treatment modality of diabetes. The main causes of deaths were coronary heart disease and stroke. Besides glycemic control, the other powerful predictors of cardiovascular mortality were age, ischemic ECG finding at baseline, smoking history, and elevated low-density lipoprotein triglycerides, which reflect typical abnormalities of lipoprotein metabolism in NIDDM (5). On the basis of these results, we hypothesized that the consequences of hyperglycemia could explain a large proportion of excessive cardiovascular mortality in NIDDM that is not attributable to conventional risk factors or lipoprotein abnormalities. Recently, Kuusisto et al. (6) confirmed the significance of glycemia in elderly Finnish NIDDM patients. In their study, the glycemic control predicted 3.5-year coronary mortality and nonfatal coronary events independent of known risk factors.

Hyperglycemia per se may enhance the progression of atherosclerosis, and it may also precipitate thrombus formation through several mechanisms. Furthermore, high blood glucose levels may induce changes in diabetic myocardium, allowing an additional explanation for its contribution to the excessive cardiovascular mortality in NIDDM (7). It has been suggested that glycation end products created from long-term hyperglycemia are a major contributor to late complications in diabetes (8). Interestingly, medial arterial calcification, a probable indicator of vascular damage, also predicted cardiovascular mortality in our study subjects (9). Keeping this in mind, the importance of metabolic control in most NIDDM patients should not be over-

looked. However, we do agree with Weir et al. (1) that dietary means and physical activity play a central role as the first line of therapy. Finally, the correction of known cardiovascular risk factors, including typical lipid abnormalities in NIDDM, may be as important as the correction of hyperglycemia when we are considering the long-term prognosis of NIDDM patients.

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References

1. Weir GC, Nathan DM, Singer DE: Standards of care for diabetes (Technical Review). *Diabetes Care* 17:1514–1522, 1994
2. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 19 (Suppl. 2):789–830, 1970
3. 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):1–81, 1982
4. U.K. Prospective Diabetes Study Group: UK prospective diabetes study (UKPDS) VIII: study design, progress and performance. *Diabetologia* 34:877–890, 1991
5. Uusitupa MIJ, Niskanen LK, Siitonen O, Voutilainen E, Pyörälä K: Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175–1184, 1993
6. Kuusisto J, Mykkänen L, Pyörälä K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
7. Uusitupa M, Pyörälä K, Laakso M: Metabolic control and macrovascular disease. In *International Textbook of Diabetes Mellitus*. Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, Eds. Chichester, U.K., Wiley, p. 1471–1485, 1992
8. Brownlee M: Glycation products and the pathogenesis of diabetic complications. *Diabetes Care* 15:1835–1843, 1992
9. Niskanen L, Siitonen O, Suhonen M, Uusitupa MI: Medial artery calcification predicts cardiovascular mortality in patients with NIDDM. *Diabetes Care* 17:1252–1256, 1994

Prevalence of IDDM In Adults in the Community

In a paper recently published in *Diabetes Care* (1), Harris and Robbins addressed the issue of prevalence of adult-onset insulin-dependent diabetes mellitus (IDDM) in the U.S. population. They found that 0.3% of the population 30–74 years old and 7.4% of all diabetic patients diagnosed at that age were individuals with IDDM. The study was based on the data from the Second National Health and Nutrition Examination Survey (2). The authors' conclusion was that adult-onset IDDM was uncommon. Given the limitations of the survey, they could not detect slowly progressive IDDM with gradual loss of β-cell function. It was suggested that a very large population base would be required to identify sufficient numbers of adult-onset IDDM cases. They also stated that for accurate diagnosis of IDDM, fasting or stimulated C-peptide should be determined.

In a recent issue of *Diabetes Care* (3), we published our experience with IDDM in adults in a community-based study (registered population = 9,573 adults ≥30 years of age) in Israel. In a study to determine the clinical characteristics of insulin-treated non-insulin-dependent diabetes and IDDM patients, we examined all known insulin-treated diabetic patients from three community clinics, regardless of age at onset of diabetes. Fasting plasma C-peptide was measured in all patients as a marker of β-cell function. A total of 588 diabetic patients were found; of the 100 insulin-treated patients, only 25% were insulinopenic (C-peptide <0.132 nmol/l). Thus, the prevalence of IDDM in the surveyed population of age 30 years or older was 0.25%, similar to that found by Harris and Robbins.

Our results differ in that in almost 64% of our IDDM patients, diabetes was diagnosed at the age of 20 or older. Of all the IDDM patients, 33% were first treated by either diet or oral agents, indicating that at least at the beginning of the disease their pancreases were able to produce insulin. From this subgroup of patients, 7 of the 14 patients diagnosed at ≥21 years of age started insulin therapy at least 1 year after the diagnosis; 4 of these patients started insulin 15.7 years after diagnosis of diabetes.

We conclude that, at least in Israel, slowly progressive adult-onset IDDM is not uncommon. It is possible that studies based upon age of diagnosis, relative body weight, and insulin treatment alone could underestimate the prevalence of IDDM among the adult population.

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