The Clinical Relevance of Fetal Hemoglobin in IDDM and NIDDM Patients

Recently published studies found elevated fetal hemoglobin (HbF) levels in insulin-dependent diabetes mellitus (IDDM) compared with nondiabetic subjects. The cutoff points for elevation were 0.5 (1,2) and 1% HbF (3) of total hemoglobin, respectively. However, values of HbF in nondiabetic adults range from 0 to 1.2%. To our knowledge, information is very limited in non-insulin-dependent diabetes mellitus (NIDDM) patients (3). Also, the association of HbF with metabolic control is discussed very controversially. One group found a weak but significant correlation between HbF and HbA_{1c} levels (2); two other groups did not (1,3). However, a delay in the fetal globin switch, with a consecutive elevation of HbF, was found in infants of diabetic mothers (4). Furthermore, in vitro and in vivo studies showed that various products like 5-azacytidine (5,10,11), hydroxyurea (6,9), and some butyrates (7,10–13) can induce γ-globin gene expression (8). So it was speculated that a state of ketoacidosis in poor metabolic control, which leads to an increase in β-hydroxybutyrate, is associated with a switch from β-chain to γ-chain expression in patients with diabetes (2). Moreover, it was suggested that this elevation could interfere with some standard methods for HbA_{1c} measurement.

For this reason, we investigated the clinical relevance of these observations in our diabetic patients. We measured HbA_{1c} and HbF levels with the standard method in our laboratory, high-performance liquid chromatography (Diamat, Bio-Rad), in 61 IDDM patients (median duration of diabetes, 7 years) and 89 NIDDM patients (median duration of diabetes, 11 years) and compared them with 38 nondiabetic control subjects. The median age in the control subjects was 76 years, in the IDDM patients it was 28 years, and in the NIDDM patients it was 69 years. The median HbA_{1c} values were: in the control subjects, 6.2% (interquartile range: 5.8/6.3%); in the IDDM patients, 8.2% (7.3/9.9%); and in the NIDDM patients, 8.0% (7.1/9.5%). The median HbF values for controls were 0.85% (0.5/1.1%) and for IDDM patients they were 0.5% (0.3/0.8%) compared with NIDDM patients who had a median HbF level of 0.5% (0.3/1.0%). No differences between control subjects and IDDM and NIDDM patients could be detected. Moreover, no association between HbF and actual blood glucose, duration of diabetes, sex, or age could be observed. Analysis of correlation showed no association between HbA_{1c} and HbF in diabetic patients or healthy subjects.

To elucidate the proposed influence of ketoacidosis on γ-chain expression, we measured HbF with radial immunodiffusion, a very sensitive method for determination of HbF, in 5 patients presenting with high HbA_{1c} values (median HbA_{1c}, 12.2%; 2 of them were newly diagnosed IDDM patients) and compared them with 5 NIDDM patients (median HbA_{1c}, 10.7%) and 5 nondiabetic control subjects (median HbA_{1c}, 5.0%). The following HbF values were observed: in IDDM patients: 0.0, 0.0, 0.0, 0.5, and 0.6%; in NIDDM patients: 0.0, 0.0, 0.0, 0.0, and 0.4%; and in nondiabetic control subjects: 0.0, 0.0, 0.0, 0.0, and 0.2%, respectively. Also with this method, we were not able to demonstrate increased HbF levels in patients with poor metabolic control or newly onset diabetes. These results could not underline the hypothesis of increased γ-chain expression as a result of increased HbA_{1c} levels, because no association between HbF and HbA_{1c} could be observed with this assay.

In summary, we could demonstrate neither any elevation of HbF levels in IDDM and NIDDM patients nor any associations between HbF levels and metabolic control (HbA_{1c}). On the basis of our findings, we conclude that elevation of HbF has no relevance in the routine of diabetes control in adult IDDM and NIDDM patients.

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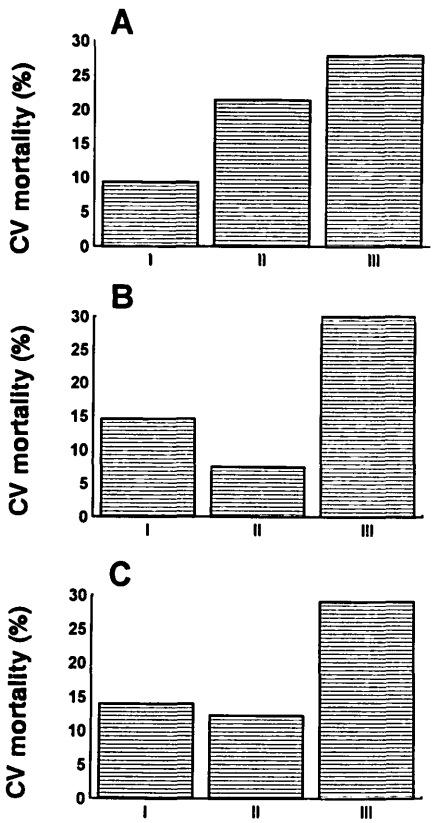

Figure 1—*Cardiovascular mortality in NIDDM patients in a 10-year follow-up from diagnosis according to the tertiles of fasting blood glucose at baseline (A) and plasma glucose (B) or HbA_{1c} (C) measured 5 years from diagnosis. Data based on Uusitupa et al. (5).*

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-