Interference of Elevated Fetal Hemoglobin on HbA_{1c} Measurements in Adult Type I Diabetic Patient

Measurements of HbA_{1c} are widely used to provide an index of average glucose control over the previous period of 8 wk (1). This routine analysis may lead to changes in diabetes treatment and improvement of metabolic control (2). An increase in fetal hemoglobin (HbF) levels has been reported in insulin-dependent (type I) diabetic patients with onset before 6 yr of age (3), suggesting a possible effect of insulin treatment on delaying transition from fetal to adult hemoglobin synthesis. Depending on the method used, HbF can falsely elevate the measured HbA_{1c} level (4). Here, we report the interference by elevated HbF in a 70-yr-old white type I diabetic woman.

Diabetes mellitus occurred in the patient at 35 yr of age and immediately required insulin therapy. Seven HbA_{1c} measurements made between 1984 and 1990 with cation-exchange microcolumn chromatography (Bio-Rad, Richmond, CA) indicated levels >14% (normal range 3.5–5.5%), whereas capillary and venous blood samples were <200 mg/dl. HbA_{1c} and HbF were determined by high-performance liquid chromatography (HPLC). With HPLC, HbF was found elevated at 8.8% (normal <0.5%). HbA_{1c} was at 8.3% with HPLC (normal range 4.3–6.1%) and 14.2% with microcolumn chromatography. Serum fructosamine (Hoffmann-La Roche, Basel) was also found increased at 315 μM (normal 180–285 μM). Total hemoglobin and erythrocyte indices were normal, and no mutant hemoglobins were individualized during electrophoresis.

In conclusion, increased HbF levels in adult patients with type I diabets mellitus may lead to misinterpretation of metabolic control. Methods of HbA_{1c} measurement in which HbF values do not interfere should be encouraged, especially in patients with excessive HbA_{1c} values obtained with ion-exchange chromatography. Although a genetic abnormality cannot be definitely excluded in our patient, this observation, if confirmed in a large number of adult patients, may suggest that some diabetic individuals present a late reactivation of HbF production.

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Lipoprotein(a) Levels in Black and White Children and Adolescents With IDDM

In their study of lipoprotein(a) levels in diabetic and control children, Levitsky et al. (1) reported the concentrations of low-density lipoprotein cholesterol (LDL-chol) and high-density lipoprotein cholesterol (HDL-chol). The METHODS section of the article does not describe the technique used for measuring or estimating LDL-chol. Levitsky et al. referred to a previous article (2) for the description of the determination of HDL-chol. However, no measurements of HDL-chol concentration were made in the article cited.

From the results provided (1; Table 2), I deduced that the Friedewald formula (3) was used to estimate the LDL-chol concentrations. For example, if we apply the Friedewald formula for their white diabetic group

$$4.21 - \frac{2.18}{5} - 1.33 = 2.44$$

we obtain the same result reported for LDL-chol. Unfortunately, the Friedewald formula must be adapted before it can be employed with measurements made in Système International (SI) units (4–9). The adaptation is necessary because the conversion factors from conventional to SI units for triglycerides and cholesterol are different. The concentration of triglycerides must be divided by 2.18 instead of 5. The correct mean concentrations of LDL-chol should be ~1.92 for the white control group, ~1.88 for the white diabetic group, ~2.13 for the black control group, and ~1.80 for the black diabetic group.

Because the mean triglyceride levels were not very different among the four groups, and thus the error was similar for each group, Levitsky et al.'s conclusion about an absence of difference in LDL-chol concentration between the groups is probably still valid.

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Reply

As Dr. Massé pointed out in his other letters on this matter (1–6), workers in the United States are prone to make post hoc mass conversions to mM after lipids are calculated in mg/dl. This is indeed the case in our studies; therefore there is no error in our low-density lipoprotein (LDL) values. Our LDL values differ from his predicted values because group means cannot be interpreted in this manner. In addition, a correction has been made for the lipoprotein(a) content of the LDL particle to give a more accurate estimated LDL cholesterol value.

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Successful Treatment of Unusual Case of Brittle Diabetes With Sulfated Beef Insulin

Brittle diabetes has been defined as episodes of hypoglycemia or hyperglycemia that, whatever their cause, constantly disrupt a patient's life (1). Recognizable causes (1,2) of brittle diabetes are *1*) errors in management by either the patient or medical personnel (including overinsulinization), *2*) intercurrent illnesses, *3*) psychological problems, and *4*) factors influencing the dynamics of insulin action. Although the latter includes insulin-binding antibodies, they have previously been implicated to cause brittle diabetes either by very high titers of insulin-binding antibodies leading to marked hyperglycemia (not hypoglycemia) and clinical insulin resistance (requirement of >200 U insulin/day) (2) or their inability to buffer the egress of subcutaneously injected insulin into the blood stream (3). This report describes a woman on conventional doses of insulin in whom high titers of insulin-binding antibodies caused brittle diabetes (both hypoglycemia and hyperglycemia). Her brittle diabetes was successfully treated by substituting sulfated beef insulin.

A 25-yr-old female insulin-dependent (type I) diabetic patient with diabetes since age 1.5 yr was referred for help with erratic control of her diabetes. Although taking beef ultralente (10 U twice a day) and beef or pork regular insulin before each meal, the patient experienced erratic swings in her blood glucose measured by self-monitoring of blood glucose ≥4 times/day. Many glucose values would be >17 mM regardless of the time of eating or insulin administration. Alternatively, the patient experienced frequent (almost daily) episodes of hypoglycemia, either during the day many hours after taking insulin and/or in the middle of the night. Various human, pork, or beef (both standard and purified) insulin preparations did not seem to help either of these problems.

When first observed, the patient was taking 22 U beef ultralente insulin and 10 U human regular insulin before supper. She ate only at supper to avoid hypoglycemia that occurred at varying unpredictable times during the day if she took regular insulin in the morning. On this regimen, her blood glucose levels usually ranged near 17 mM on awakening and gradually fell during the day. However, she had lost 22 lb, felt generally tired and depressed, and if she ate during the day, would often experience nausea associated with marked hyperglycemia. This approach limited her hypoglycemic episodes to several times a week, occurring mostly in the early overnight hours.

Workup revealed elevated insulin-binding antibodies at 18.5 mU/ml (values >10 mU/ml are assocated with clinical insulin resistance) and a delayed peak response to human insulin given either subcutaneously (9 h) or intravenously (105 min). She was started on sulfated beef regular insulin before each meal and continued to take 22 U beef ultralente insulin before supper.

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