Plasma Albumin Concentration Is a Predictor of HbA_{1c} Among Type 2 Diabetic Patients, Independently of Fasting Plasma Glucose and Fructosamine

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The importance of the HbA_{1c} assay for evaluation of long-term glucose control is well established (1–3). However, data for HbA_{1c} and average plasma glucose, in spite of their strong correlation (4–7), show considerable scatter: for a given HbA_{1c} level, average blood glucose generally varies by ~5 mmol/l (7). This hampers interpretation of the HbA_{1c} values of individual patients.

In this study of a large sample of type 2 diabetic patients, we investigated the possibility of statistical association between HbA_{1c} concentration and levels of the main glycatable circulating proteins other than hemoglobin (albumin and globulins).

RESEARCH DESIGN AND METHODS

— The diabetes outpatient clinics of our center are attended by most local diabetic patients requiring insulin or oral antidiabetics. We enrolled 4,158 diabetic patients who, in this complex in the years 1998–2003, were prescribed insulin or oral antidiabetics for type 2 diabetes diagnosed using American Diabetes Association criteria (8) and who, for glucose control monitoring, underwent regular determination of fasting HbA_{1c} accompanied, for research purposes, by determination of total protein concentration, albumin, globulins, creatinine, hemoglobin, fructosamine, and glucose; age, sex, duration of diabetes, and type of therapy were also recorded. For this report, we considered for each patient the first such profile obtained within the study period. Urinary albumin excretion (normal range 0–25 mg/24 h) was determined within 6 months of the blood profile considered in this report for 1,840 patients (subgroup UAE).

HbA_{1c} was determined with the high-performance liquid chromatography DCCT (Diabetes Control and Complications Trial)-aligned method, albumin by the bromcresol purple method, and fructosamine by the nitroblue tetrazolium method. The normal ranges in a group of 197 healthy subjects were as follows: HbA_{1c} 3.8–5.7%, albumin 35–53 g/l, and fructosamine 208–286 μmol/l. All analyses were performed in the clinical biochemistry laboratory of our center.

Subjects were classified according to their albumin concentrations (by quintiles), and the mean log (HbA_{1c}) values of these "albumin-level groups" were compared by ANOVA. Student's *t* tests and Mann-Whitney tests were used when appropriate. Stepwise multiple regression was employed to evaluate the association between HbA_{1c} and the possible predictors albumin, fructosamine, globulins, creatinine, and fasting plasma glucose (FPG).

RESULTS

— Of the total 4,158 patients, 44.6% showed good apparent glucose control (HbA_{1c} <7%), 18.6% fair control (7% ≤ HbA_{1c} ≤ 8%), and 36.8% poor control (HbA_{1c} >8%).

Figure 1 shows the variation of HbA_{1c}, fructosamine, and FPG with albumin level. HbA_{1c} differed significantly among the albumin-level groups ($P < 0.001$), decreasing with increasing albumin level. Among patients with albumin levels lower than the first quintile of the albumin concentration distribution, the proportion apparently showing poor control (HbA_{1c} >8%) was 51.9%, 2.3 times larger than in the top albumin-level group (22.4%). There were no statistically significant differences among the albumin-level groups with regards to fructosamine concentration or among the top four albumin-level groups with regards to FPG.

When patients were divided in subgroups defined by hemoglobin concentration (> or ≤123 g/l for women, > or ≤140 g/l for men) or creatinine level (> or ≤115 μmol/l), then, within each subgroup, HbA_{1c} was lower among patients with albumin concentrations higher than the mean for healthy individuals (45 g/l) than among those with lower albumin concentrations ($P = 0.042$ for the subgroup with creatinine >115 μmol/l, $P < 0.001$ otherwise). The same difference in HbA_{1c} between high- and low-albumin groups was observed when subgroup UAE was divided in subgroups with uri-

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Abbreviations: FPG, fasting plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

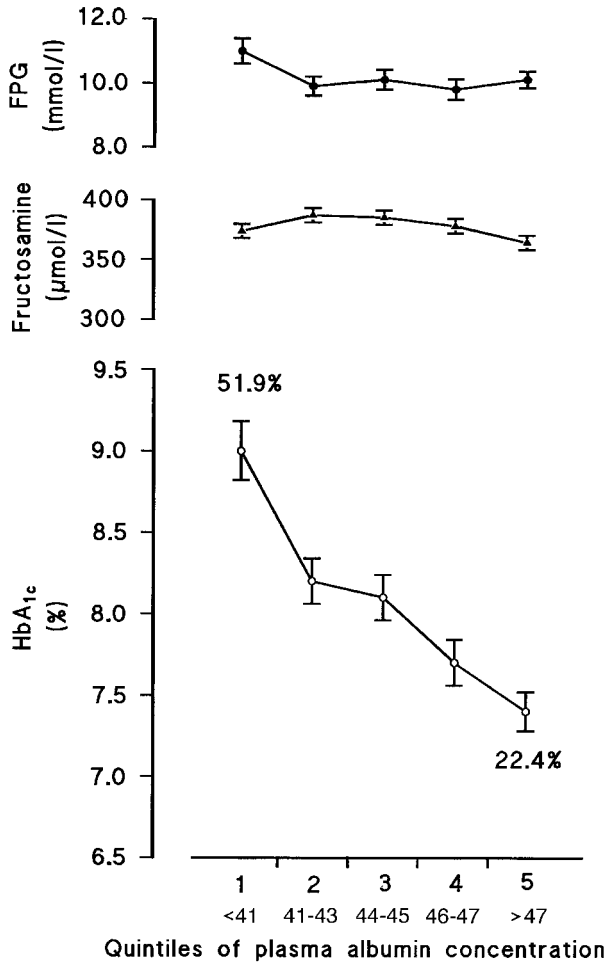

Figure 1—*Mean values of FPG, fructosamine, and HbA_{1c} in type 2 diabetic patient groups defined by serum albumin concentration (the limits of each group, the quintiles of the albumin concentration distribution, are shown in g/l). Verticle lines indicate 1.96 × SEs. Appended percentages are the percentages of the lowest and highest albumin groups with poor glucose control according to the standard criterion HbA_{1c} >8%.*

nary albumin > or ≤25 mg/24 h (P = 0.006 and $P < 0.001$, respectively).

Stepwise multiple regression showed significant correlation between HbA_{1c} and albumin, fructosamine, globulins, and FPG ($P = 0.007$ for globulins, $P <$ 0.001 for the others, $R^2 = 0.602$). As was expected, the most influential predictors were FPG and fructosamine, but albumin concentration ($r = -0.325$) accounted for 16.4% of the variance in HbA_{1c} among the 4,158 patients (compared with 23.4% for fructosamine).

CONCLUSIONS — In this study of type 2 diabetic patients, there was significant negative correlation between HbA_{1c} and serum albumin after adjustment of HbA_{1c} for fructosamine, FPG, and globulins ($P < 0.001$).

The high HbA_{1c} values of low-albumin patients and low HbA_{1c} values of high-albumin patients were not essentially due to alteration of erythrocyte life span by iron deficiency or hemolytic anemia, respectively (9), because the negative association between HbA_{1c} and albumin persisted among both anemic and nonanemic patients when these two groups were examined separately. Nor was the observed association due to poorly controlled diabetic patients having elevated vascular and renal permeability to albumin because it also persisted when patients with serum creatinine >115 μmol/l or urinary albumin >25 mg/24 h were excluded from the analysis. The possibility (10–15) that albumin levels might have been significantly affected by poor glucose control (duly reflected by high HbA_{1c}) is also unlikely in view of the lack of correlation between albumin and either FPG or fructosamine (which also weighs against the possibility of some unknown underlying variable with opposite effects on average glycemia and albumin). Moreover, the steady fall in HbA_{1c} concentration over the whole range of albumin concentrations suggests a physiological rather than a pathological relationship.

HbA_{1c}, of course, increases with FPG and fructosamine. Its falling with increasing albumin therefore implies that attainment of any given HbA_{1c} level requires a lower glucose concentration in patients with low albumin levels than in patients with higher albumin levels and, hence, that the glucose control of patients with albumin levels significantly above or below average may not be properly reflected by the standard classification in terms of HbA_{1c} measurements alone. For such patients, there may be a discrepancy between the degree of control suggested by HbA_{1c} measurements and the evolution of diabetes complications.

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