Hyperglycemia, Recognized and Unrecognized, As A Risk Factor for Stroke and Transient Ischemic Attacks
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SUMMARY Glycosylated hemoglobin concentration (GHb), which is considered an indication of glycemia over the preceding several months, was examined in 50 patients hospitalized for recent stroke or transient ischemic attacks (TIA), and compared to that in several reference populations. Patients with stroke or TIA had GHb (mean %A1 ± SD, 10.2 ± 2.3) higher than in hospital controls without cerebrovascular disease (8.3 ± 0.9, p < 0.005), and equivalent to values for ambulatory diabetic patients treated with diet or diet plus oral agents (9.5 ± 2.4) or with insulin (10.7 ± 2.9). Twenty percent (10/50) of the stroke/TIA group were previously known to have abnormal glucose tolerance or diabetes; when this subgroup was excluded, there remained 42% of the original group (21/50) with abnormal GHb (> 10% A1) not previously known to have hyperglycemia, and the difference between GHb values for the stroke/TIA patients not known to have glycemic abnormality and for the hospital control group remained significant (p < 0.005). Sixty-two percent of stroke/TIA patients (31/50) were under treatment for glycemic abnormality, or had high GHb, or both. The high prevalence of elevated GHb in this population could not be attributed to a relationship to age, sex, smoking history, hypercholesterolemia, or hypertension. We conclude that hyperglycemia commonly precedes stroke and TIA, is usually unrecognized, and has been under-appreciated as a risk factor for cerebrovascular disease.

EPIDEMIOLOGIC DATA SHOW an increased risk of stroke associated with hyperglycemia.1-3 For example, in the Framingham Study1 the incidence of thrombotic stroke was 2.5 times higher in diabetic men and 3.6 times higher in diabetic women than in those without diabetes. However, the prevalence of hyperglycemia preceding cerebrovascular events is poorly defined, so the relative importance of hyperglycemia as a risk factor is uncertain. In particular, the importance of mild hyperglycemia, as opposed to symptomatic diabetes, as a precursor of stroke is unclear. Measurement of glycosylated hemoglobin (GHb), which reflects glycemic levels for the preceding 1–3 months,4 in patients with recent stroke or transient ischemic attacks (TIA) has allowed us to address this question.

Patients and Methods

Patients
Fifty patients hospitalized on the Neurology service because of recent stroke or TIA were studied. Blood samples for GHb assay were collected within 7 days after admission. Patients with stroke were all hospitalized within several days after the event, so the interval between stroke and GHb sample collection was never more than 10 days, and usually less than a week. Hospital records were subsequently reviewed to verify the diagnosis and record admission blood pressure and serum cholesterol, history of smoking, hypertension or carbohydrate intolerance, and use of antihypertensive drugs. Patients with hemorrhagic stroke, tumors, and other disorders initially simulating thrombotic stroke or TIA were excluded, as were patients in whom the diagnosis was considered in doubt. Blood samples for GHb were also collected from four reference populations: (1) well ambulatory persons without known major illness, including diabetes mellitus and cerebrovascular disease, recruited from laboratory staff, a Dermatology clinic, and persons entering a fitness program (64 subjects; 34 men, 30 women; mean age ± SD, 37 ± 15 years); (2) patients hospitalized on the Neurology service for disorders other than cerebrovascular disease, excluding patients with known previous stroke but not excluding those with diabetes or glucose intolerance (30 subjects; 19 men, 11 women; age 54 ± 18 years); (3) diabetic outpatients treated with diet alone or diet plus oral hypoglycemic drugs (27 subjects; 6 men, 21 women; age 62 ± 11 years); and (4) diabetic outpatients taking insulin (71 subjects; 23 men, 48 women; age 56 ± 15 years).

Glycosylated Hemoglobin Assay
Glycosylated hemoglobin was determined by a modification of the Fluckiger-Winterhalter method.5 Five ml blood samples were collected in tubes containing 7.5 mg EDTA. Red cell hemolysates were prepared by hemolyzing the packed, washed red cells with 2.5 ml distilled water and freeze/thawing once. Membranes were spun down and discarded. One half ml of 0.3N oxalic acid was added to 1.0 ml lysate and incubated 1 hour at 100°C. After cooling, 0.5 ml of 40% TCA was added to the tubes and the precipitate spun down. Six-tenths ml of supernatant was incubated with 0.3 ml of 0.05 N 2-thiobarbituric acid at 40°C for 40 min. OD was read at 443 nm. Comparison of results by this method yielded excellent correlation (r = 0.90) with those by a standard column chromatographic method6 for separation of "fast" hemoglobins, allowing expression of glycosylated hemoglobin as percent

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GHb values for individual subjects in the stroke/TIA population and four reference populations. Horizontal bars represent means ± 1 SD. Normal range for GHb is 4–10% $A_1$. Means ± SD for the several groups are: ambulatory controls 7.7 ± 1.5, hospital controls 8.3 ± 0.9, stroke/TIA patients 10.2 ± 2.3, diet/oral diabetics 9.3 ± 2.4, insulin diabetics 10.7 ± 2.9. Comparison of the groups by analysis of variance, using a pooled error term, shows significant differences between the stroke/TIA group and both the ambulatory control ($p < 0.001$) and hospital control ($p < 0.005$) groups, and no significant differences between the stroke/TIA group and the diabetic groups.

A$_1$. Our normal range for persons with proven normal glucose tolerance (2 hr. plasma glucose < 140 mg/dl) is 4–10% $A_1$ (mean ± SD, 7.0 ± 1.5).

Results

Stroke versus transient ischemic attack

Twenty-eight (20 men, 8 women) of the study patients had stroke while 22 (13 men, 9 women) had TIA. The two groups were very similar. Mean age ± SD was 63 ± 13 for stroke and 63 ± 8 for TIA. Of stroke patients 16 of 28 were treated for hypertension, and of TIA patients 14 of 22. Mean diastolic blood pressures on admission were 88 ± 11 and 88 ± 12 mmHg, respectively. Of stroke patients 18 of 28 had smoked at least 15 pack-years, and of TIA patients 12 of 22. Serum cholesterol was over 225 mg/dl in 4 of 24 stroke patients, and 5 of 21 TIA patients. Glycosylated hemoglobin was 10.5 ± 2.2 in stroke and 9.8 ± 2.3 in TIA patients; this difference was not statistically significant. For comparison with the reference groups, stroke and TIA patients were considered a single group.

GHb in Stroke/TIA and Reference Groups

The figure compares GHb values for the stroke/TIA group, well ambulatory controls, hospitalized controls, and diabetic outpatients. Mean GHb ± SD for the stroke/TIA patients was 10.2 ± 2.3, which was higher than for ambulatory controls without known hyperglycemia (7.7 ± 1.5, $p < 0.001$) and hospitalized controls without known cerebrovascular disease (8.3 ± 0.9, $p < 0.005$), and similar to the values for diet/oral (9.5 ± 2.4) and insulin-treated (10.7 ± 2.9) diabetic outpatients. Because of selection, none of the ambulatory controls was known to have abnormal carbohydrate tolerance. Nevertheless, 12% (8/64) had GHb values over 10% $A_1$, which was 2 SD above the normal control mean. Patients with abnormal glucose tolerance were not excluded from the hospital control group, but none with known glucose intolerance appeared in the group collected. Of this group 7% (2/30) had GHb over 10% $A_1$. Corresponding figures for the diabetic groups were 41% (11/27) for diet/oral patients and 54% (38/71) for insulin-treated patients. Fifty-six % (28/50) of the stroke/TIA patients, of whom only 20% (10/50) were previously known to have diabetes or impaired glucose tolerance, had GHb over 10% $A_1$. Of the 10 persons with known glycemic abnormality, four were taking insulin, three took oral agents, and three were treated with diet alone. Three had GHb values below 10% $A_1$, and seven values above 10% $A_1$. When these 10 persons were excluded from the stroke/TIA population, the mean GHb decreased only slightly (from 10.2 ± 2.3 to 9.9 ± 1.8% $A_1$), and 21 (42% of the original 50) had GHb over 10% $A_1$. Mean GHb for the 40 stroke/TIA patients without previously known glycemic abnormality (9.9 ± 1.8% $A_1$) remained significantly higher ($p < 0.005$) than that for the hospital control group (8.3 ± 0.9% $A_1$) when compared by analysis of variance using a pooled error term. Finally, adding to the 28 persons with high GHb the three with GHb under 10% who were under treatment for diabetes, 62% of stroke/TIA patients (31/50) had evidence of glycemic abnormality.

Effect of age and sex on GHb in Stroke/TIA and Reference Groups

The relationship between age and GHb in the same five groups is shown in table 1. No definite effect of age was apparent in any group, when subgroups of persons under 50 years of age, 50 to 64, and over 64 were compared. In addition, linear regression analysis of data for all persons 40 years of age or older in all five groups yielded no significant correlations. When the age 40–64 and over 64 subgroups of hospital control and stroke/TIA populations were compared the differences observed when the whole groups were compared persisted. Mean GHb in stroke/TIA patients was clear-
ly higher than in hospital controls in both middle-aged ($p < 0.02$) and elderly ($p < 0.01$) subgroups. Similarly, no definite effect of sex on GHb was apparent. Mean ages were the same for men and women in the stroke/TIA group, and in all reference subgroups except the diet/oral agent-treated diabetic group, in which men were older than women (73 ± 8 vs 58 ± 9 years, $p < 0.01$). In the stroke/TIA group women had slightly higher GHb (10.9 ± 3.1) than men (9.8 ± 1.6), the difference approaching but not achieving statistical significance ($p < 0.1$). Regression analysis showed no effect of sex on the relationship between age and GHb.

Comparison of Patients with High GHb and Those With Normal GHb in the Stroke/TIA Population

Table 2 shows several clinical features of these two subgroups of the stroke/TIA population. Sex ratios were equivalent, and patients with high GHb values were of approximately the same age as those with normal GHb. While systolic blood pressures were similar, diastolic pressure on hospital admission were higher in the normal GHb subgroup ($p < 0.01$). Equivalent numbers were taking anti-hypertensive drug treatment in the two subgroups, and no differences in smoking history or prevalence of hypercholesterolemia were evident.

Stroke/TIA Patients Without Hypertension or High GHb

Both hypertension and hyperglycemia were common in the stroke/TIA population. Thirty percent (15/50) had diastolic pressures over 94 mmHg on admission, 60% (30/50) were taking antihypertensive drugs, and 72% (36/50) had either one or the other of these two indications of hypertensive disease. Similarly, 56% (28/50) had GHb over 10% $A_1$, 20% (10/50) were under drug or diet treatment for hyperglycemia, and 62% (31/50) had either one or the other of these indications of long-term glycemic abnormality. The great majority of this population (90%, 45/50) had either evidence of hypertensive disease or of glycemic abnormality. Forty-four percent (22/50) had both. Only 10% (5/50) had neither. The ages of the five patients with evidence of neither hypertension nor hyperglycemia were 58, 71, 72, 80, and 92.

**Discussion**

Evidence suggesting a greatly increased prevalence of glucose intolerance among persons with cerebrovascular disease has long been available.\(^7\) Jakobsen\(^1\) studied patients with cerebrovascular disease but without overt diabetes, finding 21% with abnormal glucose tolerance (Fajans and Conn criteria) and 50% with abnormal Prednisone-augmented glucose tolerance tests. Gertler and his colleagues\(^8, 9\) in a population with thrombotic stroke, found overt diabetes in 30% and abnormal glucose tolerance (Fajans and Conn criteria) in 59% of the rest. They concluded that over 70% of their stroke population had overt or covert diabetes mellitus. However striking, these figures have attracted little attention. The difficulties inherent in interpreting plasma glucose behavior in ill persons may in part account for this. Glucose intolerance or even fasting hyperglycemia may follow an acute vascular event, and ensuing physical inactivity and poor food intake may lead to continued glucose intolerance. Thus, glucose intolerance in a stroke patient may or may not reflect glycemia prior to the event.

Measurement of GHb rather than glucose as an indicator of prior glycemia offers a new perspective. The rate of non-enzymic glycosylation of hemoglobin is believed to depend largely or solely on plasma glucose concentration.\(^10\) Since the erythrocyte survives about 3 months, GHb measurements in patients with normal erythrocyte survival reflect plasma glucose concentrations during that period. The colorimetric assay for GHb has advantages over column methods for separation of “fast” hemoglobins. Column separations are confounded by variant hemoglobins, while the colorimetric assay for GHb has advantages over column methods for separation of “fast” hemoglobins. Column separations are confounded by variant hemoglobins, while the colorimetric assay for GHb has advantages over column methods for separation of “fast” hemoglobins.
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was, if anything, relatively lacking in stroke/TIA patients with high GHb. This negative relation between GHb and hypertension suggests the two operate as separate risk factors. The scarcity of patients with stroke or TIA who had evidence of neither hypertension nor hyperglycemia strengthens the impression that hyperglycemia and hypertension are separate, leading risk factors for cerebrovascular disease. Only one patient of 38 under 70 years of age in this study had no evidence of either hyperglycemia or hypertension.

These findings pose several questions. What mechanisms might link mild as well as severe hyperglycemia to cerebrovascular injury? Should asymptomatic persons without diabetes but with slightly elevated GHb (12% of our well ambulatory group) be considered at risk, as are persons with mild diastolic hypertension? If so, will treatment designed to lower plasma glucose after this risk? Because of the large numbers of persons involved, and the high morbidity and mortality of the disorder, these questions deserve attention.

Association with other risk factors might in theory account for the high prevalence of high GHb in the stroke/TIA population. However, no excess of smoking history or hypercholesterolemia was associated with high GHb in the study population. Hypertension method is not.11 The color method, unlike column procedures, is specific for the stable (Ketoamine) component of hemoglobin-associated carbohydrate,12 13 and is therefore little affected by recent glycemic excursions. Even if a cerebrovascular event resulted in marked and sustained elevation of plasma glucose in a previously normoglycemic person, a phenomenon not recognized in any of our study group, little effect on GHb measured by this method would ensue in the first week or two. Another attractive feature of GHb assay is that it presumably reflects generalized tissue effects of hyperglycemia. Since non-enzymic glycosylation occurs in many proteins,14 elevation of GHb suggests similarly increased glycosylation in other tissues, possibly with functional consequences.

Using this method, we found clearly higher GHb in our stroke/TIA population than in a stroke-free hospital control group. This comparison is the crucial one in these studies, since whatever small effect recent stress-induced hyperglycemia might have on GHb in the stroke/TIA group should also occur in the hospital control group with other illnesses. While 20% of the stroke/TIA population had known abnormality of glucose tolerance, 56% had high GHb values. Including both those with high GHb and those with treated diabetes and normal GHb, 62% of our stroke/TIA patients had evidence of glycemic abnormality. This proportion roughly matches the 70% of Gertler's stroke group with overt diabetes or abnormal glucose tolerance tests.8,9 Forty-two percent of our stroke/TIA population had high GHb without previously known glycemic abnormality. This figure is bracketed by the 21% and 50% of 'non-diabetic' patients with cerebrovascular disease showing abnormal glucose tolerance by standard and Prednisone-augmented glucose tolerance tests reported by Jakobsen.7 Thus our present findings demonstrate, using a new method little affected by recent illness, a high prevalence of glycemic abnormalities among patients with cerebrovascular disease.

Sixty-eight percent (21/30) of our stroke/TIA patients with high GHb, representing 42% (21/50) of the whole stroke/TIA population, had no prior knowledge of hyperglycemia. The hyperglycemia apparently present in these patients may have been overlooked in some cases due to high renal threshold, lack of contact with medical care, or inattention to symptoms. However, most patients seem likely to have had only mildly abnormal plasma glucose, with patterns consistent with the designation Impaired Glucose Tolerance, rather than Diabetes Mellitus. Some studies of coronary vascular disease suggest that relatively modest elevations of glucose confer increased coronary risk.16,17 Perhaps this is true for cerebrovascular disease as well.

Association with other risk factors might in theory account for the high prevalence of high GHb in the stroke/TIA population. However, no excess of smoking history or hypercholesterolemia was associated with high GHb in the study population. Hypertension

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