Utility of HbA_{1c} Levels for Diabetes Case Finding in Hospitalized Patients With Hyperglycemia

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OBJECTIVE — We evaluated the role of a single measurement of HbA_{1c} in a diabetes case finding in hospitalized patients with random hyperglycemia at admission.

RESEARCH DESIGN AND METHODS — From 20 March to 31 July 2000, 508 patients admitted through the emergency department of one hospital were tested for random hyperglycemia (plasma glucose [PG] >125 mg/dl). Consenting patients with hyperglycemia (without preexisting diabetes or on corticosteroids) underwent testing for HbA_{1c} levels, two fasting PG levels, and an outpatient oral glucose tolerance test (OGTT) if necessary.

RESULTS — Of the patients, 50 (9.8%) met the inclusion criteria. Of these, 70% ($n = 35$) completed the study, and 60% ($n = 21$) were diagnosed with diabetes. Patients with diabetes had higher HbA_{1c} levels than subjects without diabetes (6.8 ± 0.4 vs. 5.3 ± 0.1%, $P = 0.002$). An HbA_{1c} level >6.0% was 100% specific (14/14) and 57% sensitive (12/21) for the diagnosis of diabetes. When a lower cutoff value of HbA_{1c} at 5.2% was used, specificity was 50% (10/21) and sensitivity was 100% (7/14).

CONCLUSIONS — In acutely ill patients with random hyperglycemia at hospital admission, an HbA_{1c} >6.0% reliably diagnoses diabetes, and an HbA_{1c} level <5.2% reliably excludes it (paralleling the operating characteristics of the standard fasting glucose measurements); however, the rapidity of the HbA_{1c} level can be useful for diabetes case finding and treatment initiation early in the hospital course.

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During the past decade, the prevalence of diabetes in the general population has risen from 4.9% in 1990 to 6.5% in 1998, making it an important clinical and public health concern in the U.S. (1). According to recent estimates, there are ~16 million people with diabetes in the U.S. and nearly 5.4 million with undiagnosed diabetes (2), many of whom will have the disease for 9–12 years before clinical diagnosis (3). Hospitalization may be a missed opportunity to discover these previously undiagnosed cases of diabetes, where early detection of diabetes can lead to tighter control of blood glucose levels and a reduction in the severity of diabetes-related complications in the long term (4,5), as well as a reduction in morbidity and mortality in critically ill inpatients in the short term (6). Yet, an optimal inpatient case finding method for the early diagnosis of diabetes has not been devised.

Patients presenting to the hospital with an acute illness and found to be hyperglycemic on admission can have either stress-related hyperglycemia (7) or unrecognized impairment of glucose tolerance, including frank diabetes. Although a sizable proportion of this population will truly have diabetes, with prevalence estimates from 7 to 63% (8–11), there is at present no quick and accurate method for distinguishing between these two conditions. The oral glucose tolerance test (OGTT) is impractical because of dietary and cost constraints, it is less convenient and acceptable to patients, and it may even be contraindicated in acutely ill patients. The fasting plasma glucose (PG) test, on the other hand, would require the coordination of at least two morning fasting levels.

HbA_{1c} level is considered an important monitoring tool in treating patients with diabetes, but it is not currently recommended for screening or for the diagnosis of diabetes. Yet, HbA_{1c} level reflects the average PG to which the hemoglobin is exposed during the erythrocyte's life span of ~90 days and may be less influenced by the acute stress of illness. Although the utility of HbA_{1c} levels for diagnosis and screening of diabetes has been studied in the general population, its role in differentiating patients with true diabetes from those with random stress-induced hyperglycemia in the hospital has not been previously investigated. The purpose of this study is to evaluate the utility of the HbA_{1c} level as a diabetes case-finding tool in the inpatient setting.

RESEARCH DESIGN AND METHODS

Subjects

After obtaining approval from the Institutional Review Board of Griffin Hospital in Derby, Connecticut (a 160-bed acute care community hospital affiliate of the Yale University School of Medicine), a pro-

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Abbreviations: ADA, American Diabetes Association; OGTT, oral glucose tolerance test; PG, plasma glucose.

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

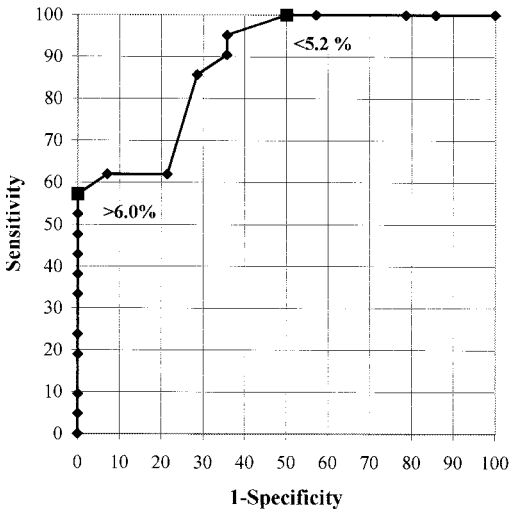

Figure 1—*Receiver operating characteristic curve for HbA_{1c} levels to diagnose diabetes in patients with random hyperglycemia (>125 mg/dl) at admission. HbA_{1c} values are expressed as the percentage of hemoglobin that is glycosylated.*

spective cohort study was conducted for all adult medical patients (aged >17 years) admitted to the hospital from 20 March to 31 July 2000. Subjects with a random PG >125 mg/dl; not on corticosteroids, hypoglycemic medications, or a diabetic diet; and not previously diagnosed with diabetes were eligible for study inclusion. Patients were further excluded for an inability or unwillingness to provide signed informed consent or to undergo further testing for HbA_{1c} level, fasting PG, or 2-h oral glucose tolerance, if required. Only patients who completed the entire study were included in the final analysis.

Protocol/design

Subjects who satisfied inclusion criteria and signed informed consent had HbA_{1c} levels added onto the admission blood sample. They subsequently had inpatient fasting PG tested on two separate occasions when they were medically stable (defined as afebrile, on a regular diet, and without intravenous fluids). If the fasting PG on both occasions was >125 mg/dl, a diagnosis of diabetes was established and no further testing was conducted. For those subjects in whom a diagnosis of diabetes could not be established based on two inpatient elevated fasting PG values, a 2-h OGTT was done after discharge from the hospital. As per current World Health Organization (12) and American Diabetes Association criteria (ADA) (13), diabetes was diagnosed if the 2-h PG value (after a 75-g oral glucose load) was >200 mg/dl.

Laboratory testing

Fresh anticoagulated blood (10 ml) was used to measure HbA_{1c} percentage. Blood was kept refrigerated until analyzed. The first half of the patients had their blood sent to the Mayo Medical Laboratory (Rochester, MN), whereas the second half had their blood analyzed in the Griffin Hospital laboratory (which is certified by the College of American Pathologists). In both cases, HbA_{1c} was quantitatively measured by an Abbott IMX Glycated Hemoglobin Assay (Abbott Laboratories, Diagnostics Division, Abbott Park, IL) that used boronate affinity binding assays to generate percent HbA_{1c} values (normal range 4.0–6.4%). These results were not available to the study investigators or the primary care providers during the hospitalization.

Statistical analysis

All data were analyzed using SAS (Statistical Analysis Software version 8.1; SAS Institute, Cary, NC), with values expressed as means ± SE. An initial power study (based on $\alpha = 0.05$, $\beta = 0.2$, and an anticipation that 50% of previously undiagnosed people with diabetes and 10% of normal individuals would have a HbA_{1c} >2 SDs above the mean) demonstrated a need for at least 14 patients in each group. Continuous variables were analyzed using the Student's *t* test, proportional outcomes were analyzed using the χ^2 statistic, and linear regression analysis was used to compare HbA_{1c} and fasting PG levels. The α was two-tailed and set at 0.05.

RESULTS — A total of 508 consecutive patients admitted through the Griffin Hospital Emergency Department were screened during the 4-month study period. Of these patients, 50 (9.8%) had an admission PG value >125 mg/dl and met all the inclusion criteria. There were 35 patients (70%) who eventually completed the study (8 refused to participate at admission, and 7 dropped out during the study). Diabetes was confirmed in 60% (21/35) of this population using criteria developed by ADA (14).

The sample population was 60% female and 94% white and ranged in age from 26 to 99 years of age with a wide range of admitting diagnoses. Those patients refusing to participate did not significantly differ from those participating with regard to age, sex distribution, or random glucose level. Random admitting PG levels ranged from 126 to 422 mg/dl. Seven subjects had HbA_{1c} levels <5.2%, 14 had HbA_{1c} levels >5.2% and <6.0%, and 14 subjects had HbA_{1c} levels >6.0%. There were no significant age, sex, or admitting diagnosis differences between the diabetes and nondiabetes groups. Patients with diabetes had significantly higher HbA_{1c} levels than subjects without diabetes (6.8 ± 0.4 vs. 5.3 ± 0.1%, $P = 0.002$).

The choice of a reasonable HbA_{1c} cutoff level was based on a receiver operating characteristic curve that balanced sensitivity and specificity for various levels of HbA_{1c} (Fig. 1). An HbA_{1c} value >6.0% was 100% (14/14) specific for the diagnosis of diabetes, with a sensitivity of 57% (12/21). The positive predictive value for this level was 100% (12/12) for diabetes. When an HbA_{1c} value >5.2% was used, the sensitivity was 100% (21/21) at the expense of a lower specificity of 50% (7/14), but it did have a negative predictive value of 100% (7/7).

Although HbA_{1c} levels generally represent prehospitalization levels of glycemia, they were well correlated with the average fasting PG levels obtained as an inpatient ($r^2 = 0.64$, $P < 0.001$) and were significantly correlated with the admission random PG level ($r^2 = 0.54$, $P < 0.001$).

CONCLUSIONS — To our knowledge, this is the first study reporting on the role of HbA_{1c} level for diabetes case finding in hospitalized patients with hyperglycemia in which an HbA_{1c} cutoff value of >6.0% has a specificity of 100%

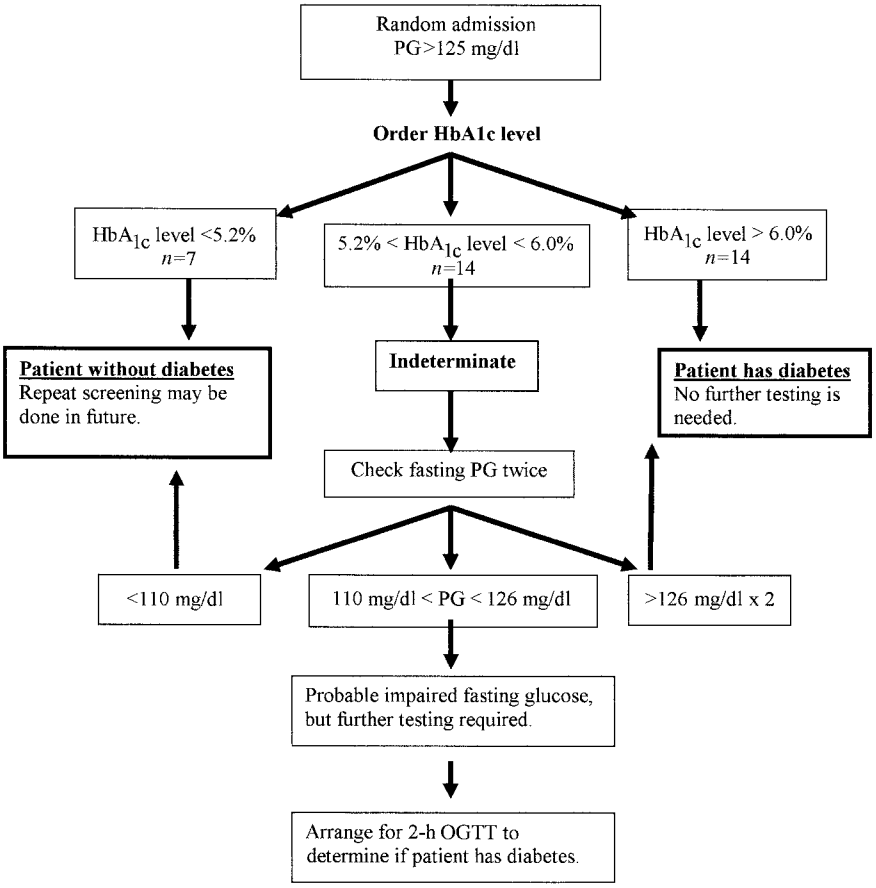

Figure 2—*Clinical decision algorithm for admitted medical patients with random hyperglycemia. The HbA$_{1c}$ level is used as an initial screening test, with indeterminant levels (5.3–6.0%) undergoing typical diabetes screening through fasting PG levels and possible 2-h OGTT.*

to detect diabetes in patients on admission. This situation may provide a golden opportunity to locate, educate, and begin treating the large number of undiagnosed patients with diabetes.

HbA$_{1c}$ and diabetes

Currently, the ADA recommends screening adults over age 45 years for diabetes with a fasting PG test and an OGTT, if needed (13). However, in the hospitalized patient, the potential presence of stress-induced hyperglycemia makes the traditional diagnosis of diabetes inaccurate and difficult to obtain in the inpatient setting (7). The HbA$_{1c}$ level, however, does not require fasting, necessitates fewer blood draws, reflects glucose metabolism over several weeks, and can be obtained at admission rather than at the minimum of 3 days required for traditional methods (two fasting glucose levels and a possible OGTT).

Published literature is split on the role of HbA$_{1c}$ levels in screening for diabetes, with some recommendations against it in the general population (14,15). Other literature has advocated its use, but in selected high-risk populations (16,17). Nevertheless, HbA$_{1c}$ levels have been shown to be highly correlated with fasting PG (15,18) and have become more standardized since 1996 because of the implementation of the National Glycohemoglobin Standardization Program (19).

The HbA$_{1c}$ level may be useful in differentiating between patients with and without diabetes, even in the presence of stress-induced hyperglycemia, and may be an ideal tool for case finding in the hospitalized patient. Similar to previously published studies on random hyperglycemia in hospitalized patients, it appears that a sizable proportion of patients with random hyperglycemia will turn out to have diabetes upon further testing, indicating a preexistent disease state rather than a stress response (8–10). Also, given the often unrecognized diagnosis of diabetes in patients with inpatient hyperglycemia (20) and the increased mortality independently associated with inpatient hyperglycemia (6,21), the HbA$_{1c}$ level may provide a more specific cue to the provider to diagnose and treat diabetes rather than the glucose level imbedded in a large chemistry panel.

Previous studies

Although dissimilar in design from our study, Krebs et al. (22) followed 159 patients with random hyperglycemia during hospitalization and tested HbA$_{1c}$ levels and fasting PG 1 year later. The use of fasting PG and HbA$_{1c}$ level avoided the need for an OGTT in 76% of patients and made the diagnosis of diabetes in about 25% of the patients with random hyperglycemia. Although we found a higher prevalence of diabetes in our population (60% of patients with hyperglycemia), the difference can best be explained by the use of the lower fasting PG cutoff level in our study (>125 vs. >140 mg/dl).

Although there are no studies that evaluate the HbA$_{1c}$ level as a case-finding tool in hospitalized patients, the operating characteristics of the HbA$_{1c}$ level have been studied in unselected populations where an HbA$_{1c}$ level of 6.1% was shown to have a sensitivity of 63% and specificity of 97% (17). While the patients in this study were selected for random hyperglycemia >125 mg/dl, the operating characteristics, and subsequent cut point selection, paralleled those in our study (sensitivity 57%, specificity 100%), suggesting that the stress response due to hospitalization had relatively little influence on the HbA$_{1c}$ level when compared with the general population. In fact, the positive predictive value in our study (the likelihood that a person has diabetes if the HbA$_{1c}$ level is >6.0%) was 100%.

Clinical decision making

How would these findings help the clinicians with clinical decision making? The results from this study and previously published literature provide a preliminary rationale for the use of the HbA$_{1c}$ level as a case-finding tool in diabetes via a three-tiered approach (Fig. 2). For the few patients with random hyperglycemia and an HbA$_{1c}$ level <5.2% (n = 7), we could rule out the diagnosis of diabetes with 100% certainty, and no additional testing would be required. For HbA$_{1c}$ lev-

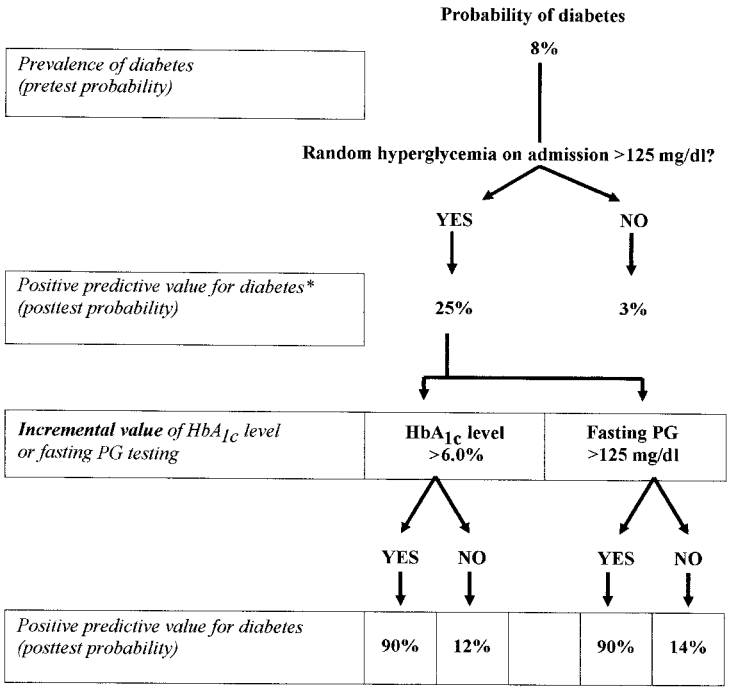

Figure 3—*Clinical decision-making analysis comparing the use of both fasting PG and HbA_{1c} level for diagnosing diabetes in hospitalized patients with random hyperglycemia. *Values are extrapolated from random fingerstick blood glucose: sensitivity 80%, specificity 80%; for HbA_{1c} level: sensitivity 60%, specificity 98%; for fasting PG: sensitivity 56%, specificity 98%. Diabetes prevalence was approximated at 8% (23).*

els >6.0% in patients with hyperglycemia, the diagnosis of diabetes is almost certain. Figure 3 illustrates how sequential testing on patients with hyperglycemia could improve the posttest probability of diabetes. Of note, in patients with random hyperglycemia, both the HbA_{1c} level and fasting PG perform comparably in clinical decision making. The HbA_{1c} level, however, can be available to the clinician much sooner, allowing for the early implementation (and monitoring) of a diabetes teaching and management plan.

Limitations

Certain limitations of this study should be acknowledged. The sample size was rather small, the patient population was generally older, and the gold standard (testing of fasting PG while hospitalized) may have been affected by the acute medical condition as well. Yet, if the fasting PG levels were spuriously elevated or depressed because of the effect of the admitting medical condition, the estimates for the diagnosis and performing characteristics for the HbA_{1c} levels could be inaccurate in the same direction. Furthermore, by not testing HbA_{1c} levels in patients who did not have random admission hyperglycemia, generalizations to all admitted patients cannot be made. Finally, it must be kept in mind that the clinical algorithm was derived from the data presented here and the performance of the algorithm in new and different populations has yet to be validated. Despite these limitations, these results parallel those studies and may aid in clinical decision making. Issues of cost, labor, laboratory use, and patient convenience and compliance will also need to be factored in to the best approach in hospitalized patients.

Summary

The use of the HbA_{1c} level can play a major role in diabetes case finding in hospitalized patients with random hyperglycemia, where the operating characteristics of the test approach those of the traditional fasting PG for the diagnosis of diabetes. An admission HbA_{1c} level is a quick and convenient tool for the diagnosis of diabetes and, in ~50% of the cases, could eliminate the need for further diagnostic testing (through fasting PG or OGTT determinations). This quicker diagnosis of diabetes with the HbA_{1c} level can also translate into an early inpatient mobilization of diabetes support services (e.g., nutrition and education), treatment, and even early medication response. Further prospective studies to examine the cost-effectiveness and patient outcomes of similar case-finding programs are warranted.

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